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1. Introduction

It is estimated that around 20–30% of all schizophrenia patients are antipsychotic treatment-resistant, providing an indication for treatment with clozapine (Hasan et al., 2012). Of those treated with clozapine, 40–70% may continue to have symptoms severe enough to warrant a description as clozapine-resistant schizophrenia (Chakos et al., 2001; Kane et al., 1988; Lieberman et al., 1994; Siskind et al., 2017).

In a meta-analysis by Siskind et al. that included in total N = 2364 patients who fulfilled criteria for treatment-resistance that included a 6-week trial of at least one antipsychotic at a dose of 600 mg/day chlorpromazine equivalents, clozapine compared to other antipsychotics in monotherapy was superior for positive symptoms, but not negative or total symptoms (Siskind et al., 2016). Several second-generation antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone) - but not first-generation antipsychotics - have been recommended for the treatment of primary negative symptoms, however the evidence is inconsistent with more studies needed to confirm efficacy (Hasan et al., 2012). For patients with partial or non-response to clozapine, several pharmacological and non-pharmacological augmentation strategies to alleviate positive or negative symptoms are discussed in the literature. There is limited evidence for combining clozapine with a second antipsychotic, with modest to absent benefit for the patient (Barbui et al., 2009; Correll et al., 2017; Siskind et al., 2018). For persisting negative symptoms, augmentation of clozapine with an antidepressant has no significant beneficial effect (Siskind et al., 2018; Veerman et al., 2014). There are a limited number of psychotherapy studies for people with clozapine-resistant schizophrenia, with two studies of cognitive behavioral therapy (CBT) showing no benefit (de Paiva Barretto et al., 2009; Morrison et al., 2018).

Non-invasive neurostimulation for clozapine-resistant schizophrenia holds promise. Electroconvulsive therapy has been shown to be a highly effective non-pharmacological augmentation strategy for positive symptoms in clozapine-resistance (Lally et al., 2016; Petrides et al., 2015; Siskind et al., 2018). Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique using repetitive application of magnetic pulses through the scalp (Arumugham et al., 2016). For the reduction of negative symptoms in schizophrenia patients, high-frequency rTMS (10 Hz) of the left dorsolateral prefrontal cortex (DLPFC) is the most frequent stimulation setting (Lefaucheur et al., 2014). A meta-analysis by Aleman et al. that included 22 randomized controlled trials (RCTs) with uni- or bilateral DLPFC stimulation showed moderate effects of rTMS of the frontal cortex for improving negative symptoms in schizophrenia (after correction for outliers: mean weighted effect size 0.31 (95% CI: 0.12–0.50; k = 18, total N = 721) with a stronger improvement for active rTMS stimulation as compared to sham (Aleman et al., 2018). However, our multicenter rTMS RCT conducted on 157 schizophrenia patients with predominant negative symptoms could not establish a superiority of active rTMS compared to sham rTMS applied to the left DLPFC (Wobrock et al., 2015).

Even though rTMS has not been studied for negative symptoms exclusively in clozapine-refractory populations, rTMS-RCTs have included patients receiving clozapine (Arumugham et al., 2016). In the RCT by Barr et al., five out of 25 patients (Barr et al., 2012), in the RCT by Fitzgerald et al. seven out of 20 patients (Fitzgerald et al., 2008) and in the RCT by Schneider et al. 10 out of 51 patients (Schneider et al., 2008) were on clozapine mono- or combination-therapy. However, no separate analyses for those patients have been conducted.

Barr et al. investigated the efficacy of bilateral high-frequency rTMS (20 Hz, right and left DLPFC at 90% RMT administered daily for total 20 sessions over 4 weeks) in the treatment of negative symptoms among 25 patients in schizophrenia (Barr et al., 2012). With the SANS and PANSS scales as primary endpoints and controlling for depression via the Calgary Depression Scale for Schizophrenia (CDSS), no significant group or time differences were found in negative symptoms after rTMS (Barr et al., 2012). In this study, five patients were on clozapine-monotherapy (780 +/− 303.2 mg per day), with two randomized to the active and three to the sham-treatment arm. In the RCT from Fitzgerald et al. (2008) participants received high-frequency bilateral rTMS or sham over 3 weeks. Twenty trains (5 s duration) of 10 Hz rTMS at 110% of the RMT were administered to each PFC daily, 5 days a week. No significant group or time differences in the Scale for the Assessment of Negative Symptoms (SANS) scores were evident (Fitzgerald et al., 2008). In the active treatment arm, four patients received clozapine monotherapy and two patients received clozapine combined with another second-generation antipsychotic. In the sham-treatment arm one patient received clozapine monotherapy. Due to the low number of clozapine patients, no significance was reported for clozapine-treatment active vs. sham (Fitzgerald et al., 2008). In the RCT from Schneider et al. (2008) three groups of 17 patients with schizophrenia were exposed to 20 treatments of either placebo, 1 Hz (100 pulses per day 52,000 total) or 10 Hz (1000 pulses per day 5 20,000 total) rTMS each at 110% motor threshold over the left dorsolateral prefrontal cortex, while being maintained on their second-generation antipsychotic. The primary outcome measure (change in SANS scores) showed a statistically significant drop at weeks 2, 4 and 8 for the high frequency (10 Hz) group, but not for the 1 Hz or placebo groups (Schneider et al., 2008). Ten patients were treated with clozapine, however the number in each of the three treatment arms was not specified (Schneider et al., 2008).

In the two RCTs of rTMS interventions specifically among clozapine patients, the focus was on refractory positive symptoms (auditory hallucinations) rather than negative symptoms (de Jesus et al., 2011; Rosa et al., 2007). The randomized sham-controlled trial from de Jesus et al. (de Jesus et al., 2011) investigated the effects of active compared with sham 1-Hz rTMS over a course of 20 days applied to the left temporoparietal cortex in schizophrenia patients (N = 17) with clozapine-resistant auditory hallucinations (de Jesus et al., 2011). The primary endpoint was the change in the 18-item Brief Psychiatric Rating Scale (BPRS). A significant reduction in BPRS scores was found in the active group compared to sham, but no significant difference in the auditory hallucinations rating scale (AHRS).

In the RCT by Rosa et al. (2007) patients with a schizophrenia diagnosis according to DSM-IV, treated with clozapine (N = 11) and still experiencing auditory hallucinations were randomly assigned to receive either active rTMS or sham stimulation using a double-masked, sham-controlled, parallel design (Rosa et al., 2007). Repetitive TMS/sham-stimulation was administered over a course of 10 days and the primary outcome was the 7-item auditory hallucinations rating scale (AHRS) (Rosa et al., 2007). The authors did not report a significant reduction in auditory hallucinations. Among published meta-analyses of active vs sham rTMS for positive or negative symptoms in schizophrenia, patients on clozapine were not specifically investigated (Aleman et al., 2018; Blumberger et al., 2010; Dlabac-de Lange et al., 2010; Freitas et al., 2009; He et al., 2017; Otani et al., 2015; Prikryl and Kucerova, 2013; Shi et al., 2014).

Since adequate treatment options for patients on clozapine with predominant negative symptoms are lacking in clinical practice, we undertook secondary analyses of the Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial (Wobrock et al., 2015), the largest available rTMS trial on the treatment of negative symptoms in schizophrenia, to re-examine the effects of add-on rTMS for patients with schizophrenia receiving clozapine. Since we consider the application of treatment-resistance criteria crucial in CLZ augmentation studies, we present the first rTMS publication that applies TRRIP criteria (Howes et al., 2017) for treatment-resistant negative symptoms in schizophrenia patients.

2. Methods

2.1. Study subjects and intervention

As outlined elsewhere (Cordes et al., 2009; Hansbauer et al., 2018; Wobrock et al., 2015), in the RESIS trial 197 patients with schizophrenia

and predominant negative syndrome were screened between 2007 and 2011. For RESIS (Wobrock et al., 2015) the inclusion criteria were International Classification of Diseases, Tenth Revision, diagnosis of schizophrenia confirmed by the MINI-interview, age 18–60 years, an illness duration of at least 1 year, stable antipsychotic medication for at least 2 weeks, a PANSS negative subscale score > 20 points, and at least one PANSS negative item ≥4 points. The TRRIP symptom criteria for treatment-resistant negative symptoms (2 PANSS negative symptom items ≥4 points, or one PANSS negative item ≥6 points) (Howes et al., 2017) were met by all our schizophrenia patients treated with clozapine at pre-treatment conditions (i.e. either at screening or baseline).

In RESIS, from 175 patients that were enrolled and randomized 157 patients received either active (N = 76) or sham (N = 81) rTMS treatment and at least one PANSS assessment prior to the rTMS intervention. A multi-block 1:1 randomization with variable block length was performed. The randomization was stratified for the study centers. It was not possible to identify the group by the patients (correct classifications: 56%) or by the blinded raters (correct classifications: 47%). For rTMS the MagPro X100 stimulator (Medtronic A/S, Copenhagen, Denmark) with a passively cooled figure-of-eight coil (Medtronic A/S) was used at all centers. The EEG International 10–20 system (F3 electrode) was applied in order to determine the stimulated target region (Herwig et al., 2001; Herwig et al., 2003; Homan et al., 1987). The following stimulation parameters were used: 10 Hz, five treatment sessions/week for a 3-week treatment period (from day 0 to day 21) with an intensity of 110% of the individual resting motor threshold and 1000 stimuli (20 trains with 50 stimuli per train, 30-s intertrain interval) (Wobrock et al., 2015). Randomization to sham rTMS implied identical treatment for the patients, but the stimulation coil was tilted over one wing at an angle of 45 degrees (Lisanby et al., 2001; Wobrock et al., 2015). Advantages and disadvantages of this procedure were discussed elsewhere (Wobrock et al., 2015). The full study description of the RESIS trial (including blinding integrity and randomization procedures) and the primary endpoint analysis are published elsewhere (Cordes et al., 2009; Wobrock et al., 2015). The RESIS trial was registered at http://clinicaltrials.gov/ with the number: NCT00783120. Based on previous RESIS publications (Hansbauer et al., 2018; Wobrock et al., 2015), we re-analyzed the data on patients treated with clozapine at the start of the study. We identified 26 patients (12 active rTMS, 14 sham rTMS) with pretreatment clozapine data in the Intention-to-treat population and those patients were included in the here presented analyses. For this secondary analysis, we focused on the change of the PANSS positive, negative, general and total values over time.

2.2. Statistical analyses

Statistical analyses were performed with SPSS23 (IBM Inc.) at a significance level of $\alpha = 0.05$. A general linear mixed model (LMM) analysis was used for the intention-to-treat population, non-restrictively assuming an unstructured covariance matrix (Krueger and Tian, 2004) in line with previous RESIS publications (Hansbauer et al., 2018; Wobrock et al., 2015). Group (active rTMS vs. sham rTMS) and the three different centers were the between-subject factors and time (all available visits pre rTMS vs. post rTMS) was the within-subject factor. The analysis included all available PANSS data from screening to day 105 (screening, baseline, day 21, follow-up visits at day 28, day 45 and day 105).

Demographic and clinical variables were compared between the groups with Fisher's exact test (gender, employment, hand preference) or with analysis of variance (ANOVA; dependent variables: age, education, left resting motor threshold, PANSS negative symptom subscale, PANSS positive symptom subscale, PANSS total scale, Global Assessment of Functioning, Calgary Depression Scale for Schizophrenia). Between group and the three centers the Freeman-Halton exact test for 2 × 3 tables was applied. As the concerning data was not normally distributed, baseline CGI scores and Montgomery Asberg Depression Rating Scale scores were both compared using Mann-Whitney *U* test and CPZ equivalents were logarithmically transformed and then analyzed with an ANOVA. Pearson correlations of PANSS and CDSS scales were applied to evaluate the relationship of psychosis-related psychopathology and depressive symptoms.

3. Results

The analyses presented here were performed on clozapine treated patients prior to the start of the intervention in the intention-to-treat (ITT) population, defined as all patients randomized to a treatment group who started at least one treatment session (Wobrock et al., 2015). Pretreatment characteristics at day 0 of both study groups are displayed in Table 1. Apart from a significant difference in employment and center distribution no significant differences in sociodemographic or clinical characteristics were observed.

For the *PANSS positive subscale*, the linear mixed model revealed a significant time effect ($F_{(6,\ 13.2)} = 4.3$, $p = 0.013$) and a significant time × group interaction ($F_{(6,\ 11.8)} = 6.4$, $p = 0.003$) was found (*see* Fig. 1 *A*). For the *PANSS negative subscale*, analyses showed a significant time effect ($F_{(6,\ 13.3)} = 15.2$, $p < 0.001$) but not a significant time × group interaction ($F_{(6,\ 11.5)} = 1.4$, $p = 0.301$) (*see* Fig. 1 *B*). For the *PANSS general subscale* a significant time effect ($F_{(6,\ 15.7)} = 23.9$, $p < 0.001$) and a significant time × group interaction ($F_{(6,\ 14.4)} = 16.8$, $p < 0.001$) were observed (*see* Fig. 1 *C*). Finally, for the *PANSS total scale* a significant time effect ($F_{(6,\ 13.1)} = 18.7$, $p < 0.001$) and a significant time × group interaction ($F_{(6,\ 11.8)} = 4.3$, $p = 0.015$) were seen (*see* Fig. 1 *D*).

As a post hoc analysis at each visit between-group comparison was performed only if time × group interactions were significant. From these subsequent analyses no significant differences between the two groups were found (*PANSS positive subscale*: all $p \geq 0.214$, *PANSS general subscale*: all $p \geq 0.215$, *PANSS total scale*: all $p \geq 0.227$).

Fig. 1 shows the course of the four PANSS variables from screening to day 105 in the rTMS- and in the sham-group. For PANSS positive, the descriptive data indicates that in the active group the improvement was more pronounced compared to the sham rTMS group. For PANSS general and PANSS total, the descriptive data indicates a more substantial improvement over time in the active group compared to the sham rTMS group.

Depressive scores evaluated by CDSS (data available for days 0, 21, 28, 45 and 105) showed a trend towards an improvement over time ($F_{(4,\ 13.52)} = 2.889$, $p = 0.063$), but no significant time × group interaction ($F_{(4,\ 12.10)} = 2.042$, $p = 0.152$) indicating a slight improvement in both groups with no significant differences between groups in the amount of change. This is principally in line with the findings of the full RESIS Sample showing a general improvement in depressive symptoms over time in both study groups (Wobrock et al., 2015).

Pearson correlations did not show a significant correlation between PANSS negative scores and CDSS at day 0, day 21, day 28, day 45 and day 105 in both groups (active rTMS: all $p \geq 0.329$; sham rTMS: all $p \geq 0.216$). However, for sham rTMS significant correlations between CDSS and PANSS positive (day 21: $r = 0.789$, $p = 0.004$; day 28: $r = 0.605$, $p = 0.048$, day 45: $r = 0.823$, $p = 0.003$), PANSS general (day 21: $r = 0.719$, $p = 0.013$; day 45: $r = 0.776$, $p = 0.008$) and PANSS total (day 21: $r = 0.687$, $p = 0.020$) could be detected, whereas for the active group no further correlations were revealed by our analyses (all $p \geq 0.108$). As in our sample no correlations between depressive and negative symptoms were detected, as only some significant correlations between CDSS and other PANSS subscales were detected in the sham group and as CDSS data is not available prior day 0, no further analyses were conducted.

During the entire study period, 2 active rTMS and 1 sham rTMS patients reported adverse events (AE) with one serious AE (hospitalization due to deterioration in symptoms) that occurred in the active rTMS group. Clozapine patients at baseline consisted of 12 patients in the active and 14 patients in the sham group. Until the end of the

Table 1
Pretreatment characteristics (active vs. sham).

	Active rTMS (N = 12)		Sham rTMS (N = 14)		Active vs. Sham		
							p
Gender (male:female)	9:3		12:2				0.63[a]
Employment (employed:not employed)	4:8		0:14				**0.033**[a]
Center (GOE:D:R)	5:5:2		1:4:9				**0.037**[b]
Hand preference (right:not right)	11:1		11:2				1.00[a]
	Mean	*SD*	*Mean*	*SD*	*F*	*df*	*P*
Age, yr	36.6	10.0	36.2	9.0	0.0	1, 24	0.92[c]
Education, yr	10.9	1.9	10.1	1.5	1.3	1, 23	0.27[c]
Left resting motor threshold	47.7	11.1	43.0	13.8	0.8	1, 21	0.39[c]
PANSS Negative symptoms[d]	24.6	4.2	27.2	3.7	2.8	1, 23	0.11[c]
PANSS Positive symptoms[d]	13.6	3.1	14.2	3.3	0.2	1, 23	0.66[c]
PANSS Total[d]	76.7	10.7	79.2	15.1	0.2	1, 23	0.64[c]
Clinical Global Impression score for severity[e]	4.7	0.8	4.9	0.8	Z=−0.7	1	0.52[f]
Global Assessment of Functioning[g]	53.5	9.2	51.7	8.7	0.2	1, 21	0.63[c]
Calgary Depression Scale for Schizophrenia[h]	5.4	4.2	4.7	3.4	0.2	1, 22	0.67[c]
Montgomery Asberg Depression Rating Scale[i]	12.4	2.7	15.2	6.6	Z = −1.1	1	0.29[f]
					F	*df*	*p*
Antipsychotic dose (chlorpromazine equivalents, day 0), mg/day	569	341	585	521	0.1	1, 23	0.81[j]
Clozapine dose (day 0) mg/day	291	159	304	191	0.0	1, 24	0.86[j]
Clozapine dose (day 21) mg/day	379	147	311	198	1.6	1, 19	0.23[j]
							P
CLZ mono (yes:no)	1:11		0:14				0.46[a]
combined with AP (yes:no)	8:4		10:4				1.00[a]
combined with MS (yes:no)	3:9		2:12				0.63[a]
combined with AD (yes:no)	5:7		6:8				1.00[a]

rTMS = repetitive transcranial magnetic stimulation, N = group size, SD = standard deviation, GOE = Göttingen, D = Düsseldorf, R = Regensburg, mg = milligram, AP = antipsychotic medication, AD = antidepressive medication, MS = mood stabilizing medication.

[a] Comparison by Fisher's exact test

[b] Comparison by Freeman-Halton exact test for 2 × 3 tables.

[c] Results from analysis of variance.

[d] PANSS denotes the Positive and Negative Syndrome Scale. Scores on the positive and negative symptom subscales of the PANSS range from 7 to 49, scores on the general symptom subscale range from 16 to 112, each with higher scores denoting more severe illness.

[e] The Clinical Global Impression score for severity ranges from 1 (not mentally ill) to 7 (extremely ill).

[f] Results from Mann-Whitney *U* test.

[g] The Global Assessment of Functioning score ranges from 1 to 100, with higher scores indicating better functioning.

[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.

[j] Comparison on logarithmic transformed variable by analysis of variance.

treatment phase 11 patients were available in each group. However, until the end of study compared to baseline 5 verum patients and 7 sham patients dropped out (for more details see legend to Fig. 1).

4. Discussion

We present a secondary analysis that investigates the effects of high-frequency rTMS applied to the left DLPFC on different PANSS scales among patients with schizophrenia on clozapine. Our sample constitutes the largest available RCT sample of clozapine patients treated with rTMS to date (N = 26) with the longest post-stimulation follow-up period. Our seven rTMS vs seven sham-patients on clozapine at day 105 are furthermore the largest sample of clozapine patients with a DLPFC rTMS add-on in a post-stimulation follow-up observation period. The included patients had high CGI-Scores and severe and persisting negative symptoms despite clozapine treatment, suggesting that this population was refractory to current clinical interventions.

In the original intention-to-treat analysis of the complete study sample, no superior effect of active rTMS compared to sham rTMS for the primary outcome parameter (change in PANSS negative subscale over time) or for various secondary outcome parameters (e.g. other PANSS subscales, depression scale, global functioning) could be established (Wobrock et al., 2015). In the here presented secondary LMM-analysis conducted on those patients with predominant negative symptoms receiving clozapine, time × group interactions were significant in the PANSS positive subscale, the PANSS general subscale and the PANSS total scale, when all PANSS measurements from screening to day 105 were included. Descriptive statistics indicate that the improvement in PANSS positive, general and total subscale was more pronounced in the active compared to the sham rTMS group explaining the significant interaction. The latter could not be established for the PANSS negative subscale, consistent with our previously reported RESIS findings (Hansbauer et al., 2018; Wobrock et al., 2015). However, between-group post-hoc statistics did not show significant differences for any visit due to the limited sample size. Other sham-controlled rTMS-RCTs have included clozapine patients (Barr et al., 2012; Fitzgerald et al., 2008; Schneider et al., 2008) and other rTMS studies focusing on the treatment of negative symptoms had clozapine patients in the reported samples, however, as noted earlier, the sample sizes were limited and the effect of clozapine was not investigated in most studies.

Our results are in keeping with the small RCT from de Jesus et al. (Rosa et al., 2007), which noted an improvement in BPRS scores following in the active vs sham groups following 160 min of rTMS (9600 pulses) over 10 days at 90% motor threshold. In a small open trial by D'Alfonso (N = 9) (d'Alfonso et al., 2002), seven clozapine-patients with persistent auditory hallucinations (mean dose: 400 mg) significantly improved after an application of 10 sessions with 1-Hz rTMS of the left auditory cortex at 80% of the motor threshold (total stimuli: N = 12.000) (d'Alfonso et al., 2002). However, another small (N = 11) RCT of rTMS among patients with schizophrenia on clozapine found no difference between active and sham groups for auditory hallucinations (Rosa et al., 2007).

In a recent meta-analysis by Aleman et al., more than half of the analyzed trials did not show a beneficial effect of active rTMS vs. sham (Aleman et al., 2018) and the largest available trial was also negative (Wobrock et al., 2015). Furthermore, protocols with high frequency

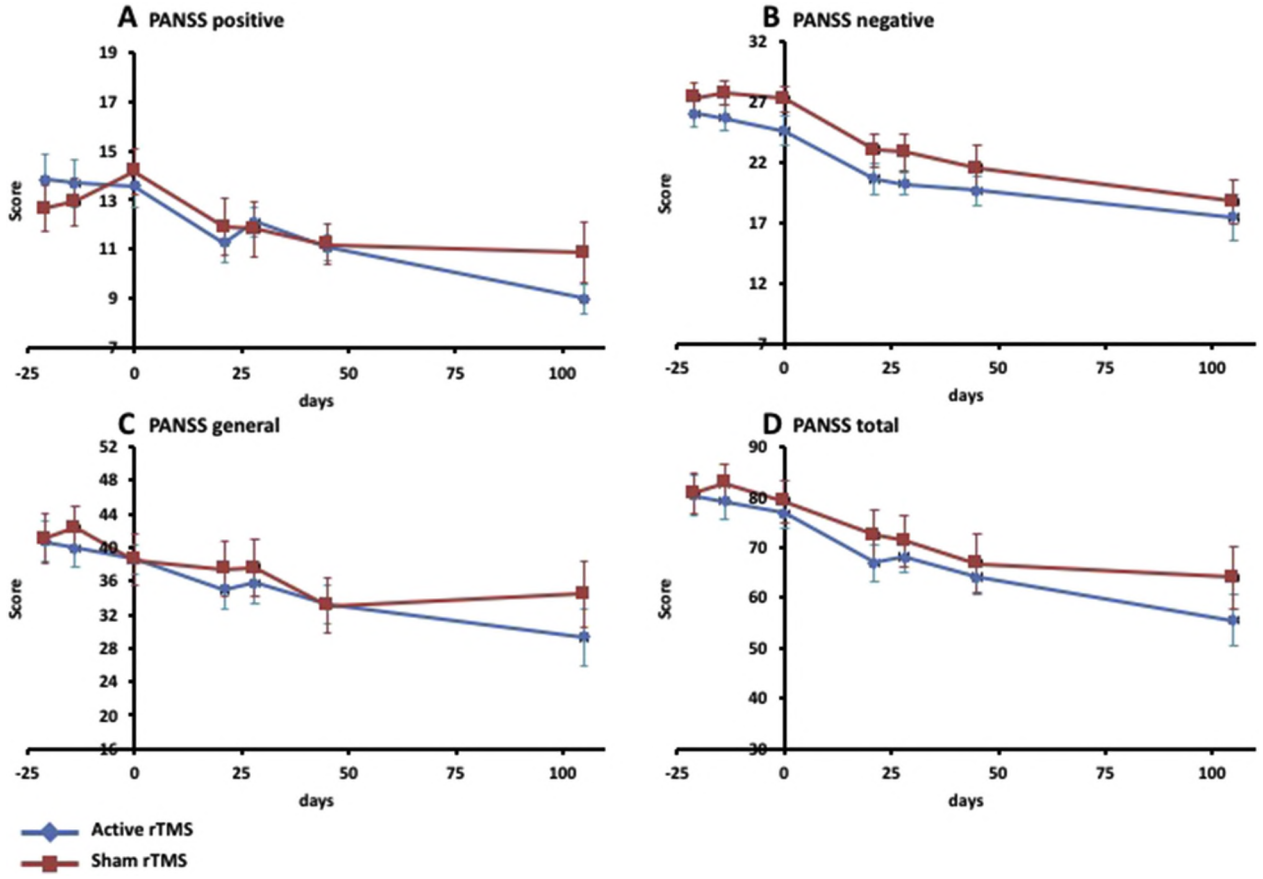

Fig. 1. The course of the four PANSS variables from screening to day 105 (FU105) in the LMM-analysis The figure represents the data for the four PANSS subscales. For PANSS positive (A) the following group sizes (N) were used for the analyses: Verum: Screening: N = 12, Baseline: N = 12, Treat 0: N = 12, Treat 21: N = 11, FU 28: N = 9, FU45: N = 11, FU105: N = 7; Sham: Screening: N = 14, Baseline: N = 14, Treat 0: N = 13, Treat 21: N = 11, FU 28: N = 11, FU45: N = 10, FU105: N = 7. For PANSS negative (B) the following N were used for the analyses: Verum: Screening: N = 12, Baseline: N = 12, Treat 0: N = 12, Treat 21: N = 11, FU 28: N = 9, FU45: N = 11, FU105: N = 7; Sham: Screening: N = 14, Baseline: N = 14, Treat 0: N = 13, Treat 21: N = 11, FU 28: N = 11, FU45: N = 10, FU105: N = 7. For PANSS general (C) the following N were used for the analyses: Verum: Screening: N = 12, Baseline: N = 12, Treat 0: N = 12, Treat 21: N = 11, FU 28: N = 9, FU45: N = 10, FU105: N = 7; Sham: Screening: N = 14, Baseline: N = 14, Treat 0: N = 13, Treat 21: N = 11, FU 28: N = 11, FU45: N = 10, FU105: N = 7. For PANSS total (D) the following N were used for the analyses: Verum: Screening: N = 12, Baseline: N = 12, Treat 0: N = 12, Treat 21: N = 11, FU 28: N = 9, FU45: N = 10, FU105: N = 7; Sham: Screening: N = 14, Baseline: N = 14, Treat 0: N = 13, Treat 21: N = 11, FU 28: N = 11, FU45: N = 10, FU105: N = 7. Error bars represents standard errors of the mean.

stimulation containing >7500 stimuli per week at an intensity of >100% motor threshold were estimated to be more effective than other protocols (Aleman et al., 2018). In our sample, the number of stimuli was lower than 7500 per week. Finally, younger patients with a shorter duration of illness may respond better to rTMS-interventions (Aleman et al., 2018) and our cohort of patients being treated with clozapine represents a more chronic sample.

Our preliminary finding of a potential beneficial effect on PANSS positive subscale raises the question of a possible link between left DLPFC stimulation and the improvement of positive symptoms. Interestingly, 20 Hz rTMS-stimulation applied to the left DLPFC showed significant improvement of BPRS scores in one small double-blind crossover trial by Rollnik et al. (N = 12) (Rollnik et al., 2000), whereas three other studies with rTMS stimulation applied to the left DLPFC showed no effect on positive symptoms (Hajak et al., 2004; Holi et al., 2004; Sachdev et al., 2005). Our effect of left DLFPC stimulation on PANSS positive scale is not presumed to be a direct effect, but this improvement of patients treated with clozapine supports the idea that these patients were not completely resistant to biological treatments and that the stimulation induced a more global improvement.

In current clinical practice, the treatment options for patients who are unresponsive or poorly responsive to clozapine are limited. The evidence for the effectiveness of psychopharmacological interventions for clozapine-refractory schizophrenia is scant, with many RCTs of poor quality (Siskind et al., 2018). Similarly psychological therapies have shown limited or absent effectiveness (de Paiva Barretto et al., 2009; Morrison et al., 2018). Electroconvulsive therapy as an add-on for patients on clozapine is most promising (Lally et al., 2016; Petrides et al., 2015). Compared to ECT as clozapine add-on, rTMS as add-on is discussed to have less side effects (Arumugham et al., 2016), whereas the efficacy of ECT in this situation is still discussed to be the best (Siskind et al., 2018). Notably, none of these interventions have been credibly shown to be effective for negative symptoms.

rTMS may be an effective augmentation option for poor or non-response to clozapine, with a low rate of side-effects, particularly for positive symptoms. However, in general the response to rTMS shows high variability and a set of factors have been identified as a possible explanation, such as age, gender, time of day, physical activity, prior history of synaptic activity, current state of the stimulated cortex, interneuron networks or genetics (Ridding and Ziemann, 2010). Since clozapine treatment induces neuroplastic changes (Ahmed et al., 2008; Konradi and Heckers, 2001; Morais et al., 2017) and specifically affects certain cortical parameters measured via TMS and EMG-detection such as cortical silent period (CSP) and short-interval cortical inhibition (SICI), compared to other antipsychotics (Liu et al., 2009), clozapine may prime possible rTMS responders.

The limitations of this secondary analysis of the RESIS trial are obvious: Since the analysis of the primary endpoint, negative symptoms, did not demonstrate significant results (Wobrock et al., 2015), subsequent secondary analyses showing a positive effect of rTMS treatment

(notably change in PANSS total, general and positive/negative subscales) should be viewed with caution due to a limitation in statistical power as previously outlined elsewhere (Hasan et al., 2016). Second, our sample of clozapine patients still represents a small number of cases. Finally, our sample consists of patients with predominant negative symptoms and for this reason significant improvements in the positive subscale might be caused by non-specific effects of rTMS treatment. Finally, the between-group comparisons were non-significant. In the original RESIS sample, we showed a correlation between negative and depressive symptoms (Wobrock et al., 2015), but the here presented sample could be underpowered to detect such a relationship. However, we are aware that negative and depressive symptoms can overlap and the differentiation is challenging. Thus, based on our correlation analyses we cannot rule out that parts of the reported improvements in the sham group are due to an improvement in depressive symptoms. For those reasons, our significant results in the LMM analysis should be interpreted with caution. However, our findings may encourage researchers to investigate the capacity of rTMS as an add-on treatment to clozapine in future prospective clinical trials, especially under application of clozapine-resistance criteria (Howes et al., 2017).

5. Conclusions

In the largest available cohort of clozapine patients with an rTMS vs. sham intervention so far, significant time × group interactions could be detected in the LMM analysis of the PANSS positive subscale, the PANSS general subscale and the PANSS total scale. This re-analysis took into account data on clozapine patients with a rTMS−/sham-intervention within a relatively long follow-up period (from screening until day 105) so that possible ongoing effects of rTMS after the 3-week intervention could be investigated for the first time in a clozapine-rTMS cohort. We could detect significant improvements in three PANSS subscales due to high-frequency active rTMS in our LMM analysis. However, our preliminary finding has to be interpreted with caution due to a low number of cases. Future prospective trials should investigate rTMS as an add-on treatment option, especially among clozapine-resistant or ultra-treatment-resistant patients with a preferably long-term follow-up period.

Conflict of interest

E. Wagner reports no conflicts of interest. T. Wobrock has received paid speakerships from Alpine Biomed, AstraZeneca, Bristol Myers Squibb, Eli Lilly, I3G, Janssen Cilag, Novartis, Lundbeck, Roche, Sanofi-Aventis, Otsuka and Pfizer, is an advisory board member of Janssen Cilag and Otsuka/Lundbeck and has accepted travel or hospitality not related to a speaking engagement longer than 5 years ago 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). B. Kunze had no conflict of interest. J. Cordes 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, research and study participation funded by the German Research Foundation and the German Bundesministerium für Bildung und Forschung, Foundation European Group for Research In Schizophrenia, ACADIA Pharmaceuticals Inc., Boehringer Ingelheim Pharma GmbH & Co. KG, Otsuka Pharmaceutical Europe Ltd. and EnVivo Pharmaceuticals. W. Wölwer 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. Winterer is Chief Executive Officer of Pharmaimage Biomarker Solutions GmbH Berlin Germany and President of Pharmaimage Biomarker Solutions Inc. Boston USA. W. Gaebel 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. Langguth is an advisory board member of Neuromod and Desyncra, received honoraria and speakers' fees from ANM, Astra Zeneca, Autifony, Lundbeck, Merz, Magventure, Neurolite, 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, Astra Zeneca, Cerbomed, Neuromod, Otonomy and Sivantos, funding for equipment from Magventure and Deymed and travel and accommodation payments from Lilly, Lundbeck, Servier and Pfizer. M. Landgrebe had no conflict of interest. P. Eichhammer had no conflict of interest. E. Frank had no conflict of interest. G. Hajak has received payments as speaker, consultant, author or for research funding during the last 5 years from Actelion, Affectis, Astra-Zeneca, 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. Ohmann had no conflict of interest. P. Verde had no conflict of interest. M. Rietschel had no conflict of interest. R. Ahmed had no conflict of interest. W.G. Honer 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. D. Siskind has no conflict of interest. B. Malchow had no conflict of interest. W. Strube has received paid speakership by Mag & More. T. Schneider-Axmann had no conflict of interest. P. Falkai was honorary speaker for Janssen-Cilag, Astra-Zeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 yearshe was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. Presently, he is a member of the advisory boards of Richter Pharma, Abbot and Otsuka. A. Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakerships from Desitin, Janssen-Cilag, Otsuka and Lundbeck. He was member of Roche, Otsuka, Lundbeck and Janssen-Cilag advisory boards.

Contributors

Author TSA undertook the statistical analysis and author EW wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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