The Tolerability of rTMS Treatment in Schizophrenia with Respect to Cognitive Function

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Abstract

Introduction: The purpose of this study was to assess tolerability and safety of high-frequency rTMS with regard to cognitive performance when conducted as "add-on" treatment in chronic schizophrenia in-patients (n = 32).

Methods: Patients, who were on stable antipsychotic treatment, were randomly assigned to verum or sham condition (double-blind). In the verum group, ten sessions of 10 Hz rTMS with a total of 10 000 stimuli were applied over the left dorsolateral prefrontal cortex (PFC) at 110 % of motor threshold over a period of two weeks. The sham group received corresponding sham stimulation. RTMS effects on cognitive performance were assessed with a neuropsychological test battery consisting of the following tests: trail making test A and B (TMT), Wisconsin card sorting test (WCST), D2 attention task and the "short test of general intelligence" (KAI).

Results: No statistically significant deterioration of cognitive performance was observed as a result of rTMS treatment. Moreover it was shown that in the verum group patients with a less favourable performance on the WCST at baseline tend to improve after rTMS treatment with regard to psychopathology as opposed to patients in the control group.

Discussion: The stability of cognitive function suggests good tolerability of rTMS treatment in schizophrenia. The absence of evidence for cognitive deterioration could be due to low and short stimulation parameters.

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Introduction

Over the past few years, rTMS has increasingly been discussed as a potential "add-on" treatment in schizophrenia illness [5]. Therefore, it is important to assess the safety and tolerability of rTMS treatment. An important issue in this respect is the question whether rTMS has unfavourable effects on cognitive performance. This is because patients with schizophrenia have already impairments in several domains of cognition, including working memory/executive function, verbal memory, language, oculomotor scanning/psychomotor speed, and general intelligence [8]. These deficits present an enormous personal and socioeconomic burden to the patients including reduction in life quality [40].

RTMS treatment has been demonstrated to be a safe and well tolerated treatment in various disease conditions including negative symptoms and auditory hallucinations in schizophrenia, tinnitus and depression within a range of parameters as defined according to a consensus statement [43]. In several safety studies, no significant mean changes in auditory threshold, and no significant EEG abnormality after 2 to 4 weeks of rTMS have been observed [31]. MRI scans of depressed patients before and after a TMS treatment trial failed to provide any evidence of TMS-induced changes including differences in prefrontal volume [29]. Rare, single cases of rTMS-associated seizures have, however, been reported since safety guidelines [43] were published limiting stimulation parameters. There is insufficient evidence to suggest a relationship between the frequency of any reported adverse effects and the stimulation intensity, session duration, or number of pulses received within a session [23]. An overview of published rTMS trials which also included systematically collected safety data concluded that as long as exclusion criteria are fulfilled and safety recommendations are applied, rTMS targeted at the prefrontal cortex is a relatively safe and well-tolerated technique with generally minor adverse effects such as localized scalp pain, headache and neck pain [33].

Cognitive symptoms were more recently recognized as part of the core pathophysiology of schizophrenia. Despite this, to date, no specific studies have uniquely focused on the treatment of cognitive symptoms with rTMS methods. However, numerous rTMS studies targeting the prefrontal cortex have evaluated changes in cognitive functioning that may be related to dysfunction in this brain region [9].

In depressive patients previous studies provided evidence that cognitive function remained stable after courses of high frequency rTMS [31]. Several studies pointed out that there would even be a possible improvement in verbal memory [31]. Evidence of modest but statistically significant improvement in measures of working memory-executive function, objective memory and fine motor speed domains over the rTMS treatment period is growing patients [31].

In schizophrenia patients suffering from auditory hallucinations studies of 1 Hz rTMS applied to the temporoparietal cortex have not found any adverse effects on memory and cognitive parameters assessed [9,25,16]. Hoffman et al. [17] even detected a marginally significant group effect for the Hopkins verbal learning test in the follow-up phase ($F=4.14$, $p=0.05$), the estimated slope was positive for the active rTMS phase, suggesting improvement in function.

The studies by Novak [30], Sachdev [38], Holi [18] Rollnik [35] and Schneider [38] investigating high-frequency rTMS (20 Hz, 15 Hz, 10 Hz) applied to the dorsolateral prefrontal cortex in schizophrenia found no significant changes in any neuropsychological measures. Cohen et al. [4] found a general improvement in all neuropsychological scores after 20 Hz rTMS, but only the effect on delayed visual memory as measured by a subtest of the Wechsler memory scale achieved significance ($p<0.05$).

Mogg [27] found that 10 Hz rTMS had a beneficial effect on cognitive function, notably delayed recall and executive function. For delayed recall in the Hopkins verbal learning test there was a significant group difference at the two-week follow-up assessment ($p=0.02$) with the real group having a score of 2.6 points better than the sham group. For the Stroop interference task there was a trend towards a group effect ($p=0.06$) with those in the real rTMS group performing slightly better than those in the sham at end-of treatment and follow-up time points.

The two domains of cognition, verbal learning and delayed visual memory are among those identified by the NIMH-MATRICS project as important for schizophrenia [13].

According to those studies which administered comprehensive batteries of neuropsychological tests to assess cognitive functions before and after prefrontal rTMS treatment no major deficits were evidenced. On the contrary, significant improvements were demonstrated in several cognitive domains [33]. Therefore there is some suggestion that prefrontal stimulation may be able to modulate cognitive symptoms. The DLPFC is a region of the "task-related network", and at least theoretically, more prone to cognitive enhancement than to core negative symptom improvement. However, to date these data are very limited and require exploration with larger and longer-term treatment studies [10].

Based on a randomized sham-controlled study, we have investigated if rTMS treatment – applied over the left dorsolateral prefrontal cortex – in partially remitted schizophrenic patients as an "add-on" therapy induces changes in cognitive performance as measured by a battery of cognitive function tests. The primary results of the study regarding the effect of rTMS on psychopathological measures are presented in a previous publication [6]. Only a few studies investigating high frequency rTMS in schizophrenia have applied a comprehensive battery of cognitive tests to probe for unintended, potentially adverse effects or to uncover potentially useful effects of rTMS [4,37,30,27]. Those high-frequency rTMS studies which have used several cognitive function tests only had small sample sizes of 4 to 17 schizophrenic patients. In these studies the authors do not state if p-values had been corrected for multiple comparisons.

In our study with a considerably larger sample ($n=32$) we focused on the assessment of "executive functions", which often correlate with abnormal activation in the left dorsolateral prefrontal cortex (DLPFC) in functional neuroimaging studies of schizophrenia and depression [11,36]. Diminished activity within the prefrontal cortex has been associated with many of the cognitive deficits that are observed in schizophrenia [7].

Imaging studies using positron emission tomography (PET) showed reduced metabolism or reduced regional cerebral blood flow at rest in the frontal lobe in patients compared to controls [45]. Similarly, early functional magnetic resonance imaging studies (fMRI) often found reduced task-related activation in the prefrontal cortex in patients with schizophrenia [3]. However, recent fMRI studies point towards a more complex dysfunction of the prefrontal cortex in schizophrenia patients consistent with the concepts of less efficient cognitive processing [2], reduced signal-to-noise-ratio [44], and altered functional connectivity between the prefrontal cortex and other brain regions [26]. See also Tan et al. [41] for a recent review.

In schizophrenia research reference is often made to the Wisconsin card sorting test (WCST) and the trail-making-test (TMT) when assessing cognitive functioning and neuropsychological risk indicators, as these tests impose demands on cognitive processes based in the frontal lobes [20]. However, no high-frequency rTMS studies in schizophrenia and only few studies in schizophrenic patients in general have used the d2-attention task. We selected the d2-attention task in addition to the WCST and the TMT because it makes particular demands on concentration and discrimination between similar stimuli under high time pressure in routine tasks [20].

Patients and Methods

Subjects

$n=35$ right-handed schizophrenic inpatients (DSM-IV) according to the International Diagnosis Checklist [15], with at least three episodes documented in their medical history were included in the study. Exclusion criteria encompassed alcohol or substance dependence disorder in the last two years, neurological disorders, implantation of a cardiac pacemaker and a medical history of brain trauma, seizures or neurosurgery. All patients were on stable antipsychotic medication for at least two weeks prior to entering the study and throughout the whole study period. In addition a co-medication of lorazepam (1 mg daily) was allowed within the study period. The study was approved by the Ethics Committee of the Heinrich-Heine University Duesseldorf (Germany). After complete description of the study, written informed consent was obtained from each subject. As the method is medically unobjectionable and potentially beneficial with regard to psychopathology and cognition there are no substantial ethical concerns arising from this study.

All patients were randomly assigned to the rTMS verum and sham groups based on block-wise randomization (verum to sham relation 4:3). Three patients dropped out before beginning

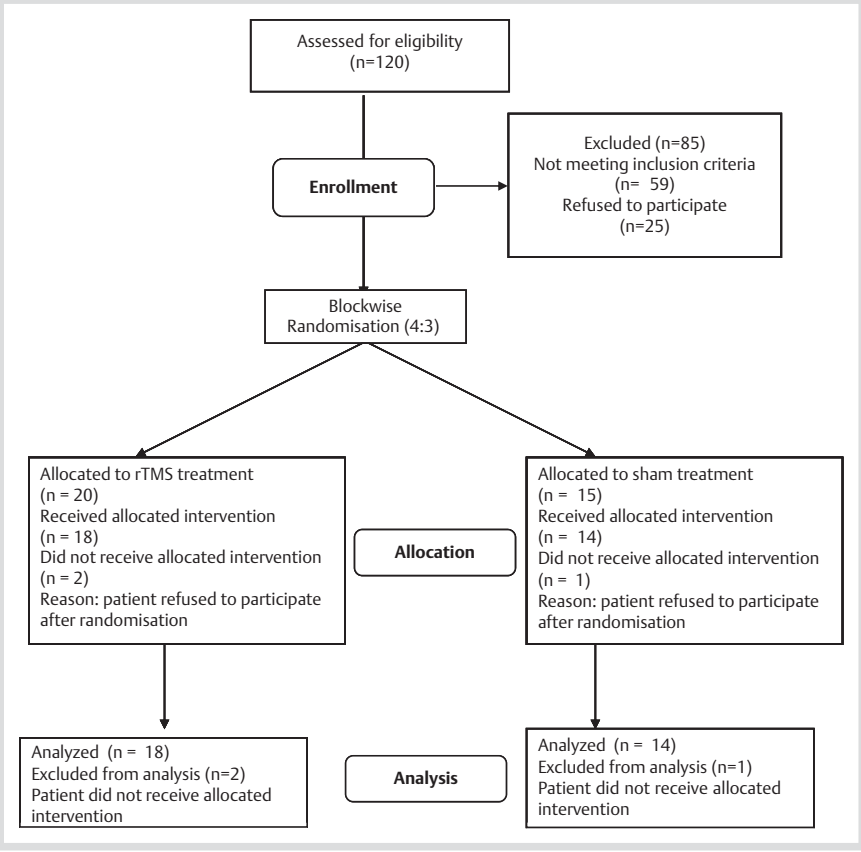

Fig. 1 Flowchart.

of the rTMS series because they refused to participate. For an overview of the clinical trial see **Fig. 1**. Both groups did not differ with respect to demographic and clinical characteristics (**Table 1**). The antipsychotic and mood stabilizing drug profile for the verum and the sham groups (18/14), respectively, were as follows: amisulprid 2/2, aripiprazol 2/2, clozapine 3/2, flupentixol 1/0, fluphenazin 1/0, haloperidol 0/1, lithium 1/0, olanzapine 4/6, perazin 1/0, pipamperon 3/1, quetiapine 1/1, risperidon 4/5, valproate 1/1, ziprasidon 1/0. There was a higher chlorpromazine equivalent dose in the control group [804 ± 366 mg versus 466 ± 249 mg, $t(26) = 2.916$, $p = 0.007$], but no medication of benzodiazepines.

rTMS Procedure

A double-blind, parallel design was applied with a sham stimulation control condition. Stimulation was performed using a MagPro X100 stimulation system and a figure-eight coil (MC-P-B70) with a diameter of 100 mm. This non-invasive magnetic stimulation system is able to deliver magnetic pulses up to 100 Hz within a magnetic field up to 4.1 Tesla. Patients in the verum group received 10 Hz rTMS 10 times between 1.00 and 3.00 p.m. during 2 weeks except on the weekends. At each session, 1 000 stimuli were applied at a frequency of 10 Hz during 20 trains (5 s per train, 55 s inter-train interval). Stimulation intensity was 110 % of the motor threshold which was assessed in advance. rTMS was implemented over the left dorsolateral prefrontal cortex (LDPC), located 5 cm anterior and in a parasagittal plane from the point of the maximum stimulation of the musculus abductor pollicis brevis. Sham stimulation was carried out in a similar manner by using a sham coil system (MC-P-B70) without induction of a magnetic field. The sham procedure elicited no tactile sensation at the site of stimulation and guaranteed that no substantial cortical stimulation occurred.

Outcome criteria

The primary outcome parameters were the first two subscales of the clinical global impression scale (CGI) [14], namely severity of illness (CGI-S) and global improvement (CGI-I). Secondary outcome parameters were changes in positive, negative and depressive symptoms as assessed with PANSS [19, 24] and global psychosocial functioning measured with GAF [28]. The results pertaining to psychopathology are presented in a previous publication [6].

Here the focus is set on tertiary outcome criteria, i.e., the performance in several neuropsychological tests. The test battery consisted of the "Kurztest für Allgemeine Intelligenz", which is the German version of a short test of general intelligence (KAI) [21], the "Mehrfach-Wortwahl-Test", a German verbal intelligence test, the D2 attention task, to assess attentional capacity [1], the trail making test A und B to assess visiomotor integration [34] and the Wisconsin card sorting test measuring perseveration and working memory [12]. During the WCST the subjects had to match a test card to one of four reference cards according to one of three rules: shape, number or colour, which is found by trial and error based on positive or negative feedback provided immediately after each matching decision. The number of correctly completed categories, the number of perseverative mistakes and perseverative answers was evaluated.

Study participants, clinical raters, and all personnel responsible for the clinical care of the patients remained blind to the allocated treatment conditions except the technical assistant who carried out the stimulation. The raters were trained medical scientists and the neurocognitive testing was carried out by a clinical psychologist. Tests were performed on the day before the

Table 1 Cinical and demographic characteristics.

	Active rTMS	Sham rTMS	Analysis
n	**18**	**14**	
Demographic characteristic			
age (mean, std. dev.)	34.5 ± 0.5	34.4 ± 10.5	n.s. *
sex (female/male)	04/14	03/11	n.s. **
age at onset (mean, std. dev.)	28.9 ± 10.4	28.3 ± 11.1	n.s. *
duration of illness (years)	5.7 ± 5.2	5.6 ± 8.8	n.s. *
number of hospitaliztions	4.1 ± 3.9	3.2 ± 3.7	n.s. *
Diagnoses (DSM-IV)			
paranoid schizophrenia	15	12	n.s. **
schizoaffective disorder	3	2	n.s. **
Concomitant medication			
typical antipsychotics (yes/no)	06/12	03/09	n.s. **
atypical antipsychotics (yes/no)	13/05	11/01	n.s. **
anticholinergica (yes/no)	00/18	00/12	n.s. **
mood stabilizers (yes/no)	00/18	01/11	n.s. **
antidepressants (yes/no)	00/18	01/11	n.s. **
chlorpromazine equivalent dose (mean, std. dev.)	466 ± 249	804 ± 366	p = 0.007 *
Baseline psychopathology			
CGI-S (mean, std. dev.)	4.75 ± 0.68	4.62 ± 0.65	n.s. *
PANSS total (mean, std. dev.)	79.06 ± 16.54	81.50 ± 23.57	n.s. *
PANSS negative (mean, std. dev.)	23.72 ± 6.76	26.79 ± 9.03	n.s. *
PANSS positive (mean, std. dev.)	14.44 ± 4.42	14.43 ± 4.60	n.s. *
PANSS depression (mean std. dev.)	11.06 ± 3.19	10.64 ± 4.73	n.s. *
MWT (mean, std. dev.)	101.18 ± 13.91	101.75 ± 16.14	n.s. *
Kai (mean, std. dev.)	107.94 ± 18.61	99.57 ± 18.76	n.s. *
D2 (mean, std. dev.)	102.93 ± 21.30	92.15 ± 13.53	n.s. *
TmTa (mean, std. dev.)	35.89 ± 30.82	48.93 ± 61.73	n.s. *
TMTb (mean, std. dev.)	86.63 ± 38.46	75.21 ± 33.74	n.s. *
WCSTvk (mean, std. dev.)	3.53 ± 2.386	3.31 ± 2.10	n.s. *
WCSTpa (mean, std. dev.)	26.00 ± 19.16	39.38 ± 33.28	n.s. *
WCSTpf (mean, std. dev.)	22.80 ± 14.96	31.00 ± 21.14	n.s. *

* Tested by independent t-test

** Tested by chi-square-test

start of the rTMS series and within 12 h after completing the last rTMS session. All adverse events spontaneously reported or observed were recorded.

Statistics

For the tertiary outcome criteria, the performance in several neuropsychological tests and for gender effects, group comparisons were made by calculating intra-individual pre-post treatment differences in cognitive performance which were compared between groups (verum versus sham) using the Mann-Whitney U-test. In addition we calculated correlations (Pearson R) between age and outcome parameters. To find out if psychopathological change can be predicted by the baseline cognitive performance, we tested for rank correlations (Spearman's *rho*) between the change in CGI, PANSS, GAF (pre-post rTMS) and the baseline (pre-rTMS) cognitive performance for each group separately. To pursue the question if cognitive change can be predicted by the baseline psychopathology, we tested for rank correlations (Spearman's *rho*) – again for each group separately – between the change in the neuropsychological tests and the baseline CGI, PANSS and GAF. Additionally these rank correlations of the groups were converted to normal random variables by the Fisher Z transformation and subsequently to standard normal random variables in order to compare them pair-wise. To find out if psychopathology was associated with cognitive performance at baseline, we tested for rank correlations (Spearman's *rho*) between CGI, PANSS, GAF and the neuropsychological test scores. A correction for multiple testing has to be applied for the results which are reported merely for explorative purposes.

Results

Patients who completed the study (n = 32) had a mean age of 34.46 ± 0.46 years in the verum group (n = 18) and 34.36 ± 10.46 years in the sham group (n = 14). In the verum condition, 14 patients were male and 4 female, in the sham condition 11 were male and 3 were female.

As no significant correlation between the chlorpromazine equivalent dose and the change in neuropsychological or psychopathological tests could be found in this sample ($p > 0.14$ for all tests), the chlorpromazine equivalent dose is not considered in the following analysis further.

There were no statistically significant ($p < 0.05$) gender effects on the dependent variables. Age did not significantly correlate with any of the primary outcome variables with one exception: we observed a positive correlation of age and Δ-values of the trail making test A, $r = -0.443$, $p = 0.024$. We did not observe any adverse event as assessed with the UKU side effect rating scale except for mild headache.

Comparing the neuropsychological test performance (pre-post difference scores) between the active and sham rTMS group, no significant group differences were found (**Table 2**). The smallest probability ($p = 0.059$, but not corrected for multiple testing) was found for the difference in Δ-values of WCST categories for the subgroup of eleven patients with WCST categories pre scores lower than four, which was the median of the sample. Accordingly, no positive effect of rTMS treatment on the cognitive performance was proven.

Table 2 Pre-/post Δ-values and significance-level from Mann-Whitney U-test.

	Active rTMS Group			Control rTMS Group			U-test
	n	Mean	SD	n	Mean	SD	p
Δ KAI	13	3.46	7.25	12	3.50	8.65	0.574 n. s.
Δ D2	12	9.67	5.47	11	10.27	8.55	0.976 n. s.
Δ trail making test A	14	0.64	15.08	12	−11.92	29.27	0.527 n. s.
Δ trail making test B	13	−0.54	29.41	11	−5.64	20.31	0.459 n. s.
Δ WCST categories	12	1.58	22.20	11	−0.27	1.95	0.091 n. s.
Δ WCST categories for patients with WCST categories pre < median (=4)	6	3.33	2.58	5	0.40	2.07	0.059 n. s.
Δ WCST perseverative answers	12	−9.00	11.54	11	−19.18	27.76	0.235 n. s.
Δ WCST perseverative mistakes	12	−8.17	9.81	11	−11.27	17.51	0.928 n. s.

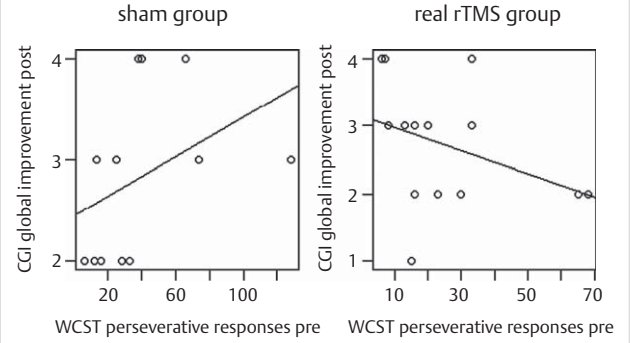

Fig. 2 Correlation WCST perseverative responses pre and CGI global improvement post.

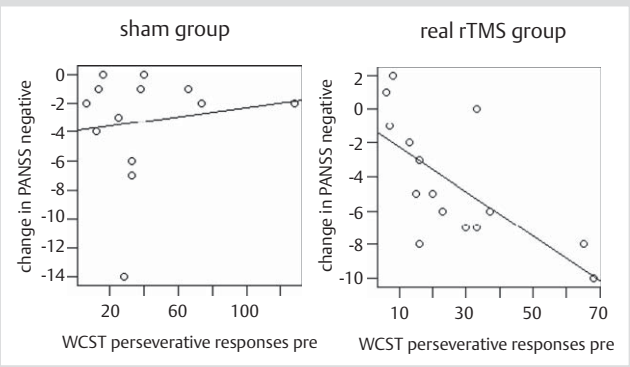

Fig. 3 Correlation WCST perseverative responses pre and change in PANSS negative.

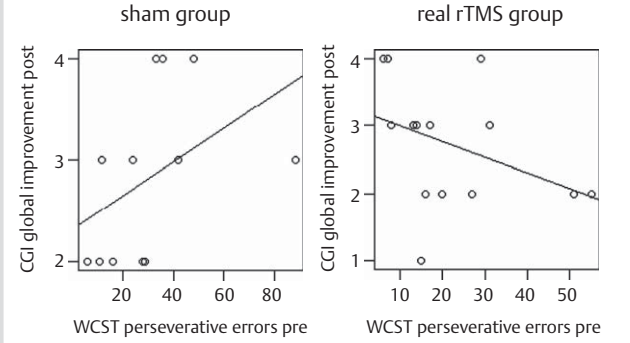

Fig. 4 Correlation WCST perseverative errors pre and CGI global improvement post.

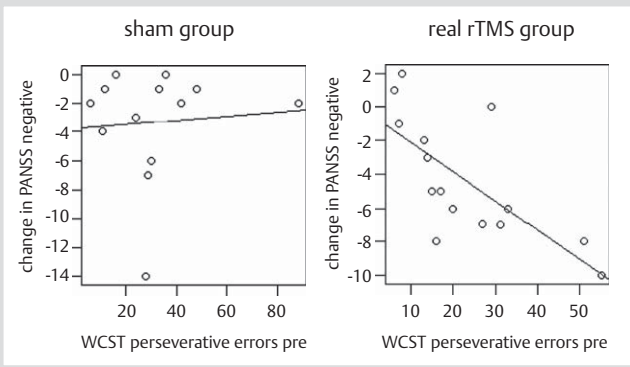

Fig. 5 Correlation WCST perseverative errors pre and change in PANSS negative.

The following results are reported merely for explorative purposes (a correction for multiple testings has to be applied: $\alpha^* = \alpha/35 = 0.0014$). In the treatment group and the control group, some correlations between the baseline psychopathological tests and the change in the neuropsychological tests tended to differ, but were partly contradictory, and are not reported here.

Additionally, the correlations between the baseline cognitive test performance and the change in psychopathological measures tended to differ in the control and treatment group: between the baseline WCST perseverative responses and the CGI global improvement post scores (◉ **Fig. 2**; control group: $r_s = 0.615$, $p = 0.033$, $n = 12$, treatment group: $r_s = -0.403$, $p = 0.153$, $n = 14$, difference: $z = 2.545$, $p = 0.011$), the baseline WCST perseverative responses and the change in PANSS positive scores (control group: $r_s = 0.275$, $p = 0.363$, $n = 13$, treatment group: $r_s = -0.612$, $p = 0.015$, $n = 15$, difference: $z = 2.322$, $p = 0.020$), the baseline WCST perseverative responses and the change in PANSS negative scores (◉ **Fig. 3**; control group: $r_s = 0.148$, $p = 0.630$, $n = 13$, treatment group: $r_s = -0.725$, $p = 0.002$, $n = 15$, difference: $z = 2.493$, $p = 0.013$), the baseline WCST perseverative errors and the CGI global improvement post scores (◉ **Fig. 4**; control group: $r_s = 0.641$, $p = 0.025$, $n = 12$, treatment group: $r_s = -0.460$, $p = 0.098$, $n = 14$, difference: $z = 2.796$, $p = 0.005$), the baseline WCST perseverative errors and the change in PANSS positive scores (control group: $r_s = 0.295$, $p = 0.329$, $n = 13$, treatment group: $r_s = -0.640$, $p = 0.010$, $n = 15$, difference: $z = 2.478$, $p = 0.013$), and the baseline WCST perseverative errors and the change in PANSS negative scores (◉ **Fig. 5**; control group: $r_s = 0.167$, $p = 0.586$, $n = 13$, treatment group: $r_s = -0.758$, $p = 0.001$, $n = 15$, difference: $z = 2.710$, $p = 0.007$). These results tend to show that in the control group a

more favourable cognitive performance as measured by the WCST at baseline was associated with an improvement in the psychopathological measures and vice versa, whereas in the active group less favourable WCST scores at baseline tended to be linked with an improvement in psychopathology after rTMS and vice versa.

Discussion

In the present sham controlled study of rTMS treatment – applied over the left prefrontal cortex – in schizophrenia patients, we observed no significant changes in a battery of neuropsychological tests including tests of executive cognitive function. Thus, the stability of cognitive function suggests a good tolerance of rTMS treatment in schizophrenia.

It has been originally investigated as a less invasive alternative to electroconvulsive therapy (ECT) in the treatment of neuropsychiatric disorders [33]. Whereas both rTMS and ECT are neurostimulation techniques, rTMS is an experimental procedure in treatment-resistant schizophrenia and ECT is a well-established one. It is good clinical practice that ECT plus antipsychotic drug treatment is superior to ECT or drug use alone in treatment-resistant schizophrenia. According to the latest Cochrane Review [42] there are some data indicating a transient and probably slight memory impairment resulting from ECT. Despite the encouraging results and excellent safety profile of rTMS, it is associated with a smaller effect size than that seen with ECT [22]. However there have not been yet any randomized trials comparing ECT with rTMS [42].

Schizophrenia patients appear to have abnormal cortical inhibition. Several lines of evidence implicate altered dopamine neurotransmission in schizophrenia [32] consistent with GABA abnormalities. GABA abnormalities in schizophrenia patients may relate to cognitive deficits and negative symptoms [39]. Moreover cerebellar pathology is implicated in schizophrenia patients. The cerebellum may cause cognitive deficits in schizophrenia patients via abnormal cortical control. Therefore studies of cerebellar cortical inhibition in schizophrenia may be relevant for the development of TMS for cognitive deficits [39]. The effect of TMS on GABA and dopamine neurotransmission has not been clearly delineated. Given the variability in cortical response to rTMS in schizophrenia, methods to optimize dosage are essential. Consideration of these factors among others may broaden the scope of utility of TMS for schizophrenia as well as enhance its efficacy [39].

The results of this study tend to show that inferior performance in certain neuropsychological aspects before treatment predicts a better response to active rTMS. Due to limitations of the study, which are discussed subsequently, a careful interpretation of the results is warranted. However, it has been shown that the significant heterogeneity in schizophrenia may impact treatment response and may have to be considered in the design of future studies [39]. Baseline patient characteristics of treatment responders including demographic and cognitive factors may be useful determinants of treatment response. Other distinctions that may be of value include the effect of etiological subgroup on treatment response and whether there is an interaction between etiological group and treatment location since these patient subpopulations differ clinically and cognitively [39].

Our study has obvious limitations. The sample size is still relatively small and might reduce the power of statistical analyses. Low dosage and short stimulation period have been used. Ten sessions and 1 000 stimuli per session at 110 % of motor threshold are relatively low. The absence of evidence for cognitive deterioration could be due to low and short stimulation parameters. The stimulation parameters have to be set into context of other rTMS studies. The previously discussed studies by Novak [30], Sachdev [37], Holi [18], Rollnik [35] and Schneider [38] which found no significant changes in any cognitive measures applied 10 or 20 sessions of 10, 15 or 20 Hz rTMS over the DLPFC with a motor threshold of 80 to 110 %. The two studies by Cohen [4] and Mogg [27] which showed improvement in some neuropsychological scores did not use substantially higher stimulation parameters. Cohen [4] applied 10 sessions of 20 Hz rTMS at 80 % MT and Mogg [27] used 10 sessions of 10 Hz at 110 % MT. Although generally in rTMS response appears to correlate with dose of treatment, no correlation becomes evident comparing the rTMS studies in schizophrenia with respect to change in cognition. The optimal parameters for rTMS in schizophrenia remain to be determined and consecutive studies have to compare systematically the multifarious variations of rTMS stimulation parameters.

The sham procedure elicited no tactile sensation at the site of stimulation. The cortical target might not be precise enough unless MRI and stereotaxic guidance is used. Moreover, multiple comparison correction is missing.

Furthermore long-term effects have to be evaluated. There should be a systematic follow-up for the emergence of potential late-effects. As the study by Mogg [27] showed, a significant group difference can become apparent only at the follow-up assessment.

To assess the full spectrum of potential cognitive effects of longer term rTMS exposure, future studies will need to include such well-validated metrics as the WRAT (wide range achievement test) and more specific cognitive measures such as the California verbal learning test [38].

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Competing Interests

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Patient Consent

Written informed consent was obtained from each patient. The study was approved by the ethic committee of the Universitiy of Duesseldorf, Moorenstr. 5, D-40225 Düsseldorf (Germany) and has been carried out in accordance with The Code of the World Medical Association (Declaration of Helsinki).

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