Research Paper

Navigated and individual α-peak-frequency–guided transcranial magnetic stimulation in male patients with treatment-refractory schizophrenia

Heli Tuppurainen, MD, PhD; Sara Määttä, MD, PhD; Mervi Könönen, PhD; Petro Julkunen, PhD; Hannu Kautiainen, BA; Soile Hyvärinen, MD; Olli Vaurio, MD; Mikko Joensuu, MD, PhD; Matti Vanhanen, PhD; Kati Aho-Mustonen, PhD; Esa Mervaala, MD, PhD; Jari Tiihonen, MD, PhD

Background: Previous electroencephalography (EEG) studies have indicated altered brain oscillatory α-band activity in schizophrenia, and treatment with repetitive transcranial magnetic stimulation (rTMS) using individualized α-frequency has shown therapeutic effects. Magnetic resonance imaging–based neuronavigation methods allow stimulation of a specific cortical region and improve targeting of rTMS; therefore, we sought to study the efficacy of navigated, individual α-peak-frequency–guided rTMS (αTMS) on treatment-refractory schizophrenia. **Methods:** We recruited medication-refractory male patients with schizophrenia or schizoaffective disorder in this double-blind, sham-controlled study. We randomized patients to a 3-week course of either active αTMS or sham stimulation applied to the left dorsolateral prefrontal cortex (DLPFC). We assessed participants with the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Scale (CGI) at baseline and after treatment. We conducted a follow-up assessment with the PANSS 3 months after intervention. **Results:** We included 44 patients. After treatment, we observed a significantly lower PANSS total score ($p = 0.029$), PANSS general psychopathology score ($p = 0.027$) and PANSS 5-factor model cognitive–disorganized factor score ($p = 0.011$) in the αTMS group than the sham group. In addition, the CGI–Improvement score was significantly higher among those who received αTMS compared with sham stimulation ($p = 0.048$). **Limitations:** The limited number of study participants included only male patients. Depression was not formally evaluated. **Conclusion:** Navigated αTMS to the left DLPFC reduced total, general psychopathological, and cognitive–disorganized symptoms of schizophrenia. These results provide evidence for the therapeutic efficacy of individual α-peak-frequency–guided rTMS in treatment-refractory schizophrenia. **Clinical trial registration:** NCT01941251; ClinicalTrials.gov

Introduction

Around 30% of patients with schizophrenia are mostly unresponsive to antipsychotic medication.[1] Treatment resistance usually refers to persistent positive symptoms, although negative and cognitive symptoms may be the main factors contributing to impaired functioning and poor clinical prognosis.[2] Clinical evidence suggests that antipsychotic treatment has limited influence on negative symptoms or cognitive deficit.[3,4] Although clozapine is considered the first-line treatment choice for antipsychotic-resistant psychotic symptoms, as many as 60% of patients respond deficiently to it.[5] Therefore, alternative approaches to managing treatment-refractory schizophrenia are in demand.

The commonly used method in treating patients with clozapine-resistant schizophrenia has been a combination of clozapine with other psychotropic drugs but with insufficient efficacy.[6] According to initial evidence, brain stimulation techniques — such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation — may be potential treatment options for medication-resistant symptoms.[6] For example, a recent retrospective study demonstrated improvement of clozapine-refractory schizophrenia with ECT augmentation.[7] Various TMS paradigms have proven their applicability in treating neuropsychiatric disorders such as schizophrenia.[8]

Functional neuroimaging studies have shown reduced activity in the dorsolateral prefrontal cortex (DLPFC) among patients with schizophrenia.[9] According to a large meta-analysis, treatment of negative schizophrenia symptoms with repetitive TMS (rTMS) over the left DLPFC resulted in moderate

Correspondence to: H. Tuppurainen, Niuvanniemi Hospital, Niuvankuja 65, FI-70240 Kuopio, Finland; heli.tuppurainen@niuva.fi

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improvement of symptoms.[10] Amelioration in cognitive functions has also been observed after high-frequency rTMS to the DLPFC among patients with first-episode and chronic schizophrenia, as well as healthy participants.[11] However, a recent meta-analysis found that active rTMS was not superior to sham with regard to cognitive improvement in schizophrenia or other mental conditions.[12]

Brain α-band (8–12 Hz) oscillations have shown an association with the most basic cognitive processes, such as attention and perception.[13] A previous electroencephalography (EEG) study reported reduced α-band activity at rest and during sensory or cognitive tasks in schizophrenia.[14] A decrease in α-power has been associated with negative symptoms of schizophrenia.[15] In addition, improvement in negative symptoms after clozapine treatment has been found to correlate with the enhancement of α-band oscillations in the frontal cortex on EEG.[16] Recent studies using individual α-peak-frequency have demonstrated improvement in negative, positive, and total schizophrenia symptoms after frontal rTMS.[17,18] It has been proposed that individual α-frequency guided rTMS (αTMS) could potentially improve the efficacy of rTMS therapies.[19]

Studies using magnetic resonance imaging (MRI)-based neuronavigation with rTMS to target DLPFC have shown behavioural and clinical superiority to previously used methods based on external landmarks of the scalp surface or EEG 10–20 electrode placement system.[20,21] It has been postulated that more personalized and precise rTMS targets in the brain could potentially improve therapeutic effect for psychiatric conditions through neural networks and connectivity.[22] Considering the advantages of navigated rTMS and the putative relevance of frontal α-band modulation on schizophrenia symptoms, we sought to examine the efficacy of navigated, individualized αTMS applied to the left DLPFC for overall and various symptom dimensions of treatment-refractory patients with schizophrenia.

Methods

Participants

We recruited inpatients with schizophrenia in this randomized, sham-controlled, rater-blinded, and patient-blinded clinical trial from March 2013 to December 2015 at Niuvanniemi Hospital, Forensic Psychiatric Clinic of the University of Eastern Finland. The inclusion criteria were a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosis of schizophrenia or schizoaffective disorder, age 18–65 years, and male sex. The response to noninvasive brain stimulation has shown variation among females across the menstrual cycle that may confound interpretation of the results.[23] There was also a limited availability of eligible female patients for the study because only 15% of the total number of inpatients in Niuvanniemi Hospital are female. Therefore, we recruited only male patients. Patients had to be refractory to current clinical care, defined with the Clinical Global Impression–Severity Scale (CGI; ≥ 4 points at baseline).[24]

Exclusion criteria included diagnosis of a major mental illness other than schizophrenia or schizoaffective disorder, serious somatic illness, progressive neurologic illness, recent brain damage (< 3 mo previously), sequela of serious brain damage or unstable epilepsy, and ECT treatment within 3 months preceding the intervention. We also excluded patients who had contraindications for rTMS. Patients must have been on antipsychotic medication for at least 3 months before study entry.

Patients' existing drug treatment was kept unchanged for 2 weeks before and during the intervention. Otherwise, patients followed their accustomed regimen.

We randomized patients into the αTMS or the sham group. Groups were balanced regarding clozapine use by separate randomization processes for clozapine- and non-clozapine-medicated patients. Patients, raters, and clinical staff were blind to the intervention received except for the person administering TMS at the Navigated Brain Stimulation (NBS) Unit of Kuopio University Hospital.

Determining resting motor threshold and individual α frequency

Before beginning the study, we scanned participants with a 1.5 T MRI scanner. No patients were excluded from the study for contraindications for MRI exam such as MR unsafe implants, medical materials and devices, or claustrophobia.[25] We acquired structural 3D T_1-weighted MR images with a resolution of 1 mm × 1 mm × 1 mm for neuronavigation in TMS. An experienced neuroradiologist screened all the structural MRIs before intervention for any neuroanatomical exclusion criteria.

We determined the resting motor threshold and individual α frequency in a separate TMS session before beginning the intervention. The patient's motor representation area of the right abductor pollicis brevis muscle was mapped around the motor hand knob region to find the site where motor-evoked potentials of maximal amplitude were repeatedly recorded.[26] At this site, the coil was rotated (within ± 90°) to find the optimal direction that maximized motor-evoked potential amplitudes. At this configuration, the individual resting motor threshold was determined using the TMS Motor Threshold Assessment Tool 2.0 (amplitude limit ≥ 50 μV).[27,28] Additional details are available in Säisänen and colleagues[29] and Julkunen.[30] Muscle activity was monitored online and recorded by stimulus-locked electromyography (EMG) with an integrated eXimia EMG device. During the TMS session, participants sat in an adjustable chair with a headrest that ensured a stable head position.

For individual α frequency, we measured 3 minutes of EEG with eyes closed using a 64-channel EEG amplifier and an electrode cap with 61 EEG contacts (Brain Products GmbH, BrainVision Recorder, version 1.20) with electrodes positioned according to the 10–10 international system. In addition to EEG, we also recorded bipolar electro-oculography and monopolar electrocardiography signals. The skin–electrode impedance was set at 5 kΩ or less. The ground and reference electrodes were positioned on the forehead. Horizontal and

vertical eye movements were detected by recording the electro-oculogram with 2 electrodes located to the left and right of the external canthi. We determined individual α frequency from each patient's average α peak frequency, obtained from 5 frontal electrode leads (F7, F3, Fz, F4, and F8) using custom-made MATLAB script on converted and downsampled (to 1 kHz) EEG. In the individual α frequency procedure, we chose an epoch demonstrating α frequency visually from the EEG, filtered to 8–12-Hz band and divided into 4-second sections.[31] We constructed the frequency spectrum with the fast Fourier transformation for the sections with overlapping windows of 50%, and used mean amplitude spectra to detect the individual α frequency within the filtered band. We used the resulting α frequency at 1 Hz precision as treatment frequency for rTMS.

Repetitive transcranial magnetic stimulation procedure

The patients received a 3-week intervention of individual α-peak-frequency–guided rTMS at 110% resting motor threshold or sham stimulation over the left DLPFC, as adjunctive therapy.

For the first 20 patients, we administered TMS using a Magstim Rapid² stimulator (Magstim Company) and a biphasic figure-of-8 coil or sham coil with an identical appearance. The stimulator was triggered with neuronavigation software (eXimia 3.1, Nexstim). For the remaining patients, we administered TMS using a Nexstim NBS and a biphasic figure-of-8 cooled coil (version 4.2). For sham stimulations, the same coil was used, with a spacer of 75 mm and an intensity of 50% of maximum stimulator output. We focused rTMS on the left DLPFC (Figure 1), and defined the stimulation target as the junction of Brodmann areas 46 and 9, based on each individual participant's MRI scan.[32] Although the properties of the 2 stimulation systems we used were different, the coil dimensions were very similar, and the intensity of stimulation in both systems was adjusted based on the individual resting motor threshold, accounting for the crucial system-dependent differences in induced cortical excitation. The localization of the stimulation was based on the computed electric field in both systems.

During the rTMS sessions, patients received 24 trains of pulses. The trains were 5 seconds in duration and the interval between train onsets was 30 seconds.[33] The frequency of stimulation was defined according to the individual α frequency. During the stimulation, patients were allowed to watch television to keep vigilance high. The rTMS protocol followed the safety guidelines for rTMS applications.[34]

Clinical assessments

Four experienced investigators assessed clinical measures. The primary outcome parameters were changes in total, positive, negative, and general psychopathology sum scores of the Positive and Negative Syndrome Scale (PANSS) after 3 weeks of intervention.[35] The intraclass correlation coefficient (ICC) for PANSS total and subscores varied from 0.70 to 0.84 between the raters. The secondary outcome measure was the CGI–Improvement Scale after treatment.[24] We conducted an additional analysis using the PANSS 5-factor model to further evaluate the effects of αTMS on diverse symptomatology of schizophrenia.[36] The 5-factor symptom domains were organized as negative (PANSS items N1, N2, N3, N4, N6, G7, G13, and G16), cognitive–disorganized (PANSS items P2, N5, N7, G5, G10, G11, and G15), positive (PANSS items P1, P3, P5, P6, G9, and G12), excited (PANSS items P4, P7, G8, and G14), and depressive–anxiety (PANSS items G1, G2, G3, G4, and G6) factors (Appendix 1, available

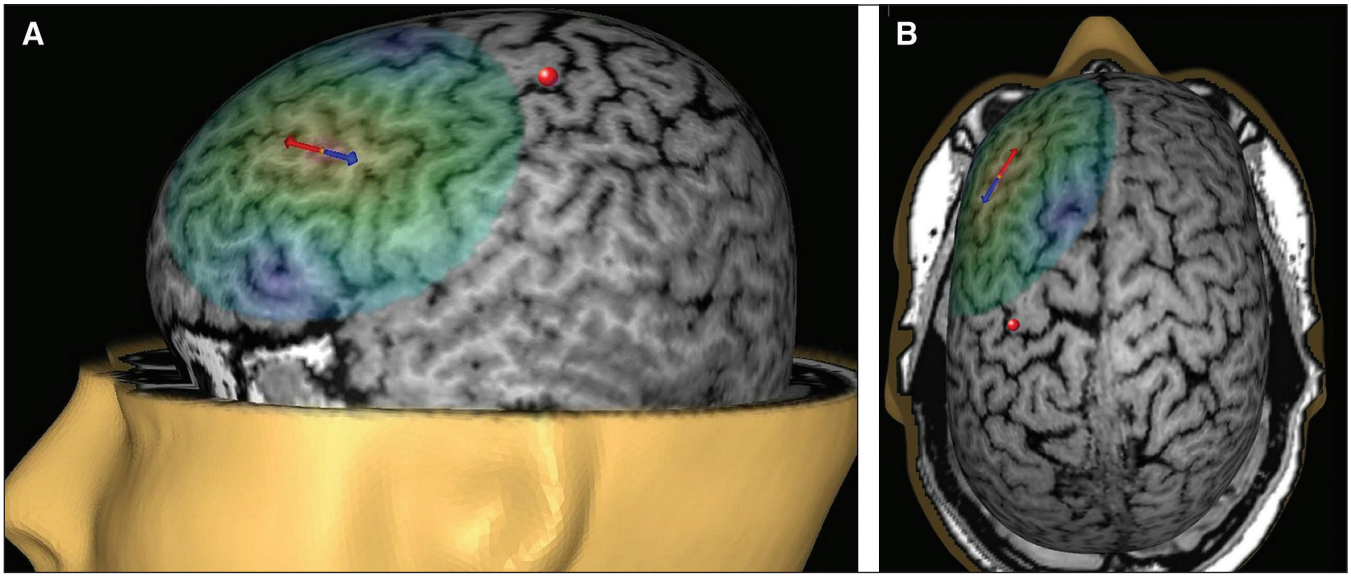

Figure 1: (A) Lateral and (B) superior views of the therapy target site of an individual patient, visualized on the brain surface, at a 21-mm depth from the scalp on the dorsolateral prefrontal cortex. The direction of induced current is presented with arrows. The optimal motor representation site for the abductor pollicis brevis muscle is shown with a red dot.

at https://www.jpn.ca/lookup/doi/10.1503/jpn.230063/tab-related-content).

We determined clinical ratings at baseline (PANSS and CGI–Severity), after treatment (PANSS and CGI–Improvement), and at the 3-month follow-up (PANSS). The follow-up assessment was conducted without controlling for drug or other treatments for severe symptoms. A nuse collected information on adverse events during the intervention at daily interviews. At the post-treatment visit, the patients were asked about which group they were a part of.

Statistical analysis

We determined the intended sample size based on the primary outcome (PANSS total). We required a sample of about 48 patients (24 in each group) to detect a 5-point difference between the groups in the change in the PANSS total score ($\alpha = 0.05$, power = 80%). We presented the characteristics by group as means with standard deviations for continuous variables and as frequencies with percentages for categorical variables. We conducted statistical comparisons between groups using the Student *t* test and permutation test for continuous variables, and the Fisher exact test for noncontinuous variables. We analyzed repeated measures of PANSS original and 5-factor scores between groups using mixed-effects models with an unstructured covariance structure (using the Kenward–Roger method to calculate the degrees of freedom). Use of mixed models allowed for analysis of unbalanced data sets without imputation; thus, we analyzed all available data, using the full analysis set. Repeated measurements were performed at baseline, after treatment, and at follow-up. We calculated effect size using the Cohen *d* statistic (considering 0.20 small, 0.50 moderate, and 0.80 large).[37] We calculated correlation coefficients by the Spearman method. We determined 95% confidence intervals (CIs) for the effect sizes and correlations by bias-corrected bootstrapping (10 000 replications). All statistical analyses were performed with Stata, version 17.0 (StataCorp LP).

Ethics approval

The study protocol was approved by the Research Ethics Committee of Hospital District of Northern Savo (93/2012, 11.12.2012). Written informed consent was acquired from all participants after detailed description of the study.

Results

Demographic and clinical characteristics

We included 44 right-handed, male patients with schizophrenia (Figure 2). The αTMS group did not differ significantly from the sham group (Table 1). A total of 33 patients were on clozapine treatment. The other frequently used antipsychotics were olanzapine ($n = 8$), risperidone ($n = 4$), and quetiapine ($n = 4$). Only a subset of patients were on antipsychotic monotherapy (6 in each group), while others received 2 or more antipsychotics with or without antiepileptic or antidepressant treatment. Adjunctive antiepileptic drugs were

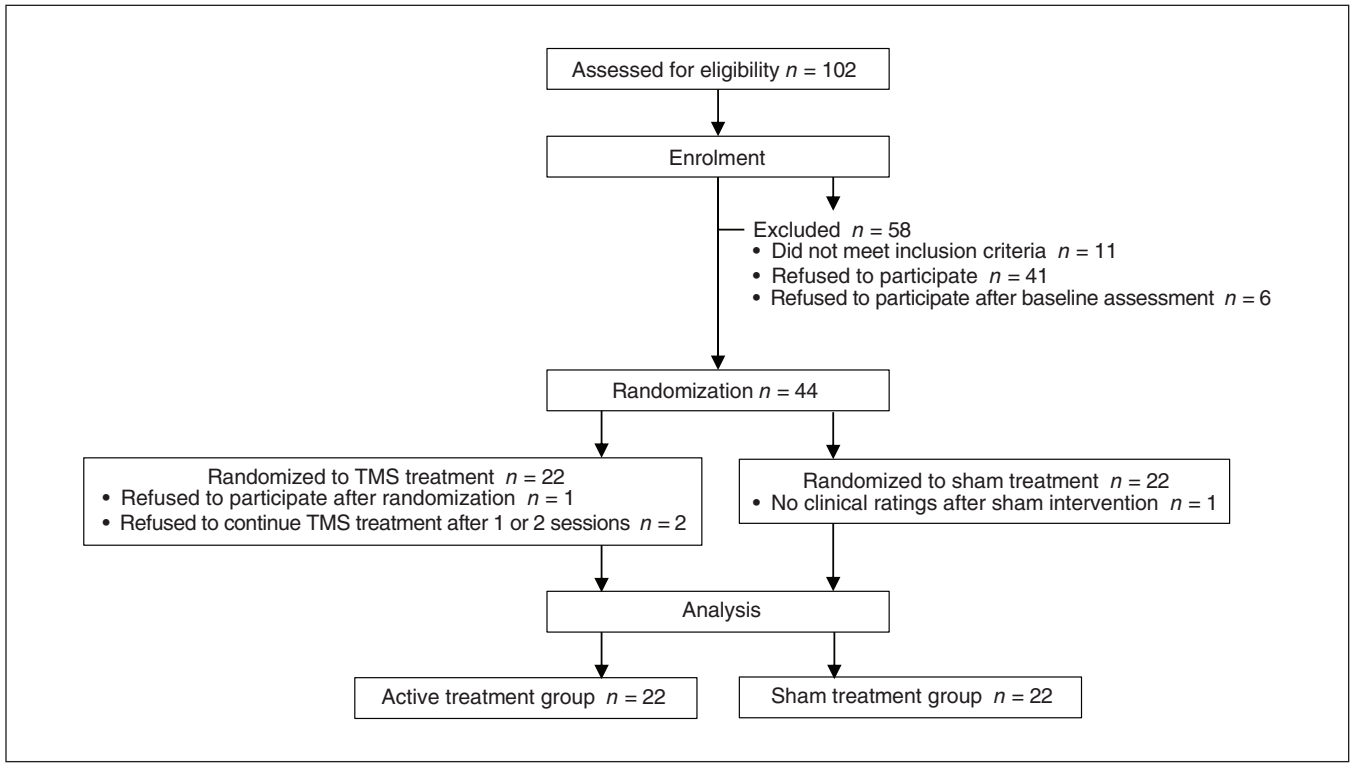

Figure 2: Study flowchart. TMS = transcranial magnetic stimulation.

Table 1: Demographic and clinical characteristics at baseline

Variable	No. (%) of participants* Sham *n* = 22	αTMS *n* = 22	*p* value
Age, yr, mean ± SD	37 ± 10	38 ± 12	0.79
Clozapine use	18 (82)	15 (68)	0.49
Chlorpromazine equivalent dose, mg/d, mean ± SD	535 ± 288	507 ± 177	0.70
Antidepressant use	7 (32)	7 (32)	1.00
Antiepileptic drug use	13 (59)	11 (50)	0.54
Previous ECT	2 (9)	3 (14)	0.98
PANSS score, mean ± SD			
Total	83 ± 16	85 ± 12	0.64
Positive	20 ± 6	20 ± 5	0.93
Negative	22 ± 5	22 ± 4	0.90
General psychopathology	41 ± 8	43 ± 7	0.37
PANSS 5-factor score, mean ± SD			
Negative	22 ± 5	23 ± 5	0.48
Cognitive	20 ± 4	20 ± 3	0.62
Positive	18 ± 6	19 ± 4	0.54
Excited	9.0 ± 2.5	8.7 ± 3.2	0.76
Depressive	13 ± 3	14 ± 3	0.43
CGI-S score, mean ± SD	4.8 ± 0.8	4.9 ± 0.8	0.57
Resting motor threshold, mean ± SD	47.6 ± 11.8	45.7 ± 15.5	0.66
IAF, Hz, median (range)	9 (8–10)	9 (8–12)	0.64

αTMS = individual α-peak-frequency–guided transcranial magnetic stimulation; CGI-S = Clinical Global Impression Severity Scale; ECT = electroconvulsive therapy; IAF = individual α-frequency; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.
*Unless indicated otherwise.

sodium valproate (n = 3 in the αTMS group, n = 8 in the sham group), lamotrigine (n = 6 in the αTMS group, n = 4 in the sham group), and topiramate (n = 2 in the αTMS group, n = 1 in the sham group). None of the study participants received benzodiazepines.

The patients received a median of 15 (range 13–15) active or sham sessions over the 3-week intervention period. The number of pulses per session did not differ between the study groups, with a mean of 1061 (standard deviation [SD] 115) pulses in the αTMS group and a mean of 1058 (SD 88) pulses in the sham group (p = 0.93). Three patients in the αTMS group did not complete the treatment regimen. One of them withdrew consent after randomization, and 2 patients discontinued after 1–2 αTMS sessions because of adverse effects. One of these patients experienced deterioration of psychotic symptoms and the second patient described pain at the stimulation site. All patients in the sham group completed the protocol. However, 1 patient in the sham group was erroneously not clinically assessed after the intervention.

Most participants reported adverse events with no intergroup statistical difference (n = 17 in the αTMS group, n = 18 in the sham group, p = 0.73) (Table 2). One patient in the sham group had nonepileptic seizures without EEG changes after the last rTMS session, and 3 other sham-treated participants reported pre-epileptic sensations, such as dissociative aura. Most adverse events were mild and did not require specific treatment except for 1 patient in the sham group whose headache was treated with painkillers.

Table 2: Adverse events

Adverse event	No. (%) of participants* Sham *n* = 22	αTMS *n* = 22
Mild adverse events		
Tiredness	15 (68)	12 (55)
Headache	14 (64)	8 (36)
Pain	2 (9)	4 (18)
Dizziness	2 (9)	5 (23)
Nausea	1 (5)	1 (5)
Pre-epileptic sensations	3 (14)	0 (0)
Other	11 (50)	11 (50)
Serious adverse events		
Exacerbation of psychotic symptoms	0 (0)	1 (5)
Seizures	1 (5)	0 (0)

αTMS = individual α-peak-frequency–guided transcranial magnetic stimulation.
*No statistical differences between groups.

After the 3-week intervention, most participants in both groups assumed that they had received real stimulation (n = 14 in the αTMS group, n = 15 in the sham group).

Treatment efficacy

Pre–post PANSS total and general psychopathology scores decreased significantly in the αTMS group compared with the sham group (Table 3). No significant group differences on positive or negative symptoms were found. Additional analysis of the PANSS 5-factor model score changes revealed significant improvement in cognitive–disorganized symptoms after αTMS treatment compared with sham stimulation, but not on the negative, positive, excited, or depressive–anxiety factors (Table 3).

At the 3-month follow-up assessment, we observed a significant improvement from baseline on the PANSS total and general psychopathological scores, and on the 5-factor cognitive–disorganized and positive scores, in the αTMS group compared with the sham group (Table 4). No significant group differences on the other subscales were found.

We observed a significant difference in post-treatment CGI–Improvement values between the study groups, with a mean change of 0.6 (SD 1.2) in the αTMS group and a mean change of –0.2 (SD 1.4) in the sham group (p = 0.048), favouring αTMS treatment.

Supplementary analysis of the pre–post PANSS total score change was performed using data from clozapine-treated patients (n = 15 in the αTMS group, n = 18 in the sham group). In this subgroup, we observed a significant decrease in PANSS total scores in the αTMS group (mean –3.5, 95% CI –6.9 to –0.2), compared with the sham group (mean 1.9, 95% CI –1.2 to 4.9; p = 0.019, d = 0.82).

There were no significant correlations between the change in PANSS total scores and individual α frequencies (r = 0.04,

Table 3: Differences between the study groups in Positive and Negative Syndrome Scale (PANSS) original and 5-factor scores after treatment

	Baseline		Change after treatment			
PANSS	Sham Mean ± SD	αTMS Mean ± SD	Sham Mean (95% CI)	αTMS Mean (95% CI)	*p* value*	Effect size†
Original						
Total	83 ± 16	85 ± 12	1.1 (–1.6 to 3.9)	–3.3 (–6.2 to –0.4)	0.029	–0.64 (–1.25 to –0.02)
Positive	20.1 ± 5.7	20.0 ± 4.5	0.3 (–0.6 to 1.3)	–0.8 (–1.8 to 0.1)	0.091	–0.47 (–1.10 to 0.17)
Negative	21.9 ± 5.2	22.0 ± 4.2	0.2 (–0.7 to 1.2)	–0.7 (–1.8 to 0.3)	0.18	–0.40 (–1.00 to 0.19)
General	40.6 ± 7.5	42.5 ± 6.8	0.6 (–0.8 to 2.0)	–1.7 (–3.1 to –0.2)	0.027	–0.65 (–1.27 to –0.04)
Five-factor model						
Negative	22.0 ± 5.5	23.1 ± 5.1	0.1 (–0.9 to 1.1)	–0.8 (–1.8 to 0.3)	0.24	–0.34 (–0.91 to 0.22)
Cognitive–disorganized	20.2 ± 4.4	19.6 ± 3.4	0.9 (–0.0 to 1.7)	–0.8 (–1.7 to 0.1)	0.011	–0.77 (–1.39 to –0.14)
Positive	18.3 ± 5.7	19.3 ± 4.4	0.5 (–0.4 to 1.3)	–0.6 (–1.5 to 0.3)	0.081	–0.50 (–1.16 to 0.15)
Excited	9.0 ± 2.5	8.7 ± 3.2	–0.2 (–0.6 to 0.2)	–0.4 (–0.8 to 0.1)	0.56	–0.13 (–0.75 to 0.50)
Depressive–anxiety	13.1 ± 3.4	13.9 ± 3.0	–0.1 (–1.0 to 0.8)	–0.6 (–1.6 to –0.3)	0.43	–0.23 (–0.83 to 0.38)

αTMS = individual α-peak-frequency–guided transcranial magnetic stimulation; CI = confidence interval; SD = standard deviation.
**p* value between changes.
†Negative values indicate better scores in the αTMS group, positive values indicate better values in the sham group.

Table 4: Differences between the study groups in Positive and Negative Syndrome Scale (PANSS) original and 5-factor score changes at 3-month follow-up

	Change at follow-up			
PANSS	Sham Mean (95% CI)	αTMS Mean (95% CI)	*p* value*	Effect size† (95% CI)
Original				
Total	2.3 (–0.6 to 5.1)	–2.2 (–5.3 to 0.8)	0.038	–0.55 (–1.26 to –0.1)
Positive	0.9 (–0.1 to 1.9)	–0.2 (–1.3 to 0.9)	0.17	–0.35 (–1.02 to 0.32)
Negative	–0.1 (–1.0 to 0.9)	–0.4 (–1.4 to 0.9)	0.66	–0.12 (–0.73 to 0.56)
General	1.4 (–0.1 to 2.8)	–1.7 (–3.2 to –0.2)	0.005	–0.77 (–1.52 to –0.13)
Five-factor model				
Negative	–0.2 (–1.3 to 0.8)	–0.6 (–1.3 to 0.8)	0.62	–0.13 (–0.71 to 0.54)
Cognitive–disorganized	0.7 (–0.2 to 1.5)	–0.8 (–0.2 to 1.5)	0.022	–0.73 (–1.37 to –0.04)
Positive	1.3 (0.4 to 2.2)	–0.3 (–1.3 to 0.7)	0.020	–0.61 (–1.22 to –0.10)
Excited	0.2 (–0.4 to 0.8)	–0.0 (–0.7 to 0.6)	0.61	–0.08 (–0.73 to 0.54)
Depressive–anxiety	0.3 (–0.6 to 1.3)	–0.5 (–1.5 to 0.5)	0.26	–0.29 (–0.97 to 0.36)

αTMS, individual α-peak-frequency–guided transcranial magnetic stimulation; CI = confidence interval.
**p* value between changes.
†Negative values indicate better scores in the αTMS group, positive values indicate better values in the sham group.

95% CI –0.42 to 0.49), age (r = –0.06, 95% CI –0.50 to 0.41), chlorpromazine equivalent dose (r = 0.16, 95% CI –0.31 to 0.57), antidepressant use (r = –0.12, 95% CI –0.54 to 0.36), or antiepileptic drug use (r = –0.31, 95% CI –0.67 to 0.16) in the αTMS treatment group.

Discussion

This randomized, double-blind, and sham-controlled study found a statistically significant improvement in PANSS total and general psychopathological schizophrenia symptoms after 3 weeks of neuronavigated αTMS, targeted to the left DLPFC. After treatment, we did not observe any significant differences in positive and negative symptom scales. The findings in PANSS total and general psychopathological scores persisted through the 3-month follow-up, indicating a long-lasting therapeutic effect of αTMS on schizophrenia symptoms. A significant decrease in positive symptoms after the follow-up period was observed in the αTMS group, compared with the sham group.

We observed significantly higher clinical global improvement after treatment among those who received the αTMS stimulation compared with those who received the sham treatment. This result on the secondary outcome measure confirms the findings in primary outcome parameters.

A previous αTMS study reported a reduction of PANSS total and positive symptoms in the treatment group after 2 weeks of bilateral frontal or parietal stimulation, compared with the sham group, but no group differences on negative symptoms.[18] In that study, rTMS was given with a circular

coil placed either on the midfrontal or midparietal area, and individual α frequency was determined from central electrode leads. These authors had formerly shown the superior efficacy of bilateral αTMS over the DLPFC on mitigating the negative symptoms among patients with schizophrenia who predominantly expressed negative symptoms, compared with sham treatment.[17] Both studies located the TMS coil with the international EEG 10–20 system. These differences in rTMS procedure and patients selection may explain the different results regarding negative symptoms between the current study and previous studies.

We did not observe any significant treatment effect on negative schizophrenia symptoms, which diverged from the previous positive findings after high-frequency rTMS applied to the left frontal area.[10] The median of stimulation frequency (individual α frequency) used in our study was 9 Hz, which was slightly lower than that used in most previous trials of high-frequency rTMS. In a recent meta-analysis of factors associated with the clinical efficacy of noninvasive brain stimulation, a stimulation frequency of 20 Hz or greater predicted a better rTMS-induced improvement in negative schizophrenia symptoms.[38] Consequently, application of individual peak α frequency in rTMS therapy may not be optimal for the treatment of negative symptoms.

Previously, high-frequency rTMS over the left DLPFC has shown no effect or has been associated with worsening of positive schizophrenia symptoms.[39,40] However, a recent study with neuronavigated 10-Hz rTMS of the left DLPFC detected a significant decrease in the positive symptoms of veterans with schizophrenia.[41] This finding, together with our result showing favourable effects on positive symptoms, may be related to brain network modulation at the cortico-subcortical level.[42]

In the present study, we performed an additional analysis of schizophrenia symptoms by employing the PANSS 5-factor model. The results suggested a decrease in cognitive–disorganized symptom scores after left frontal αTMS and at the 3-month follow-up. Although the PANSS 5-factor cognitive–disorganized factor score cannot replace formal neuropsychological assessment, cognitive–disorganized symptoms have exhibited significant inverse relationships with neurocognitive function among patients with schizophrenia.[39] Brain oscillatory α-band abnormalities have been shown to be related to deficient cognitive and sensory processes and to various clinical symptoms in schizophrenia.[14,43] Our findings on cognitive–disorganized schizophrenia symptoms are in congruence with these observations.

The severity of schizophrenia symptoms was substantially high in the present study group, yet consensus criteria for the treatment-resistant schizophrenia were not employed.[44] As clozapine is the treatment of choice for antipsychotic-resistant schizophrenia, participants who respond inadequately to clozapine are in the urgent need for effective adjunct therapies. Therefore, we performed supplementary analysis of the pre–post PANSS total score change exclusively among clozapine-treated patients, which found significant improvement of overall schizophrenia symptoms in the αTMS group compared with the sham group. This result is in line with the outcome of the primary study population. However, a recently published pairwise meta-analysis found no significant differences between rTMS (n = 26) and sham groups (n = 28) for total, positive, and negative symptoms of clozapine-resistant schizophrenia.[45] One of the 3 included studies used 10-Hz rTMS over the left DLPFC for patients with predominantly negative schizophrenia symptoms (n = 12 in the active group, n = 14 in the sham group) and reported the beneficial efficacy of active rTMS for total, general psychopathological, and positive symptoms (but not for negative symptoms).[46] These results are in agreement with our findings on treatment for clozapine-refractory schizophrenia.

Previously, functional MRI–navigated rTMS to the left temporoparietal cortex has been successfully applied to the treatment of persistent auditory hallucination in schizophrenia.[47,48] Evidence from rTMS studies on major depression has indicated the clinical superiority of DLPFC-targeted stimulation with MRI-guided navigation compared with traditional methods.[49] In addition to its usage for neuronavigation, the individually set stimulus frequency used here may have promoted the rTMS-induced decrease in schizophrenia symptoms among seriously affected patients.

Limitations

The relatively small sample size may have contributed to the treatment effect not reaching statistical significance in all outcomes. However, αTMS significantly improved total, general psychopathological, and cognitive–disorganized schizophrenia symptoms compared with sham stimulation (d = 0.64–0.77). Given the lack of suitable female patients for the study, and the difficulty in accounting for potential contributors in treatment outcome for females (e.g., menstrual cycle),[23] the study sample consisted of male patients, which restricts generalization of the results to cover both sexes.

We assessed schizophrenia symptoms using only the PANSS, meaning that the evaluation of treatment effect on depressive symptoms was not extensive. However, additional symptom analysis with the PANSS 5-factor model revealed no significant difference on the depressive–anxiety factor between study groups (d = 0.23). It should also be noted that patients with major depressive or bipolar disorder were not included the study.

The definition of a treatment-refractory state before the study was based merely on assessment with the CGI–Severity Scale. Experienced clinicians who had been working closely with the patients with chronic schizophrenia performed the rating, which increased reliability of these assessments. However, application of the standard criteria for treatment-resistant schizophrenia would have been appropriate if available in the beginning of this clinical trial.[39]

Many participants in this study had concomitant antidepressant or antiepileptic medication that may have weakened the clinical efficacy of rTMS by decreasing cortical excitability.[50] This effect could be compensated by increasing the stimulation intensity, which could induce more rTMS-related adverse effects. Despite the high rate of adverse events reported equally in both study groups, adverse effects were

mild and led to discontinuation of the stimulation period in only 2 cases. A relatively low total number of stimuli (≤ 15 000) and brief stimulation period of 3 weeks in the present study could result in attenuated results. The positive findings of the pre–post treatment effect on theoretically meaningful clinical parameters, combined with the extended therapeutic efficacy that we observed, may have been strengthened by prolonging the rTMS period or by increasing the number of applied stimuli.[51,52]

Finally, our follow-up assessment was conducted 3 months after intervention without controlling for drug or other treatments. For that reason, our significant results at this time point should be interpreted with caution.

Conclusion

We investigated the efficacy of neuronavigated αTMS on various dimensions of schizophrenia, which revealed beneficial effects on overall schizophrenia symptoms and on general psychopathological and cognitive–disorganized symptom domains of schizophrenia, as assessed with the PANSS. These results sustained through the 3-month follow-up period, at which point improvement in 5-factor positive symptoms was also detected. These findings support the application of navigated and individual α-peak-frequency–guided rTMS to the left DLPFC as an efficient complementary therapy for patients with treatment-refractory schizophrenia. However, future neuronavigated rTMS studies are needed to replicate these preliminary results using a larger cohort, applying treatment-resistant schizophrenia criteria, and including of both sexes.

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Affiliations: From the Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland (Tuppurainen, Hyvärinen, Vaurio, Joensuu, Vanhanen, Aho-Mustonen, Tiihonen); the Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland (Määttä, Könönen, Julkunen, Mervaala); the Department of Clinical Radiology, Kuopio University Hospital, Kuopio, Finland (Könönen); the Department of Technical Physics, University of Eastern Finland, Kuopio, Finland (Julkunen); the Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland (Kautiainen); the Folkhälsan Research Center, Helsinki, Finland (Kautiainen); Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland (Mervaala); the Department of Clinical Neuroscience, Karolinska Institutet, and Center for Psychiatry Research, Stockholm City Council, Stockholm, Sweden (Tiihonen).

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