Schizophrenia Bulletin vol. 42 no. 3 pp. 608–618, 2016
doi:10.1093/schbul/sbv142
Advance Access publication October 3, 2015

Cognitive Effects of High-Frequency rTMS in Schizophrenia Patients With Predominant Negative Symptoms: Results From a Multicenter Randomized Sham-Controlled Trial

Alkomiet Hasan*[,1,13], Birgit Guse[2,13], Joachim Cordes[3], Wolfgang Wölwer[3], Georg Winterer[4], Wolfgang Gaebel[3], Berthold Langguth[5], Michael Landgrebe[5,6], Peter Eichhammer[5], Elmar Frank[5], Göran Hajak[7], Christian Ohmann[8], Pablo E. Verde[8], Marcella Rietschel[9], Raees Ahmed[10], William G. Honer[11], Berend Malchow[1], Susanne Karch[1], Thomas Schneider-Axmann[1], Peter Falkai[1], and Thomas Wobrock[2,12]

[1]Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany; [2]Department of Psychiatry and Psychotherapy, Georg-August-University Göttingen, Göttingen, Germany; [3]Department of Psychiatry and Psychotherapy, Heinrich-Heine University, Düsseldorf, Germany; [4]The Charité – Universitätsmedizin Berlin, Berlin, Germany; [5]Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany; [6]Department of Psychiatry, Psychosomatics and Psychotherapy, kbo-Lech-Mangfall-Klinik, Agatharied, Germany; [7]Department of Psychiatry, Psychosomatics and Psychotherapy, Sozialstiftung Bamberg, Bamberg, Germany; [8]Coordination Centre for Clinical Trials, Heinrich-Heine University, Düsseldorf, Germany; [9]Department of Genetic Epidemiology in Psychiatry, Institute of Central Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany; [10]Institut für anwendungsorientierte Forschung und klinische Studien GmbH, Göttingen, Germany; [11]Institute of Mental Health, The University of British Columbia, Vancouver, British Columbia, Canada; [12]County Hospitals Darmstadt-Dieburg, Groß-Umstadt, Germany

[13]These authors contributed equally to the article.

*To whom correspondence should be addressed; Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Nussbaumstr. 7, D-80336 Munich, Germany; tel: +49 (0) 89 4400 55511, fax: +49 (0) 89 4400 55530, e-mail: alkomiet.hasan@med.uni-muenchen.de

Cognitive impairments are one of the main contributors to disability and poor long-term outcome in schizophrenia. Proof-of-concept trials indicate that repetitive transcranial magnetic stimulation (rTMS) applied to the left dorsolateral prefrontal cortex (DLPFC) has the potential to improve cognitive functioning. We analyzed the effects of 10-Hz rTMS to the left DLPFC on cognitive deficits in schizophrenia in a large-scale and multicenter, sham-controlled study. A total of 156 schizophrenia patients with predominant negative symptoms were randomly assigned to a 3-week intervention (10-Hz rTMS, 15 sessions, 1000 stimuli per session) with either active or sham rTMS. The Rey Auditory Verbal Learning Test, Trail Making Test A and B, Wisconsin Card Sorting Test, Digit Span Test, and the Regensburg Word Fluency Test were administered before intervention and at day 21, 45, and 105 follow-up. From the test results, a neuropsychological composite score was computed. Both groups showed no differences in any of the outcome variables before and after intervention. Both groups improved markedly over time, but effect sizes indicate a numeric, but nonsignificant superiority of active rTMS in certain cognitive tests. Active 10-Hz rTMS applied to the left DLPFC for 3 weeks was not superior to sham rTMS in the improvement of various cognitive domains in schizophrenia patients with predominant negative symptoms. This is in contrast to previous preliminary proof-of-concept trials, but highlights the need for more multicenter randomized controlled trials in the field of non-invasive brain stimulation.

Key words: schizophrenia/negative symptoms/cognition/repetitive magnetic stimulation/brain plasticity

Introduction

Within the complex symptomatology of schizophrenia, cognitive deficits are one of the main contributors to disability and impaired social and occupational functioning.[1,2] Deficits in several separable cognitive domains are primary symptoms, are frequently present before the onset of schizophrenia, and are stable over time.[3,4] One recent meta-analysis confirmed disease-related impairments in different cognitive domains and the deficits are estimated to be in average up to 2.5 SDs from the normal population.[5]

In the light of the importance of cognitive impairments in schizophrenia patients, there is an active search for novel treatments. Second-generation antipsychotics were initially proposed to have a marked impact on cognitive

deficits, but those effects were later shown to be modest at best[6] and the proposed superiority compared to first-generation antipsychotics was inconsistent.[7] Psychosocial interventions including cognitive remediation, standardized neurocognitive training, metacognitive training, or exercise are also proposed to be potential treatment options.[8–10] However, novel biological treatments targeting the neural mechanism of cognitive impairments and brain plasticity in schizophrenia are still lacking.[11]

Supported by the results of functional neuroimaging and electrophysiological studies, dysfunction within the dorsolateral prefrontal cortex (DLPFC) as well as impaired DLPFC connectivity is proposed to contribute to the physiological mechanism of cognitive deficits in schizophrenia.[12] In this model, impaired DLPFC functions results in deficits of proactive control leading consecutively to impairments in executive functioning and control, as well as in working and episodic memory.[12] Therefore, modulation of DLPFC activity may be a potential treatment option. Repetitive transcranial magnetic stimulation (rTMS) provides noninvasive modulation of cortical excitability and induction of plasticity.[13] rTMS was specifically proposed to be an efficacious treatment of memory deficits in schizophrenia.[14] Single-center studies with limited sample sizes of 10–18 patients in the active group showed that high-frequency rTMS applied to the left DLPFC improved short-term auditory verbal memory,[15] working memory,[16] and facial affect recognition[17] in schizophrenia. Conversely, some studies failed to find a beneficial effect of active rTMS applied to the left DLPFC on long-term verbal memory, attention, and on different tests of frontal executive functioning.[15,18,19]

The efficacy of high-frequency rTMS for the treatment of cognitive symptoms requires a larger study with appropriate controls. The primary objective of this first randomized, multicenter sham-controlled study was to investigate the efficacy of high-frequency 10-Hz rTMS applied to the left DLPFC for the treatment of negative symptoms, and the results were recently reported.[20] The secondary objective was to improve neurocognitive deficits in a large sample of severely affected schizophrenia patients with predominant negative symptoms. As negative symptoms and cognitive deficits share separable but related etiologies and as both contribute to the functional impairments of schizophrenia patients,[3] a beneficial effect in such a population would be clinically meaningful and would allow for sustained changes in clinical practice.

Methods

Study Subjects

As detailed elsewhere,[20] 197 inpatients and outpatients from 3 German university hospital centers were enrolled in this multicenter randomized, sham-controlled, rater-blinded, and patient-blinded clinical trial. The inclusion criteria were an ICD-10 diagnosis of schizophrenia (according to MINI-Plus[21]), age 18–60 years, and illness duration of at least 1 year. Further inclusion criteria were a predominant negative syndrome (Positive and Negative Syndrome Scale [PANSS][22]), a negative subscore >20 points, one of items N1–N7 scoring ≥4, and stable antipsychotic medication in the 2 weeks before intervention with no reduction of ≥10% in PANSS Negative subscore over this time. The full inclusion and exclusion criteria are detailed elsewhere.[20,23]

Intervention

Participants entered a pretreatment assessment 12–16 days before the baseline visit (day 0). Subsequently, patients entered the 3-week parallel group rTMS intervention (active vs sham rTMS as add-on treatment) until day 21, followed by a 12-week extension phase with no further intervention. Neuropsychological assessments took place 2 weeks before the start of the intervention (pretreatment visit) and at days 21, 45, and 105 (for trial study plan, see Wobrock et al[20]). Before intervention, patients were randomly assigned via a computer-generated multiblock randomization schedule.

Further, 10-Hz rTMS was applied to the left DLPFC, using the EEG-10/20 system for coil placement (F3 corresponding to Brodmann's areas 8, 9, or 46 on the medial frontal gyrus[24,25]). For sham rTMS, the stimulation coil was tilted over one wing at an angle of 45° leading to similar skin sensations, but substantially reduced biological activity[26] (for details, see Wobrock et al [20]). Patients received 15 treatment sessions in 3 weeks and received 1000 stimuli (20 trains with 50 stimuli per train, 30 second intertrain interval) with an intensity of 110% of the individual resting motor threshold per session. To guarantee high comparability, all participating sites used the same stimulators (Medtronic MagPro-X100) and passively cooled MCF-B65 figure-of-eight coils.

Written informed consent was obtained from all participants before study inclusion. The published trial protocol[23] was approved by the local ethics committees and the trial was conducted in line with the Declaration of Helsinki. The Coordination Centre for Clinical Trials Duesseldorf (http://www.uniklinik-duesseldorf.de/kks) provided study monitoring and trial organization. The trial was registered at http://www.clinicaltrials.gov (NCT00783120) and the protocol was published.[27] The complete study description of the RESIS trial (including blinding and randomization procedures) appears elsewhere.[20,23]

Neurocognitive Assessments and Outcome Measures

The main outcome measure was performance in the following tests:

The *Verbaler Lern- und Merkfähigkeitstest (VLMT: Verbal Learning and Memory Test)* is the German Version of the Rey Auditory Verbal Learning Test.[27]

It contains multiple parameters of declarative verbal memory including suprarange, learning efficiency, long-term decoding ability, recall, and recognition. Seven trials are administered with the outcome measures of the verbal learning performance (sum of trials 1–5) and the performance decrease after delay (trial 5 minus trial 7, difference between maximum performance of immediate and delayed recall, higher raw values indicating greater decrease).

The *Trail Marking Test* was used to investigate complex visual scanning, motor speed, and the ability to shift strategies.[28] Patients had to draw lines to connect either consecutively numbered circles (Trail Making Test-A [TMT-A]) or to connect consecutively alternating numbered and letters circles (TMT-B). The outcome measures were the times to complete TMT-A/TMT-B.

The *Wisconsin Card Sorting Test (WCST)*[29] was used to assess perseveration and abstract reasoning. This test provides objective measures of overall success and identifies specific sources of difficulty with the task using stimulus and response cards containing 4 forms in different colors and numbers. The participant sorts the cards according to color, form, and number and must alter their approach as unannounced shifts in the sorting principle occur. The outcome measures are the number of trials administered (used cards), the number of total correct cards, and the number of total errors.

The *Digit Span Test* (DST, subtest of the Hamburg-Wechsler Intelligence Test[30]) is a screening instrument for components of working memory, attention, and concentration. The patient must memorize then recall a numeric sequence of 2–9 digits forwards and backwards. The outcome measures are the scores for recalled digits forward and backward.

The *Regensburg Word Fluency Test (RWT)* is a German instrument for phonemic and categorical verbal fluency that also assesses cognitive flexibility.[31] Words of semantic or formal-lexical categories must be generated during a specified period. The outcome measures are the number of correct words with the letter "S" (1), the number of correct words switching G-R letters (2a, pretreatment, day 45) or H-T letters (2b, day 21, day 105), the number of correct given names (3), the number of garments-flowers (switching) (4a, pretreatment, day 45), or the number of correct sports-fruits (switching) (4b, day 21, day 105). We assessed the items generated after 1 and 2 minutes.

Neurocognitive Composite Score. For the construction of the composite *z* score, variables with smaller values representing better performance were first multiplied by −1 so that for all variables, larger values implied better test results. Second, all measures were transformed to standardized *z* scores, by subtracting the sample mean at pretreatment from the individual values and dividing the results by the pooled pretreatment SD. Third, for each of the 5 neuropsychological tests, the *z* scores were summed up resulting in 5 domain scores, and the results were *z*-transformed. Finally, a cognitive composite score was calculated as the mean of the 5 domain scores. This composite score was converted to a composite *z* score, which served as the primary neuropsychological outcome variable.

Sample Size and Statistical Analyses

The power calculation for this study was based on the primary study endpoint (change in PANSS Negative subscore after 3 wk of intervention) and is described elsewhere.[20] For the neuropsychological variables presented here, post hoc power analyses using actual sample sizes and observed variances σ^2 were calculated. A sufficient power of $1-\beta > .8$ was achieved simulating the following assumed mean differences

$$\theta = \text{active rTMS}\left(\mu_{\text{day 21}} - \mu_{\text{pretreatment}}\right) - \text{sham rTMS}\left(\mu_{\text{day 21}} - \mu_{\text{pretreatment}}\right)$$

composite *z* score: θ = 0.5, DST: θ = 1.5, TMT time: θ = 24 seconds, VLMT trials 1–5: θ = 7, VLMT difference trials 5 minus 7: θ = 2, VLMT total errors: θ = 3, WCST: θ = 7, RWT: θ = 5[32] ($\mu_{\text{day X}}$ denotes the mean for the concerning group [active rTMS or sham rTMS] at day X).

The analysis was implemented for the intention-to-treat (ITT) population, defined as all patients randomized with pretreatment data for at least one neuropsychological assessment. As a consequence of the study design (neuropsychological assessment 14 d before intervention start), the sample described herein differs from the ITT population for the primary outcome measure of the PANSS Negative subscore.[20] Dependent variables were the neuropsychological test results (DST, TMT, VLMT, WCST, RWT), and the independent factor was group (active/sham). Demographical and clinical variables were compared between the groups with likelihood ratio tests for categorical variables and with ANOVA or nonparametric Mann-Whitney *U* tests for continuous variables and were related to neuropsychological test results.

For continuous variables, Kolmogorov-Smirnov tests of the normal distribution were performed. If there were significant deviations from the normal distribution, logarithmic transformation was used. If after this transformation an outcome variable was still not normally distributed, nonparametric Wilcoxon tests were applied to explore time effects and Mann-Whitney tests were used to analyze group differences. For analysis of interactions between time and group, an outcome variable was dichotomized by its median, and for this transformed variable, Breslow-Day tests for homogeneity of the ORs were applied.

As a primary analysis, if the normality could be assumed, neuropsychological test results were analyzed with the general linear mixed model for longitudinal

data, nonrestrictively assuming an unstructured covariance matrix.[33] The repeated factor was time of visit (pretreatment/day 21), fixed factors were generally group, study center, and gender, and the covariate was duration of education. Age and chlorpromazine equivalent dosage were entered into the model as additional covariates if they showed a significant influence in the initial analyses. For secondary analyses, the same mixed-model design was applied, however, taking all data from pretreatment through the extension phase into account. Effect sizes for the interaction between group and time of measurement were calculated by subtracting the mean score at day 21 from the mean score at pretreatment for each group, subsequently determining the difference between the 2 groups (rTMS active/rTMS sham) and then dividing the results by the pooled SDs.[34] Possible correlations between changes in neuropsychological test results and changes in symptomatology (PANSS Positive and Negative score) as well as severity of the illness (Clinical Global Impression [CGI]) were assessed by Spearman correlations. Since only the composite *z* score was the primary neuropsychological outcome variable and since an adjustment of the type I error probability would decrease the test power extremely, the results were not corrected for multiple testing, as otherwise the probability of detecting existing mean differences would have been too low.

Results

Study Subjects

In total, 197 patients were screened and 175 patients were randomly assigned to one of the 2 intervention arms.[20] From this sample, 156 patients (77 active and 79 sham rTMS) received at least one neuropsychological assessment prior to the rTMS intervention. One hundred and seven of these patients (51 active and 56 sham rTMS) remained in the trial until the first postintervention visit (day 21). Sociodemographic variables are presented in table 1. The CONSORT chart, with a detailed drop-out analysis, is reported elsewhere.[20] Differences in sample

Table 1. Demographical and Clinical Data Before Treatment

Variable	Active rTMS (N = 77)		Sham rTMS (N = 79)		Active vs Sham		
					LR χ^2	*df*	*P*
Gender (male:female)	66:11		57:22		4.4	1	.037[a]
Employment (employed:not employed)	14:63		9:70		1.4	1	.23[a]
Center (Duesseldorf:Göttingen:Regensburg)	23:23:31		24:23: 32		0.0	2	.99[a]
Hand preference (right:not right)	64:10		65:10		0.0	1	.97[a]
Antidepressant use (yes:no)	26:49		29:50		0.1	1	.79[a]
	N	Mean ± SD	*N*	Mean ± SD	*F*	*df*	*P*
Age (y)	77	36.4 ± 10.6	79	35.5 ± 9.0	0.3	1, 154	.56[b]
Education (y)	73	11.5 ± 1.9	78	11.2 ± 2.0	0.6	1, 149	.44[b]
Left resting motor threshold	64	46.7 ± 7.9	67	46.2 ± 10.9	0.1	1, 129	.77[b]
Severity of illness and treatment							
PANSS Negative symptoms[c]	68	25.6 ± 4.7	74	25.2 ± 3.8	0.3	1, 140	.61[b]
PANSS Positive symptoms	67	14.2 ± 4.4	71	13.0 ± 3.7	2.8	1, 136	.094[b]
PANSS Total	67	80.0 ± 15.7	71	75.7 ± 13.7	3.0	1, 136	.088[b]
Clinical Global Impression score for severity[d]	64	4.6 ± 0.9	68	4.7 ± 0.9	$Z = -0.3$, $df = 1$, $P = .73$[e]		
Global Assessment of Functioning[f]	63	52.0 ± 11.6	68	53.4 ± 10.9	0.5	1, 129	.48[b]
Antipsychotic dose (chlorpromazine equivalents; mg/d)	65	586 ± 440	73	588 ± 481	0.0	1, 135	.78[g]
Depression related							
Calgary Depression Scale for Schizophrenia[h]	65	5.1 ± 3.6	71	5.2 ± 3.9	0.0	1, 134	.90[b]
Montgomery Asberg Depression Rating Scale[i]	68	14.8 ± 6.0	73	13.7 ± 6.2	1.0	1, 139	.30[b]

Note: Demographical and clinical data before treatment. *F*, *F* statistic; LR χ^2, likelihood ratio chi-square statistic; *P*, type I error probability; Z, Z statistic. PANSS, Positive and Negative Syndrome Scale; rTMS, transcranial magnetic stimulation.
[a]Comparison by likelihood ratio test.
[b]Comparison by ANOVA.
[c]Scores on the Positive and Negative symptom subscales of the PANSS range from 7 to 49, with higher scores indicating more severe illness.
[d]The Clinical Global Impression score for severity ranges from 1 (not mentally ill) to 7 (extremely ill).
[e]Comparison by Mann-Whitney *U* test.
[f]The Global Assessment of Functioning score ranges from 1 to 100, with higher scores indicating better functioning.
[g]Comparison on logarithmic transformed variable by ANOVA—however, descriptive statistics (means, SDs) are presented for the untransformed variable.
[h]The Calgary Depression Scale for Schizophrenia ranges from 0 to 27, with higher scores indicating more severe depression.
[i]The Montgomery Asberg Depression Rating Scale ranges from 0 to 60, with higher scores indicating more severe depression.

sizes between publications (see primary outcome elsewhere[20]) relate to the timing of the preintervention neurocognitive assessment.

Neurocognitive Performance Before and After Intervention (Pretreatment vs Day 21)

Mixed-model ANCOVAs revealed no significant "time × group" interactions for any of the applied neurocognitive tests. Regarding the main factor "time," we found a significant improvement in the DST performance (forwards) (active rTMS: +4.4%, sham rTMS: +7.5%; $F_{1, 114.2} = 5.5$, $P = 0.021$) and in the performance speed of TMT-A (active rTMS: −14.9%, sham: −2.6 %; $F_{1, 106.2} = 5.7$, $P = 0.019$). For all other analyses, no significant improvement over time or "time × group" interaction was observed. However, for most analyses, the "time × group" interactions indicate greater numerical improvements in the active group (table 2). For WCST (trials administered and total correct), Wilcoxon tests did not reveal significant effects. Breslow-Day tests did not reveal inhomogeneities in the ORs for the WCST performance.

Neurocognitive Performance During the Study Extension Phase (Pretreatment Until Day 105)

Mixed-model ANCOVA (factor time: pretreatment until days 21/45/105) did not show any significant "time × group" interactions. Several significant effects of the main factor "time" were observed, primarily explained by an improvement in both groups at day 105. Significant effects (main factor "time": pretreatment until day 105) were observed for the performance in DST (forward) (active rTMS: +6.7 %, sham: +9.9%; $F_{3, 82.4} = 5.0$, $P = 0.003$), in TMT-A (time) (active rTMS: +18.5%, sham: −10.7%; $F_{3, 83.0} = 6.4$, $P = 0.001$), in TMT-B (time) (active rTMS: −24.4%, sham: −8.8%; $F_{3, 76.9} = 4.8$, $P = 0.004$), and in WCST total errors (active rTMS: −44.2%, sham: −37.9%; $F_{3, 52.2} = 6.4$, $P = 0.001$). There was deterioration over time for VLMT trial 1–5 (active rTMS: −6.0%, sham: −11.1%; $F_{3, 75.7} = 4.5$, $P = 0.006$). For WCST performance (trials administered, total correct), Friedman tests did not reveal any significant time effects. Breslow-Day tests did not reveal inhomogeneities of the ORs in the WCST performance (table 3).

Center Effects

All analyses were adjusted for the factor study center. Supplementary tables 1 and 2 show all data for all 3 centers separately.

Neurocognitive Composite Score

Compared to the single domain results, the sample size for the *z* composite score was limited as many patients had missing data in at least one of the neurocognitive tests (table 2). A mixed-model ANCOVA showed a significant effect of "time" (pretreatment vs day 21) ($F_{1, 49.9} = 6.4$, $P = 0.015$), but no significant "time × group" interaction ($F_{1, 44.6} = 0.5$, $P = 0.47$). A similar pattern was observed including all timepoints ("time": $F_{3, 48.0} = 3.9$, $P = 0.014$; "time × group": $F_{3, 33.3} = 1.0$, $P = 0.39$). As the sample size for the *z* composite score was limited, we further analyzed the domain-specific *z* scores, but these mixed-model ANCOVAs neither revealed significant "time × group" interactions from pretreatment to day 21 (all $F < 2.2$; all $P > 0.14$) nor from pretreatment to day 105 (all $F < 1.6$; all $P > 0.22$). For the analysis of day 21 compared to pretreatment, significant time effects were observed for the domain *z* scores TMT ($F_{1, 99.6} = 6.7$, $P = 0.011$) and WCST ($F_{1, 75.5} = 4.2$, $P = 0.045$), and for the analysis over all timepoints, significant improvement was found for domain *z* scores DST ($F_{3, 83.3} = 4.6$, $P = 0.005$), TMT ($F_{3, 75.6} = 8.2$, $P < 0.001$), and WCST ($F_{3, 55.3} = 5.2$, $P = 0.003$) (tables 2 and 3).

Correlations Between Changes in Neuropsychological Tests and Psychopathology

We calculated correlations between the change in PANSS scores and neurocognitive performance at day 21 (immediately after rTMS) and at day 105 (at the end of the 12-wk extension phase). Results are displayed in table 4, but no clear differential pattern between active and sham rTMS emerged.

Discussion

We compared the efficacy of a 3-week intervention with active or sham 10-Hz rTMS applied to the left DLPFC on cognitive performance in schizophrenia patients with predominant negative symptoms. Both groups showed improvement in multiple cognitive domains over time without a significant superiority of active rTMS. The results of our large-scale multicenter trial contrast preliminary findings providing evidence for rTMS-induced cognitive improvements in schizophrenia. However, the direction of the changes and the effect sizes of the interactions may favor active rTMS. Despite our large sample size of 156 and a sufficient statistical power, the relatively high SDs across subjects and centers may contribute to the lack of interaction effects.

Different single-center rTMS studies characterized by heterogeneous methodologies showed a beneficial effect of active rTMS on single cognitive domains including working memory (*n*-back), facial affect recognition, semantic verbal fluency, and short-term verbal memory.[15–17,19] Working memory (0 to 2-back) performance was assessed in a subgroup of our sample (25 schizophrenia patients from one study center), but we did not observe any differences between active and sham rTMS in task performance or brain activation changes.[35] Barr

Table 2. Neuropsychological Test Results in Active and Sham rTMS Before Treatment and After 21 d

	Active rTMS				Sham rTMS										
	Pretreatment		Day 21		Pretreatment		Day 21		Factor Time			Time × Group			
	N	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	*N*	Mean ± SD	*F*	*df*	*P*	*F*	*df*	*P*	Effect Size[a]
Composite *z* score	41	–0.024 ± 1.1	27	0.298 ± 1.0	43	0.023 ± 0.9	26	0.057 ± 1.1	6.4	1, 49.9	.015	0.5	1. 44.6	.47	0.28
DST—domain *z* score	70	0.14 ± 1.1	48	0.36 ± 1.1	75	–0.13 ± 0.9	52	–0.04 ± 1.0	3.1	1, 105.1	.080	0.3	1, 102.0	.57	0.14
DST—forward (score)	70	8.0 ± 2.2	48	8.4 ± 2.1	75	7.3 ± 2.1	52	7.8 ± 2.0	5.5	1, 114.2	.021	0.2	1, 112.6	.64	–0.09
DST—backward (score)[b]	70	6.2 ± 2.2	48	6.6 ± 2.1	75	5.9 ± 1.6	52	5.8 ± 2.0	0.0	1, 102.8	.87	2.8	1, 100.8	.10	0.39
TMT—domain *z* score	70	0.00 ± 1.1	45	0.33 ± 0.9	76	0.00 ± 0.9	52	0.06 ± 1.1	6.7	1, 99.6	.011	0.8	1. 94.6	.38	0.27
TMT—A version: time (s)[b]	73	38.7 ± 21.0	48	33.0 ± 13.5	78	38.3 ± 15.8	52	37.3 ± 26.2	5.7	1, 106.2	.019	0.1	1, 104.1	.81	0.13
TMT—B version: time (s)[b]	71	97.5 ± 60.9	45	81.2 ± 46.8	76	87.8 ± 39.3	53	91.2 ± 46.0	3.8	1, 100.9	.054	2.0	1, 95.9	.16	0.30
VLMT—domain *z* score	63	–0.04 ± 1.0	46	–0.06 ± 1.0	70	0.03 ± 1.0	51	–0.23 ± 1.0	1.8	1, 108.4	.19	2.1	1, 107.9	.15	0.24
VLMT—sum trial 1–5 (score)	66	35.1 ± 17.8	46	33.8 ± 19.8	72	37.5 ± 17.4	52	36.1 ± 17.3	0.8	1, 101.1	.42	0.2	1, 99.0	.67	0.00
VLMT—difference trial 5 minus 7	63	2.6 ± 2.4	46	2.5 ± 2.6	70	2.7 ± 1.9	51	3.4 ± 2.4	0.8	1, 107.7	.36	2.3	1, 107.7	.13	0.35
WCST—domain *z* score	51	–0.18 ± 1.1	31	0.13 ± 0.9	51	0.18 ± 0.8	31	0.26 ± 0.9	4.2	1, 75.5	.045	1.7	1, 74.1	.20	0.24
WCST—trials administered (score)[c]	56	42.8 ± 7.1	34	42.1 ± 6.5	53	43.2 ± 5.3	34	41.9 ± 7.8	$Z = -0.8$, $df = 1$, $P = .43$			$\chi^2 = 3.0$, $df = 5$, $P = .69$			–0.11
WCST—total correct score[c]	58	33.3 ± 7.6	37	34.5 ± 6.8	58	34.5 ± 7.8	37	35.5 ± 6.5	$Z = -0.6$, $df = 1$, $P = .56$			$\chi^2 = 2.1$, $df = 5$, $P = .83$			0.02
WCST—total errors[b]	66	9.6 ± 7.6	38	7.5 ± 5.1	61	8.3 ± 6.5	37	8.6 ± 7.4	2.1	1, 83.6	.15	0.7	1, 81.7	.42	0.15
RWT—domain *z* score[d]	66	0.01 ± 1.1	45	–0.03 ± 1.1	65	–0.01 ± 0.9	50	0.01 ± 0.9	0.1	1, 98.9	.72	0.7	1, 94.4	.73	–0.06
RWT—S-words: correct words 1 min	66	12.4 ± 4.7	46	12.5 ± 4.1	67	12.1 ± 4.6	50	12.3 ± 3.5	0.0	1, 108.4	.91	0.1	1, 106.1	.79	–0.01
RWT—S-words: correct words 2 min	66	6.8 ± 3.6	46	5.9 ± 4.0	66	6.3 ± 3.1	50	6.3 ± 3.3	1.2	1, 96.6	.28	2.6	1, 95.3	.11	–0.28
RWT—G/R-words: correct words 1 min[d]	66	10.5 ± 4.0	28	10.4 ± 3.6	67	10.8 ± 3.5	36	10.8 ± 3.9	0.0	1, 74.7	.86	0.1	1, 70.3	.81	0.00
RWT—G/R-words: correct words 2 min[d]	66	6.1 ± 3.1	28	5.5 ± 3.3	64	6.7 ± 3.0	36	5.8 ± 4.4	2.0	1, 69.1	.16	0.2	1, 66.4	.65	0.09
RWT—first names: correct words 1 min	67	17.5 ± 5.5	45	17.3 ± 5.7	67	17.8 ± 5.1	51	18.4 ± 4.8	0.2	1, 104.2	.67	1.5	1, 101.1	.23	–0.14
RWT—first names: correct words 2 min	67	9.7 ± 4.5	45	10.4 ± 5.1	66	10.2 ± 4.4	51	9.8 ± 4.0	0.0	1, 103.8	.90	0.8	1, 101.8	.36	0.24
RWT—garments/flowers: correct 1 min[d]	64	10.9 ± 3.2	29	11.3 ± 4.2	67	11.4 ± 2.7	36	10.8 ± 2.9	0.0	1, 68.7	.98	0.1	1, 66.7	.81	0.34
RWT—garments/flowers: correct 2 min[d]	64	5.2 ± 3.1	29	4.2 ± 2.9	65	5.3 ± 2.4	35	4.5 ± 2.1	9.4	1, 78.8	.003	0.2	1, 77.0	.67	–0.05

Note: Neuropsychological test results in active and sham rTMS before treatment and after 21 d. *df*, degrees of freedom; *F*, *F* statistic; *N*, group size; *P*, type I error probability; χ^2, χ^2 statistic; *Z*, *Z* statistic. DST, Digit Span Test; rTMS, repetitive transcranial magnetic stimulation; RWT, Regensburg Word Fluency Test; TMT, Trail Making Test; VLMT, Verbal Learning and Memory Test; WCST, Wisconsin Card Sorting Test. The domain *z* scores for the DST, TMT, VLMT, WCST, and RWT and the composite *z* score were computed from the raw values as described in the "Statistical Analysis" section. DST: The patient has to repeat digit sequences of increasing length. TMT: The patient has to connect numbers from 1 to 25 in ascending order (part A) and 25 numbers and letters in alternating order (part B). For each part, the required time in seconds is measured. VLMT: A learning list of 15 words is verbally presented, followed by direct recall of the patient. After the fifth trial, an interference list is read and also followed by a free recall. Directly after this (trial 6) and after 20 min (trial 7), the patient again has to recall the words of the original learning list. WCST: Initially, 4 cards are presented to the patient. The patient is told to sort the cards, but not how to sort. However, he or she gets a response whether the sorting was right or wrong. After the patient gives, a certain number of right answers the sorting category changes. The number of used cards, the number of correct trials, and the number of errors is recorded. RWT: The patient has to create words beginning with a letter or belonging to a category within 2 min. The correct words that are generated in the first minute and in the second minute is recorded. The following tasks are offered to the patient: (1) words beginning with S; (2a) words beginning with G alternating with words beginning with R (pretreatment, day 45); (2b) words beginning with H alternating with words beginning with T (day 21, day 105); (3) first names; (4a) garments alternating with flowers (pretreatment, day 45); (4b) sports alternating with fruits (day 21, day 105).

[a]Effect sizes for the interaction between group and time of measurement were calculated by subtracting the mean score at day 21 from the mean score before treatment for each group, subsequently determining the difference between the 2 groups (rTMS active, rTMS sham) and then dividing the results by the pooled SDs.

[b]Normality assumption was rejected by Kolmogorov-Smirnov test. Therefore, the analysis was performed on the logarithmic transformed variable that was tested to be normally distributed. However, descriptive statistics (means, SDs) are presented for the original variables.

[c]Normality assumption was rejected by Kolmogorov-Smirnov test. After variable transformations, normality assumption was still violated. Therefore, nonparametric Wilcoxon test was used for analysis of time effects between pretreatment and day 21. For analysis of time × group interaction, the variables were dichotomized (high and low, subdivided by the median) and then Breslow-Day tests were applied to analyze the homogeneity of the ORs across the measurement times between the 2 groups.

[d]As for the Regensburg Word Fluency Test, there was no valid data at day 21 for the alternating tasks (2a) G/R-words and (4a) garments/flowers, the analysis for the corresponding variables compares the pretreatment with day 45 data. As well, effect sizes for time × group interaction for these variables refers to day 45 compared to pretreatment data. For this reason, RWT domain *z* score was constructed only from RWT (1) S-words and RWT (3) prenames.

Table 3. Neuropsychological Test Results in Active and Sham rTMS Before Treatment, After 21 d, and at Follow-up (Day 45, Day 105)

	Active rTMS				Sham rTMS										
	Pre ($N = 73$)	Day 21 ($N = 48$)	Day 45 ($N = 30$)	Day 105 ($N = 30$)	Pre ($N = 78$)	Day 21 ($N = 53$)	Day 45 ($N = 39$)	Day 105 ($N = 28$)	Factor Time			Time × Group			
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*F*	*df*	*P*	*F*	*df*	*P*	Effect Size[a]
Composite *z* score	−0.02 ± 1.1	0.30 ± 1.0	0.02 ± 1.1	0.27 ± 1.2	0.02 ± 0.9	0.06 ± 1.1	0.07 ± 1.1	0.29 ± 1.0	3.9	3, 48.0	.014	1.0	3, 33.3	.39	0.02
DST—domain *z* score	0.14 ± 1.1	0.36 ± 1.0	0.33 ± 1.2	0.55 ± 1.1	−0.13 ± 0.9	−0.04 ± 1.0	0.00 ± 1.1	0.10 ± 1.0	4.6	3, 83.3	.005	1.5	3, 76.2	.23	0.19
DST—forward (score)	8.0 ± 2.2	8.4 ± 2.1	8.1 ± 2.4	8.5 ± 2.1	7.3 ± 2.1	7.8 ± 2.0	7.7 ± 1.9	8.0 ± 1.9	5.0	3, 82.4	.003	0.4	3, 74.4	.75	−0.09
DST—backward (score)[b]	6.2 ± 2.2	6.6 ± 2.1	6.7 ± 2.4	7.1 ± 2.4	5.9 ± 1.6	5.8 ± 2.0	6.0 ± 2.2	6.0 ± 2.0	0.8	3, 77.3	.50	2.7	3, 70.6	.055	0.43
TMT—domain *z* score	0.0 ± 1.1	0.33 ± 0.9	0.33 ± 1.1	0.55 ± 1.0	0.00 ± 0.9	0.06 ± 1.1	0.11 ± 0.9	0.22 ± 0.9	8.2	3, 75.6	<.001	0.8	3, 64.8	.52	0.33
TMT—A version: time (s)[b]	38.7 ± 21	33.0 ± 13	32.1 ± 15	31.5 ± 16	38.3 ± 16	37.3 ± 26	34.6 ± 13	34.2 ± 12	6.4	3, 83.0	.001	0.8	3, 74.4	.49	0.24
TMT—B version: time (s)[b]	97.5 ± 61	81.2 ± 47	86.4 ± 67	73.7 ± 44	87.8 ± 39	91.2 ± 46	92.6 ± 48	80.1 ± 39	4.8	3, 76.9	.004	0.6	3, 67.9	.65	0.27
VLMT—domain *z* score	−0.04 ± 1.0	−0.06 ± 1.0	−0.20 ± 1.3	−0.13 ± 1.2	0.03 ± 1.0	−0.23 ± 1.0	−0.21 ± 1.1	−0.08 ± 1.0	1.2	3, 71.6	.33	0.8	3, 70.3	.48	0.02
VLMT—sum trial 1–5 (score)	35.1 ± 18	33.8 ± 20	32.3 ± 20	33.0 ± 21	37.5 ± 17	36.1 ± 17	33.3 ± 19	33.3 ± 16	4.5	3, 75.7	.006	1.7	3, 71.4	.17	0.12
VLMT—difference trial 5 minus 7	2.6 ± 2.4	2.5 ± 2.6	2.8 ± 2.4	2.7 ± 2.5	2.7 ± 1.9	3.4 ± 2.4	2.9 ± 2.6	2.6 ± 2.1	0.4	3, 72.6	.77	0.9	3, 71.8	.45	−0.06
WCST—domain *z* score	−0.18 ± 1.1	0.13 ± 0.9	0.44 ± 0.9	0.46 ± 1.3	0.18 ± 0.8	0.26 ± 0.9	0.38 ± 0.8	0.70 ± 0.8	5.2	3. 55.3	.003	0.5	3, 50.1	.69	0.12
WCST—trials administered (score)[c]	42.8 ± 7.1	42.1 ± 6.5	41.6 ± 6.2	40.3 ± 4.5	43.2 ± 5.3	41.9 ± 7.8	42.3 ± 5.1	41.1 ± 3.7	$\chi^2 = 6.6$, $df = 3$, $P = .087$			$\chi^2 = 7.7$, $df = 11$, $P = .74$			0.04
WCST—total correct score[c]	33.3 ± 7.6	34.5 ± 6.8	35.1 ± 7.7	32.1 ± 9.2	34.5 ± 7.8	35.5 ± 6.5	34.9 ± 6.7	35.1 ± 5.9	$\chi^2 = 1.2$, $df = 3$, $P = .75$			$\chi^2 = 6.5$, $df = 11$, $P = .84$			−0.26
WCST—total errors[b]	9.6 ± 7.6	7.5 ± 5.1	5.7 ± 5.3	5.3 ± 6.4	8.3 ± 6.5	8.6 ± 7.4	6.3 ± 4.1	5.2 ± 4.0	6.4	3, 52.2	.001	0.7	3, 50.8	.55	0.29
RWT—domain *z* score[d]	0.01 ± 1.1	−0.03 ± 1.1	−0.04 ± 1.2	0.15 ± 1.2	−0.01 ± 0.9	0.01 ± 0.9	−0.18 ± 1.1	0.15 ± 1.1	0.2	3, 79.8	.89	0.7	3, 71.3	.58	−0.02
RWT—S-words: correct words 1 min	12.4 ± 4.7	12.5 ± 4.1	13.4 ± 5.3	13.0 ± 5.1	12.1 ± 4.6	12.3 ± 3.5	12.2 ± 4.6	12.1 ± 3.7	0.8	3, 74.4	.51	0.2	3, 70.8	.87	0.13
RWT—S-words: correct words 2 min	6.8 ± 3.6	5.9 ± 4.0	5.8 ± 3.6	6.0 ± 4.0	6.3 ± 3.1	6.3 ± 3.3	6.6 ± 3.6	6.8 ± 3.0	0.4	3, 77.5	.77	1.9	3, 74.7	.14	−0.40
RWT—H/T-words: correct words 1 min[d]		11.4 ± 3.8		11.1 ± 4.2		11.8 ± 3.7		12.3 ± 4.2	0.1	1, 64.2	.72	0.7	1, 58.0	.40	−0.18
RWT—H/T-words: correct words 2 min[d]		5.8 ± 2.6		6.9 ± 3.7		6.0 ± 2.6		6.1 ± 3.7	1.2	1, 58.2	.29	1.4	1, 54.4	.22	0.32
RWT—first names: correct words 1 min	17.5 ± 5.5	17.3 ± 5.7	17.4 ± 5.3	18.8 ± 5.8	17.8 ± 5.1	18.4 ± 4.8	16.8 ± 5.4	19.2 ± 6.1	1.3	3, 74.9	.28	0.2	3, 70.3	.56	−0.03
RWT—first names: correct words 2 min	9.7 ± 4.5	10.4 ± 5.1	9.6 ± 5.0	11.2 ± 4.1	10.2 ± 4.4	9.8 ± 4.0	9.8 ± 5.3	10.6 ± 4.6	0.7	3, 75.9	.54	1.9	3, 72.0	.21	0.23
RWT—sports/fruits: correct 1 min[d]		12.3 ± 2.7		11.9 ± 3.1		12.1 ± 3.0		11.9 ± 3.1	0.8	1, 60.4	.38	0.1	1, 53.6	.74	−0.08
RWT—sports/fruits: correct 2 min[d]		5.9 ± 2.6		6.7 ± 2.1		6.0 ± 2.1		5.9 ± 2.1	0.6	1, 66.8	.43	1.8	1, 64.4	.19	0.38

Note: Neuropsychological test results in active and sham rTMS before treatment, after 21 d, and at follow-up (day 45, day 105). *df*, degrees of freedom; *F*, *F* statistic; *N*, group size; *P*, type I error probability; Pre, pretreatment; χ^2, χ^2 statistic. DST, Digit Span Test; rTMS, repetitive transcranial magnetic stimulation; RWT, Regensburg Word Fluency Test; TMT, Trail Making Test; VLMT, Verbal Learning and Memory Test; WCST, Wisconsin Card Sorting Test. The domain *z* scores for the DST, TMT, VLMT, WCST, and RWT and the composite *z* score were computed from the raw values as described in the "Statistical Analysis" section.

[a]Effect sizes for the interaction between group and time of measurement were calculated by subtracting the mean score at day 105 from the mean score before treatment for each group, subsequently determining the difference between the 2 groups (rTMS active, rTMS sham) and then dividing the results by the pooled SDs.

[b]Normality assumption was rejected by Kolmogorov-Smirnov test. Therefore, the analysis was performed on the logarithmic transformed variable that was tested to be normally distributed. However, descriptive statistics (means, SDs) are presented for the original variables.

[c]Normality assumption was rejected by Kolmogorov-Smirnov test. After variable transformations, normality assumption was still violated. Therefore, nonparametric Friedman test was used for analysis of time effects from pretreatment to day 105. For analysis of time × group interaction, the variables were dichotomized (high and low, subdivided by the median) and then Breslow-Day tests were applied to analyze the homogeneity of the ORs across the measurement times between the 2 groups.

[d]As for the Regensburg Word Fluency Test, there was no valid data before treatment and at day 45 for the alternating tasks (2b) H/T-words and (4b) sports/fruits, the analysis for the corresponding variables compares the day 21 with the day 105 data. As well, effect sizes for time × group interaction for these variables refer to day 105 compared to day 21 data. RWT domain *z* score was constructed only from RWT (1) S-words and RWT (3) prenames.

Table 4. Correlation Between Change in Neuropsychological Test Results and PANSS Change

	Pretreatment to Day 21				Pretreatment to Day 105			
	Change in PANSS Scores				Change in PANSS Scores			
	Active rTMS		Sham rTMS		Active rTMS		Sham rTMS	
Cognitive Change	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Composite *z* score	−0.03	−0.38	0.25	−0.10	−0.44	0.14	−0.17	−0.34
DST—domain *z* score	0.06	0.08	0.15	0.15	0.24	0.03	−0.17	0.08
DST—forward (score)	0.04	−0.02	0.19	0.11	−0.10	0.19	0.20	0.24
DST—backward (score)	0.08	0.01	0.10	0.10	−0.09	−0.06	0.10	0.00
TMT—domain *z* score	−0.03	−0.27	−0.18	−0.26	0.05	0.09	−0.14	−0.19
TMT—A version: time (s)	0.19	0.09	0.29*	0.20	0.19	0.13	0.15	0.54*
TMT—B version: time (s)	0.31*	−0.05	0.13	0.16	0.04	0.11	0.14	−0.02
VLMT—domain *z* score	0.07	0.15	0.00	−0.04	0.14	0.12	−0.06	0.00
VLMT—sum trial 1–5 (score)	0.20	0.06	0.08	0.00	0.25	0.11	0.14	0.29*
VLMT—difference trial 5 minus 7	−0.11	−0.09	0.08	−0.01	−0.16	−0.03	0.21	0.00
WCST—domain *z* score	0.17	−0.19	0.04	0.15	−0.57*	0.04	−0.33	−0.09
WCST—trials administered (score)	0.02	0.23	0.09	0.26	0.10	0.23	0.16	−0.03
WCST—total correct score	−0.09	0.35	0.31	0.01	0.23	0.24	0.16	0.40*
WCST—total errors	0.02	−0.02	−0.13	−0.12	−0.10	−0.08	−0.05	−0.14
RWT—domain *z* score[a]	−0.06	0.09	−0.13	−0.10	0.09	0.28	−0.12	−0.26
RWT—S-words: correct words 1 min	−0.01	0.08	0.14	−0.09	0.00	−0.07	0.09	0.21
RWT—S-words: correct words 2 min	0.11	0.10	−0.15	−0.11	0.05	−0.07	0.00	−0.15
RWT—G/R-words - H/T-words: correct words 1 min[a]	−0.03	−0.02	0.31	0.27	0.04	−0.37	0.23	0.30
RWT—G/R-words - H/T-words: correct words 2 min[a]	0.09	0.10	0.21	−0.14	0.21	0.00	−0.38*	0.06
RWT—first names: correct words 1 min	−0.07	−0.09	−0.13	−0.12	−0.01	−0.31*	−0.07	−0.22
RWT—first names: correct words 2 min	0.23	−0.18	−0.10	0.13	−0.16	−0.11	0.17	−0.02
RWT—garments/flowers - sports/fruits: correct 1 min[a]	−0.55*	−0.07	0.23	0.12	−0.14	0.27	0.02	0.05
RWT—garments/flowers - sports/fruits: correct 2 min[a]	−0.32	−0.02	0.20	0.05	−0.16	−0.53*	0.32	0.04

Note: Spearman correlation coefficients. DST, Digit Span Test; rTMS, repetitive transcranial magnetic stimulation; RWT, Regensburg Word Fluency Test; TMT, Trail Making Test; VLMT, Verbal Learning and Memory Test; WCST, Wisconsin Card Sorting Test. The domain *z* scores for the DST, TMT, VLMT, WCST, and RWT and the composite z score were computed from the raw values as described in the "Statistical Analysis" section. Between differences in neuropsychological scores and differences in psychopathological scores Spearman correlation coefficients were computed. For all variables, differences between day 21 and pretreatment and between day 105 and pretreatment were calculated, the exception is given below:
[a]RWT: (2a) Difference for words beginning with G alternating with words beginning with R was calculated between day 45 and pretreatment. (2b) Difference for words beginning with H alternating with words beginning with T was calculated between day 105 and day 21. RWT: (4a) Difference for garments alternating with flowers was calculated between day 45 and pretreatment. (4b) Difference for sports alternating with fruits was calculated between day 105 and day 21. RWT domain *z* score was constructed only from RWT (1) S-words and RWT (3) prenames.
*$P < 0.05$.

et al used 4 weeks of neuronavigated 20-Hz rTMS and displayed their effects only in the 3-back condition, with no significant main effects or interactions in the linear models, consistent with our previous observation of no effects in 1/2-back conditions. Other studies using classic neuropsychological tests (eg, processing speed, attention, verbal learning, or problem solving) also failed to demonstrate a general beneficial effect of rTMS on cognition in schizophrenia.[15,18,19] The limited sample size, the single-center designs, and the different outcome parameters complicate the interpretation of previously reported positive findings.

Several reasons why our study failed to show differences between active and sham rTMS can be considered. The duration of our intervention might account for the negative finding as cognitive performance was tested before and after rTMS within a timeframe of 5 weeks to 3 months (last follow-up at day 105). This observation period may have been too short to evaluate changes in cognitive performance. A network meta-analysis indicates that in antipsychotic trials, an intervention period of at least 6 months is needed to detect possible changes in cognitive assessments.[5] Furthermore, the effect of practice (eg, exposure, familiarity, procedural learning)[36] needs to be taken into consideration. Our participants received several testing sessions within 3 months and it is likely that many patients were tested previously in regular clinical care. The practice-related increase in cognitive performance in both groups would result in a reduction of the active sham-difference, making it difficult to disentangle an effect of active rTMS. The application of cognitive paradigms less sensitive to practice effects such

as randomized *n*-back task with high load (3-back) or a facial recognition task[16,17] may be more suited to detecting differences between groups. On the other hand, there is a clear, consensus-based recommendation concerning cognitive tests to be used in schizophrenia trials,[37] and the cognitive domains investigated here as well the tests used have a significant overlap with the MATRICS Consensus Cognitive Battery. The application of more comprehensive and broader cognitive battery may have resulted in different findings. Our assessments cover the main domains of impaired cognition in schizophrenia[12] and we had no rationale for the use of other tests. However, the neurocognitive outcome was a secondary outcome and other trials showing a beneficial effect of rTMS on cognition in schizophrenia used higher stimulation frequencies or longer stimulation periods.[16] Both factors may also contribute to the negative finding observed in our trial. The study has several limitations. As outlined elsewhere,[20] focus on less-affected, early episode patients, longer stimulation periods, application of more rTMS stimuli and a higher stimulation frequency may have led to different results. At present, there is still no consensus about the optimal stimulation parameters for the treatment of cognitive deficits in schizophrenia and further research is needed. From a methodological perspective, our sham condition (45° tilted coil) and the use of the EEG-10/20 system can be discussed as further limitations. For sham rTMS, different methods including sham coils not producing any magnetic field, 45°–90° tilted active coils, and active coils placed at noninvolved cortical regions are available.[38] The 45° tilted coil method was chosen for this study,[20] as it results in similar skin sensations with substantially reduced biological activity compared with active rTMS[26] and our analysis of blinding integrity showed that neither patients nor raters were able to distinguish between active and sham rTMS (see Wobrock et al[20]). We used the EEG-10/20 method to determine the position of the left DLPFC. Despite the fact that most studies in the field use the same approach, the application of neuronavigation[16] or improved F3 localization (eg, BeamF3 heuristic)[39] could have helped to reveal a beneficial effect of active rTMS. A coil placement using individual structural or functional images has the potential to reduce the variability within and across subjects,[20] but further research is needed to clarify the importance and the cost-effectiveness of such approaches in the context of therapeutic noninvasive brain stimulation. More specific limitations relate to the absence of a specific effect of rTMS on general psychopathology and the predominant negative symptoms in our sample. Both groups showed an improvement in PANSS, depression ratings, and global functioning, with no between-group differences.[20] Correlation analyses could not establish a relationship between symptomatic and cognitive outcome in our sample of severely affected patients suffering from predominant negative symptoms. Dependent on the cognitive test, inconsistent correlations between negative symptoms (assessed by PANSS) and cognitive measures were reported, possibly based on the limited assessment of verbal output in the PANSS.[3] Therefore, the use of PANSS might have concealed possible correlations of symptomatic and cognitive outcomes in our trial. Although negative symptoms and cognitive deficits show moderate correlations in meta-analyses,[40] and we investigated patients with prominent negative symptoms, the present findings cannot directly be generalized to the wider group of patients with schizophrenia. From a statistical perspective, the large SDs across subjects and study sites might explain the lack of significance in the linear mixed models. The direction of effect sizes (positive effect size favoring active rTMS; negative effect size favoring sham rTMS; table 2) of nonsignificant interactions suggests a tendency towards superiority of active rTMS in certain cognitive domains. Furthermore, one could only speculate whether the combination of rTMS with other methods to improve cognition in schizophrenia (eg, cognitive remediation) would be more effective than rTMS alone. Finally, it remains unclear whether a focus on social cognition rather than on neurocognition would have been a more promising strategy to show a beneficial effect of rTMS in our sample of schizophrenia patients suffering from predominant negative symptoms.

In conclusion, we present the first multicenter, large-scale evaluation of 3-week 10-Hz rTMS applied on cognitive symptoms in a sample of well-characterized schizophrenia patients with predominant negative symptoms. Although we were not able to reveal a significant difference between active and sham rTMS, analyses of effect sizes indicate that further investigations are warranted. More multicenter randomized clinical trials are needed in the field of noninvasive brain stimulation to confirm or to disprove findings from small proof-of-concept trials. Finally, our results are in line with several other negative reports on biological and nonbiological interventions illustrating the difficulty of treating cognitive symptoms in schizophrenia.[11]

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft Grant No. FA-210/1. M.R. received additional funding by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme (grant 01ZX1314G).

Acknowledgments

We wish to thank Ms. Louise Marshall for the support in manuscript editing. A.H. has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received a paid speakership from Desitin, Otsuka, and Lundbeck. He was member of a advisory board of Roche. B.G. had no conflict of interest. J.C. was a member of an advisory board of Roche, accepted travel or hospitality not related to a speaking engagement from Servier, support for symposia from Inomed, Localite, Magventure, Roche, Mag & More, NeuroConn, Syneika, FBI Medizintechnik, Spitzer Arzneimittel, and Diamedic. W.W. has received paid speakerships from Bristol-Myers Squibb, Essex Pharma, Janssen-Cilag, Lilly Deutschland, and Pfizer Neuroscience. He is a member of the Neuroscience Academy of Roche Pharma. G.W. had no conflict of interest. W.G. has received symposia support from Janssen-Cilag GmbH, Neuss, Lilly Deutschland GmbH, Bad Homburg, and Servier, Munich. He is a member of the Faculty of the Lundbeck International Neuroscience Foundation (LINF), Denmark. B.L. received honoraria and speakers' fees from ANM, AstraZeneca, Autifony, Lundbeck, Merz, Magventure, Novartis, Pfizer, and Servier; research funding from the Tinnitus Research Initiative, the German Research Foundation, the German Bundesministerium für Bildung und Forschung, the American Tinnitus Association, AstraZeneca, and Cerbomed; funding for equipment from Magventure and Deymed; and travel and accommodation payments from Lilly, Lundbeck, Servier, and Pfizer. M.L. had no conflict of interest. P.E. had no conflict of interest. E.F. had no conflict of interest. G.H. has received payments as speaker, consultant, author, or for research funding during the last 5 years from Actelion, Affectis, AstraZeneca, Bayerische Motorenwerke, Bundesministerium für Bildung und Forschung, Bundesministerium für Strahlenschutz, Bristol-Meyers Squibb, Cephalon, Daimler Benz, Deutsche Forschungsgesellschaft, Elsevier, EuMeCom, Essex, Georg Thieme, Gerson Lerman Group Council of Healthcare Advisors, GlaxoSmithKline, Janssen-Cilag, Lilly, Lundbeck, Meda, Merck, Merz, Novartis, Pfizer, Proctor & Gamble, Sanofi-Aventis, Schering-Plough, Sepracor, Servier, Springer, Urban & Fischer, and Volkswagen. C.O. had no conflict of interest. P.E.V. had no conflict of interest. M.R. had no conflict of interest. R.A. had no conflict of interest. W.G.H. is an unpaid member of the Advisory Board of In Silico Biosciences, and a paid consultant to Otsuka/Lundbeck, Roche, Novartis, Eli Lilly, MDH Consulting, and the Canadian Agency on Drugs and Technology in Health. B.M. had no conflict of interest. S.K. had no conflict of interest. T.S.-A. had no conflict of interest. P.F. was honorary speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, Bristol Myers Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years, but not presently, P.F. was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. T.W. has received paid speakerships from Alpine Biomed, AstraZeneca, Bristol Myers Squibb, Eli Lilly, I3G, Janssen Cilag, Novartis, Lundbeck, Roche, Sanofi-Aventis, Otsuka, and Pfizer, and has accepted travel or hospitality not related to a speaking engagement from AstraZeneca, Bristol-Myers-Squibb, Eli Lilly, Janssen Cilag, and Sanofi-Synthelabo; and has received restricted research grants from AstraZeneca, Cerbomed, I3G, and AOK (health insurance company).

References

1. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull*. 2000;26:119–136.
2. Ventura J, Wood RC, Hellemann GS. Symptom domains and neurocognitive functioning can help differentiate social cognitive processes in schizophrenia: a meta-analysis. *Schizophr Bull*. 2013;39:102–111.
3. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: what is the nature of their relationship? *Schizophr Bull*. 2006;32:250–258.
4. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 2004;72:29–39.
5. Désaméricq G, Schurhoff F, Meary A, et al. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. *Eur J Clin Pharmacol*. 2014;70:127–134.
6. Hasan A, Falkai P, Wobrock T, et al.; World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry*. 2012;13:318–378.
7. Keefe RS, Bilder RM, Davis SM, et al.; CATIE Investigators; Neurocognitive Working Group. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007;64:633–647.
8. Moritz S, Veckenstedt R, Andreou C, et al. Sustained and "sleeper" effects of group metacognitive training for schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2014;71:1103–1111.
9. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry*. 2011;168:472–485.
10. Malchow B, Keller K, Hasan A, et al. Effects of endurance training combined with cognitive remediation on everyday functioning, symptoms, and cognition in multiepisode schizophrenia patients. *Schizophr Bull*. 2015;41:847–858.
11. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectrum*. 2014;19 (suppl 1):38–52; quiz 35–37, 53.

12. Barch DM, Ceaser A. Cognition in schizophrenia: core psychological and neural mechanisms. *Trends Cogn Sci (Regul Ed)*. 2012;16:27–34.
13. Ziemann U, Paulus W, Nitsche MA, et al. Consensus: motor cortex plasticity protocols. *Brain Stimul*. 2008;1:164–182.
14. Lett TA, Voineskos AN, Kennedy JL, Levine B, Daskalakis ZJ. Treating working memory deficits in schizophrenia: a review of the neurobiology. *Biol Psychiatry*. 2014;75:361–370.
15. Oh SY, Kim YK. Adjunctive treatment of bimodal repetitive transcranial magnetic stimulation (rTMS) in pharmacologically non-responsive patients with schizophrenia: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35:1938–1943.
16. Barr MS, Farzan F, Rajji TK, et al. Can repetitive magnetic stimulation improve cognition in schizophrenia? Pilot data from a randomized controlled trial. *Biol Psychiatry*. 2013;73:510–517.
17. Wölwer W, Lowe A, Brinkmeyer J, et al. Repetitive transcranial magnetic stimulation (rTMS) improves facial affect recognition in schizophrenia. *Brain Stimul*. 2014;7:559–563.
18. Mittrach M, Thünker J, Winterer G, et al. The tolerability of rTMS treatment in schizophrenia with respect to cognitive function. *Pharmacopsychiatry*. 2010;43:110–117.
19. Dlabac-de Lange JJ, Bais L, van Es FD, et al. Efficacy of bilateral repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: results of a multicenter double-blind randomized controlled trial. *Psychol Med*. 2015;45:1263–1275.
20. Wobrock T, Guse B, Cordes J, et al. Left prefrontal high-frequency repetitive transcranial magnetic stimulation for the treatment of schizophrenia with predominant negative symptoms: a sham-controlled, randomized multicenter trial. *Biol Psychiatry*. 2015;77:979–988.
21. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 (suppl 20):22–33; quiz 34–57.
22. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
23. Cordes J, Falkai P, Guse B, et al. Repetitive transcranial magnetic stimulation for the treatment of negative symptoms in residual schizophrenia: rationale and design of a sham-controlled, randomized multicenter study. *Eur Arch Psychiatry Clin Neurosci*. 2009;259 (suppl 2):S189–S197.
24. Herwig U, Padberg F, Unger J, Spitzer M, Schönfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biol Psychiatry*. 2001;50:58–61.
25. Herwig U, Satrapi P, Schönfeldt-Lecuona C. Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr*. 2003;16:95–99.
26. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry*. 2001;49:460–463.
27. Müller H, Hasse-Sander I, Horn R, Helmstaedter C, Elger CE. Rey Auditory-Verbal Learning Test: structure of a modified German version. *J Clin Psychol*. 1997;53:663–671.
28. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19:203–214.
29. Grant DA, Berg EA. *Wisconsin Card Sorting Test*. Göttingen, Germany: Hogrefe Testzentrale; 1993.
30. Tewes U. *Hamburg-Wechsler-Intelligenztest für Erwachsene. Handbuch und Testanweisung. Revision*. Bern, Switzerland: Verlag Hans Huber; 1991.
31. Aschenbrenner S, Tucha O, Lange KW. *Regensburger Wortflüssigkeits-Test (RWT): Handanweisung*. Göttingen, Germany: Hogrefe, Verlag für Psychologie; 2000.
32. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39:175–191.
33. Krueger C, Tian L. A comparison of the general linear mixed model and repeated measures ANOVA using a dataset with multiple missing data points. *Biol Res Nurs*. 2004;6:151–157.
34. Honer WG, Thornton AE, Chen EY, et al.; Clozapine and Risperidone Enhancement (CARE) Study Group. Clozapine alone versus clozapine and risperidone with refractory schizophrenia. *N Engl J Med*. 2006;354:472–482.
35. Guse B, Falkai P, Gruber O, et al. The effect of long-term high frequency repetitive transcranial magnetic stimulation on working memory in schizophrenia and healthy controls–a randomized placebo-controlled, double-blind fMRI study. *Behav Brain Res*. 2013;237:300–307.
36. Goldberg TE, Goldman RS, Burdick KE, et al. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry*. 2007;64:1115–1122.
37. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165:203–213.
38. Dollfus S, Lecardeur L, Morello R, Etard O. Placebo response in repetitive transcranial magnetic stimulation trials of treatment of auditory hallucinations in schizophrenia: a meta-analysis [published online ahead of print June 18, 2015]. *Schizophr Bull*. doi: 10.1093/schbul/sbv076
39. Mir-Moghtadaei A, Caballero R, Fried P, et al. Concordance between BeamF3 and MRI-neuronavigated target sites for repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex. *Brain Stimul*. 2015;8:965–973.
40. Ventura J, Hellemann GS, Thames AD, Koellner V, Nuechterlein KH. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis. *Schizophr Res*. 2009;113:189–199.