Efficacy of high-frequency repetitive transcranial magnetic stimulation on PANSS factors in schizophrenia with predominant negative symptoms – Results from an exploratory re-analysis

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1. Introduction

In general, negative symptoms contribute substantially to the disease-associated burden (Buchanan, 2007) of schizophrenia. They have primarily been defined as an absence of normal behaviours, including social withdrawal, lack of initiative and pleasure, flattened emotional response and poverty of speech (Andreasen and Flaum, 1991). Prefrontal high-frequency repetitive transcranial magnetic stimulation (rTMS) has been investigated regarding its capacity to improve negative symptoms in schizophrenia patients (Lefaucheur et al., 2014). It is hypothesized that rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) may increase local cortical activity to compensate for the pathological hypofrontality (Andreasen et al., 1997; Hill et al., 2004; Jin et al., 2006; Lefaucheur et al., 2014). Moreover, it is discussed that prefrontal high-frequency rTMS has the potential to modulate extrastriatal and mesostriatal dopaminergic pathways that may be involved in the pathophysiology of schizophrenia negative symptoms (Cho and Strafella, 2009; Strafella et al., 2001). One meta-analysis of 13 publications (N = 328 participants) (Shi et al., 2014) showed a beneficial effect of high-frequency rTMS for this indication, whereas one recent meta-analysis of 7 publications (N = 412) could not establish this superiority of active rTMS compared to sham rTMS (He et al., 2017). Apart from methodological differences in terms of stimulation frequency, stimulation duration or control conditions, different definitions and measures of negative symptoms may contribute to the inter-study heterogeneity. Several psychometric interviews and scales are available to evaluate negative symptoms in schizophrenia (Garcia-Portilla et al., 2015). In 2011 and 2013 the clinical assessment interview for negative symptoms (CAINS) and the brief negative symptom scale (BNSS) were published and recommended for the use in clinical schizophrenia trials (Kirkpatrick et al., 2011; Kring et al., 2013). Earlier rTMS trials used mainly the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) to assess negative symptoms, whereas more recently published trials also used the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). It has to be mentioned that some rTMS trials showed an improvement of negative symptoms when analysing the SANS, but not when analysing the PANSS negative subscale (Dlabac-de Lange et al., 2015; Prikryl et al., 2007; Prikryl and Kucerova, 2013) and the largest available meta-analysis revealed higher effect sizes (0.8 vs. 0.41) when the SANS rather than the PANSS negative subscale was investigated (Shi et al., 2014). These findings indicate that different and more specific assessments of negative symptoms may be needed and that the PANSS negative subscale may be not optimal to disentangle a specific effect of rTMS for this indication.

The PANSS is a semi-structured diagnostic interview to assess typical symptom domains of schizophrenia and contains a balanced representation of three subdomains: (Positive symptoms (7 items), Negative symptoms (7 items) and General Pathology (16 items)). Each of the 30 PANSS items is rated using a 7-point scale where 7 represents the highest severity and 1 the absence of the symptom (Garcia-Portilla et al., 2015; Kay et al., 1987). Since its introduction, the PANSS is the most widely used assessment tool to measure psychopathology in schizophrenia treatment trials and is considered to be suitable to assess positive, negative and general symptoms in relation to each other (Kane, 2013). Despite its widespread use in clinical trials, considerable controversy exists about that three-subdomain structure and whether it is precise enough to capture and distinguish the complex psychopathology of schizophrenia. Moreover, the PANSS negative symptoms subscale has been discussed not to represent negative symptoms adequately, because avolition and anhedonia are not sufficiently covered (Garcia-Portilla et al., 2015; Marder et al., 2011). Therefore, various PANSS factor analyses with 2–7 alternative PANSS factors have been developed to overcome this inherent limitation of PANSS (Lieburg et al., 2013; Marder et al., 2011, 1997; Wallwork et al., 2012). Due to the diversity and multidimensionality of negative symptoms in schizophrenia, Lieburg et al., (2013) investigated whether negative symptoms assessed by PANSS can be assigned to two major domains. On the base of exploratory and confirmatory factor analysis two PANSS subdomains for negative symptoms in psychotic disorders were established. One factor (core negative symptoms) consisted of the PANSS items flat affect, poor rapport, lack of spontaneity, mannerisms and posturing, motor retardation, and avolition. The second factor (social emotive withdrawal) was composed of emotional withdrawal, passive social withdrawal, and active social avoidance (Lieburg et al., 2013). In the search for a broad consensus PANSS factor model, Wallwork et al. compared 29 literature derived five-factor PANSS models (Wallwork et al., 2012). After analysing factor loadings for the individual PANSS items and factor-to-subscale correlations they finally proposed a five-factor-model with 20 items, categorized into positive, negative, disorganized, excited and emotional/depressed PANSS factors (Wallwork et al., 2012).

Based on the largest available rTMS trial on the treatment of negative symptoms in schizophrenia, we aimed to explore the relationship between rTMS efficacy and different multidimensional PANSS factors with an emphasis on alternative negative symptom factors. To achieve this overall goal, we re-analyzed the available data of the Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Negative Symptoms in Schizophrenia (RESIS) trial (Wobrock et al., 2015). In the RESIS intention-to-treat (ITT) analysis, active rTMS was not superior to sham rTMS in improving negative or other symptoms in schizophrenia (Wobrock et al., 2015). For the here presented analyses, we first used the PANSS negative symptom two-factor model (Lieburg et al., 2013) to disentangle the specific rTMS effects on different negative symptom factors. In a second exploratory step, we applied the PANSS consensus five-factor model (Wallwork et al., 2012) for a broader analysis of rTMS effects on schizophrenia symptom domains.

2. Material and methods

2.1. Study subjects and intervention

From 2007–2011, 197 patients with schizophrenia and predominant negative syndrome were screened for the RESIS trial. Of those, 175 patients were enrolled and randomly assigned to one of the two treatment arms of this multicenter randomized controlled trial. 157 patients received either active (N = 76) or sham (N = 81) rTMS treatment and at least one PANSS assessment prior to the rTMS intervention. At all centers the MagPro X100 stimulator (Medtronic A/S, Copenhagen, Denmark) with a passively cooled figure-of-eight coil (Medtronic A/S) was used for rTMS and the stimulated target region for active rTMS was determined with the EEG International 10–20 system (F3 electrode, left DLPFC) (Herwig et al., 2001, 2003; Homan et al., 1987). Stimulation parameters were: 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). Patients randomized to sham rTMS received the identical treatment, but the stimulation coil was tilted over one wing at an angle of 45 degrees (Lisanby et al., 2001; Wobrock et al., 2015). The complete study description of the RESIS trial (including blinding and randomization procedures) and the primary endpoint analysis appears elsewhere (Cordes et al., 2009; Wobrock et al., 2015). The RESIS trial was registered at http://clinicaltrials.gov/ with the number: NCT00783120.

2.2. Efficacy measures (PANSS factors)

For this secondary analysis, we first calculated the two factors for negative symptoms in psychotic disorders as established by Lieburg et al. (2013). This approach comprises six PANSS items categorized to factor 1 (= core negative symptoms: N1 + N3 + N6 + G5 + G7 + G13) and three items in factor 2 (= social and emotive withdrawal: N2 + N4 + G16) (Lieburg et al., 2013). This first analysis was performed to provide an

alternative approach to the primary outcome of RESIS (change in PANSS negative subscale after three weeks) (Wobrock et al., 2015) that may have allowed to detect active-sham-differences. Next, we decided to provide an alternative approach for RESIS secondary outcomes (change in the other PANSS subscales, change in depressive symptoms) (Wobrock et al., 2015) by using the PANSS five-factor consensus model (Wallwork et al., 2012). This model comprises 20 PANSS items categorized to the following 5 factors: positive factor (P1 + P3 + P5 + G9), negative factor (N1 + N2 + N3 + N4 + N6 + G7), disorganized factor (P2 + N5 + G11), excited factor (P4 + P7 + G8 + G14) and emotion/depression factor (G2 + G3 + G6). These exploratory analyses were performed with the intention to detect novel effects of rTMS on other schizophrenia symptom domains than tested in our primary analyses (Wobrock et al., 2015). We first calculated the change of the described PANSS factors after three weeks of intervention (day 0 to day 21) and then extended our analyses for the complete RESIS timespan (screening phase up to day 105).

2.3. Statistical analyses

All analyses were carried out in SPSS23 (IBM Inc.) with a significance level of $\alpha = 0.05$. The normality of all outcome variables was examined with Kolmogorov-Smirnov tests and Levene's test was used to check variance homogeneity. For the intention-to-treat population, all outcome parameters (PANSS factors) were analyzed with general linear mixed model analysis, nonrestrictively assuming an unstructured covariance matrix (Krueger and Tian, 2004) in accordance to foregoing publications (Wobrock et al., 2015). Group (active rTMS vs. sham rTMS) was the between-subject factor and time (pre rTMS vs. post rTMS) was the within-subject factor. The first analysis used day 0 as starting point and day 21 as study endpoint (before and directly after the rTMS intervention). For consecutive analyses of the follow-up period, we extended the model from the screening phase to day 105 (end of extension phase). Group x time interaction were contrasted to test whether PANSS factor changes over time depend on the respective group membership. In case of significance, post hoc comparisons day 21 vs. day 0 were performed separately for each group on the one hand, and for each item from which the concerning factor was constructed on the other hand. All analyses for PANSS factors were controlled for study center and gender. Correlation analyses were performed between PANSS factors and age, years of education and CPZ equivalents. If they showed a significant influence linear mixed model was additionally adjusted for these covariates (that were CPZ equivalents at treat0 for PANSS positive factor, education for disorganized and excited factor). Baseline between-group differences were analyzed with independent *t*-tests and χ^2-tests. As the concerning data was not normally distributed, baseline CGI scores were compared using Mann-Whitney *U*-test and CPZ equivalents were logarithmically transformed and then analyzed. Although we were able to provide a relatively large sample it was only possible to present an exploratory analysis concerning the two PANSS factor-models. The significance level of $\alpha = 0.05$ was not adjusted. Therefore, the results must be interpreted with caution, as the probability for random results is larger than in prospective analyses.

3. Results

3.1. Study subjects

The here presented analyses were performed 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). Baseline characteristics of both study groups are displayed in Table 1. Apart from a significant difference in gender distribution no significant differences in sociodemographic or clinical characteristics exist. The Consolidated Standards of Reporting Trials (CONSORT) diagram and the study plan have been published elsewhere (Wobrock et al., 2015). Sample sizes for each time point of the here presented analyses are described in the figure legends.

3.2. Normality, variance homogeneity

For all PANSS factors, Kolmogorov-Smirnov tests detected no significant deviation from normal distribution assumption. Levene's tests did not result into significant variance inhomogeneities except for PANSS negative factor 1 (Lieburg) before start of the intervention (= day 0) (verum: standard deviation = 4.24, sham: standard deviation = 3.57; $p = 0.011$). In order to ensure comparability between the approaches parametric linear mixed model was used for all PANSS factors.

3.3. Two-factor model on negative symptoms

No baseline differences between both study groups could be detected for any of the analyzed PANSS factors (see Table 1).

3.4. Short-term effects on the two-factor model

PANSS negative factor 1 ($F_{(1,\ 117.5)} = 19.3$, $p < 0.0005$) and factor 2 ($F_{(1,\ 121.3)} = 31.1$, $p < 0.0005$) improved in both groups from day 0 to day 21, but no significant group · time interaction could be observed (factor 1: $F_{(1,\ 115.4)} = 0.4$, $p = 0.54$; factor 2: $F_{(1,\ 119.2)} = 0.6$, $p = 0.42$).

3.5. Long-term effects on the two-factor model

The same pattern could be observed for the extended analyses from screening to day 105 confirming a significant effect of time for both factors (factor 1: $F_{(6,\ 106.1)} = 9.4$, $p < 0.0005$; factor 2: $F_{(6,\ 106.9)} = 16.10$, $p < 0.0005$), but no significant group · time interaction (factor 1: $F_{(6,\ 102.7)} = 0.4$, $p = 0.90$; factor 2: $F_{(6,\ 104.7)} = 1.4$, $p = 0.21$). Table 2 contains descriptive statistics at day 0 and at day 21 and results for interactions between time (day 21 vs day 0) and group including effect sizes. Please see also Fig. 1 for a visualization of the time course and the sample size per time point.

3.6. Consensus five-factor PANSS model (positive and negative symptoms, disorganization, excitement and emotion (Wallwork et al., 2012))

No baseline differences between both study groups could be detected for any of the analyzed five PANSS factors (see Table 1).

3.7. Short-term effects on the five-factor model

Apart from the PANSS excitement factor ($F_{(1,\ 122)} = 1.4$, $p = 0.24$) and from PANSS positive factor ($F_{(1,\ 119.4)} = 1.5$, $p = 0.23$), all other factors improved significantly independent of group until day 21 (PANSS negative factor: $F_{(1,\ 117.1)} = 33.0$, $p < 0.0005$; PANSS disorganization factor: $F_{(1,\ 118)} = 8.4$, $p = 0.005$; PANSS emotion/depression factor: $F_{(1,\ 124.3)} = 8.2$, $p = 0.005$). For PANSS excitement factor, a significant group · time interaction ($F_{(1,\ 120.4)} = 4.5$, $p = 0.035$) could be observed, however, only when no correction for multiple testing was applied. This interaction was post-hoc contrasted by paired samples *t*-tests showing an improvement in the active rTMS group ($t_{(58)} = 2.4$, $p = 0.021$), but no changes in the sham group ($t_{(59)} = -0.6$, p = 0.57), pointing to a larger PANSS improvement (day 21 vs. day 0) in the active rTMS group. All other interactions were not significant (PANSS negative factor: $F_{(1,\ 115.6)} < 0.1$, $p = 0.86$; PANSS positive factor: $F_{(1,\ 114)} = 1.5$, $p = 0.22$; PANSS disorganization factor: $F_{(1,\ 115.2)} = 0.3$, $p = 0.57$; PANSS emotion/depression factor: $F_{(1,\ 121.3)} = 2.6$, $p = 0.11$).

3.8. Long term effects on the five-factor model

The extended analyses including follow-up data until day 105 also

Table 1
Baseline characteristics.

	Active rTMS ($N = 71$)		Sham rTMS ($N = 75$)		Active vs. Sham		
Variable					LR χ^2	df	p
Gender (male : female)	59 : 12		51 : 24		4.5	1	0.034[a]
Employment (employed : not employed)	14 : 57		10 : 65		1.1	1	0.30[a]
Center (Duesseldorf : Goettingen : Regensburg)	20 : 24 : 27		21 : 24 : 30		0.1	2	0.96[a]
Hand preference (right : not right)	58 : 10		61 : 10		0.0	1	0.92[a]
Antidepressant use (yes : no)	28 : 43		27 : 47		0.1	1	0.71[a]
	Mean	SD	Mean	SD	F	df	p
Age, yr	35.8	10.3	35.4	9.1	0.1	1, 144	0.80[b]
Education, yr	11.5	1.9	11.3	2.0	0.3	1, 139	0.58[b]
Left resting motor threshold	46.6	8.1	46.9	11.7	0.0	1, 129	0.88[b]
Severity of illness and treatment							
Liemburg PANSS negative Factor1[c]	17.97	4.39	18.01	3.45	0.0	1, 144	0.95[b]
Liemburg PANSS negative Factor2[c]	10.93	2.39	10.75	2.52	0.2	1, 144	0.65[b]
Wallwork PANSS Positive[d]	7.91	3.33	7.19	2.77	2.0	1, 142	0.16[b]
Wallwork PANSS Negative[d]	20.96	4.24	21.24	3.57	0.2	1, 144	0.66[b]
Wallwork PANSS Disorganization[d]	9.59	2.81	9.04	2.82	1.4	1, 144	0.24[b]
Wallwork PANSS Excitement[d]	6.66	2.18	6.31	2.03	1.0	1, 144	0.31[b]
Wallwork PANSS Emotion[d]	8.28	3.19	7.32	3.09	3.4	1, 143	0.069[b]
Clinical Global Impression score for severity[e]	4.6	0.9	4.7	0.9	$Z = -0.6$	1	0.57[f]
Global Assessment of Functioning[g]	52.0	11.7	52.5	10.9	0.1	1, 135	0.78[b]
Antipsychotic dose (chlorpromazine equivalents), mg/day	564	433	583	468	0.0	1, 137	0.97[h]
Depression related							
Calgary Depression Scale for Schizophrenia[i]	5.1	3.6	5.1	3.9	0.0	1, 141	0.95[b]
Montgomery Asberg Depression Rating Scale[j]	14.8	6.1	13.5	6.2	1.6	1, 143	0.21[b]

Abbreviations: LR χ^2, likelihood ratio chi square statistic; df, degrees of freedom; SD, standard deviation; F, F statistic; Z, Z statistic; yr, years; mg, milligram.
[a] Comparison by likelihood ratio test.
[b] Comparison by analysis of variance.
[c] PANSS category as calculated by Liemburg et al. (2013) (compare section Efficacy Measures (PANSS factors)).
[d] PANSS category as calculated by Wallwork et al. (2012) (compare section Efficacy Measures (PANSS factors)).
[e] The Clinical Global Impression score for severity ranges from 1 (not mentally ill) to 7 (extremely ill).
[f] Comparison by Mann-Whitney U-test.
[g] The Global Assessment of Functioning score ranges from 1 to 100, with higher scores indicating better functioning.
[h] Comparison on logarithmic transformed variable by analysis of variance.
[i] The Calgary Depression Scale for Schizophrenia ranges from 0 to 27, with higher scores indicating more severe depression.
[j] The Montgomery Asberg Depression Rating Scale ranges from 0 to 60, with higher scores indicating more severe depression.

showed significant time effects for PANSS negative factor ($F_{(6,\ 105)} = 17.9$, $p < 0.0005$), PANSS positive factor ($F_{(6,\ 101.5)} = 5.5$, $p < 0.0005$), PANSS disorganization factor ($F_{(6,\ 110.3)} = 6.2$, $p < 0.0005$) and PANSS emotion/depression factor ($F_{(6,\ 111.8)} = 4.4$, $p < 0.0005$) and a trend towards an effect for PANSS excitement factor ($F_{(6,\ 103)} = 2.1$, $p = 0.054$). Again, no significant time · group interaction for the aforementioned 4 factors (PANSS negative factor: $F_{(6,\ 101.9)} = 0.6$, $p = 0.70$; PANSS positive factor: $F_{(6,\ 95.3)} = 1.2$, $p = 0.34$; PANSS disorganization factor: $F_{(6,\ 105.5)} = 0.6$, $p = 0.72$; PANSS emotion/depression factor: $F_{(6,\ 107)} = 0.7$, $p = 0.64$) were observed, and

Table 2
Descriptive Statistics at baseline and directly after the intervention. Results from mixed model analyses for interaction between group and time including effect sizes.

	Active rTMS				Sham rTMS							
	Day 0 ($N = 71$)		Day 21 ($N = 60$)		Day 0 ($N = 75$)		Day 21 ($N = 62$)		Interaction between group and time of measurement			
Outcome measure	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	F	df	p[a]	Effect Size[b]
PANSS Factor												
Liemburg PANSS negative Factor1[c]	17.97	4.39	17.13	5.14	18.01	3.45	16.39	4.29	1.5	1, 114.0	0.22	0.12
Liemburg PANSS negative Factor2[c]	10.93	2.39	9.57	2.88	10.75	2.52	9.68	3.03	0.0	1, 115.6	0.86	− 0.08
Wallwork PANSS Positive[d]	7.91	3.33	7.33	3.08	7.19	2.77	6.97	3.20	0.4	1, 115.4	0.54	− 0.18
Wallwork PANSS Negative[d]	20.96	4.24	19.03	5.57	21.24	3.57	18.85	5.18	0.6	1, 119.2	0.42	0.11
Wallwork PANSS Disorganization[d]	9.59	2.81	8.98	2.77	9.04	2.82	8.46	2.85	0.3	1, 115.2	0.57	0.01
Wallwork PANSS Excitement[d]	6.66	2.18	6.07	1.89	6.31	2.03	6.35	2.46	4.5	1, 120.4	0.035	0.29
P4: Excitement	2.15	1.11	1.88	1.17	1.92	1.09	1.82	1.19	2.1	1, 115.0	0.15	0.15
P7: Hostility	1.28	0.56	1.12	0.32	1.25	0.55	1.29	0.78	3.5	1, 109.4	0.062	0.35
G8: Uncooperativeness	1.39	0.84	1.22	0.56	1.25	0.57	1.37	0.73	3.7	1, 114.5	0.058	0.44
G14: Poor Impulse control	1.87	1.03	1.87	1.02	1.88	0.93	1.87	0.98	0.1	1, 115.1	0.83	0.01
Wallwork PANSS Emotion[d]	8.28	3.19	7.20	2.59	7.32	3.09	7.08	3.30	2.6	1, 121.3	0.11	0.27

[a] Results from intention-to-treat analysis, statistics for interaction between group and time of measurement.
[b] According to Cohen's d, 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 day 0 for each group, then determining the difference between the two groups (rTMS active, control subjects) and dividing the results by the pooled standard deviations. Therefore, negative effect sizes indicate an advantage for placebo as compared with the verum group.
[c] PANSS factor as calculated by Liemburg et al. (2013) (compare section Efficacy Measures (PANSS factors)).
[d] PANSS factor as calculated by Wallwork et al. (2012) (compare section Efficacy Measures (PANSS factors)).

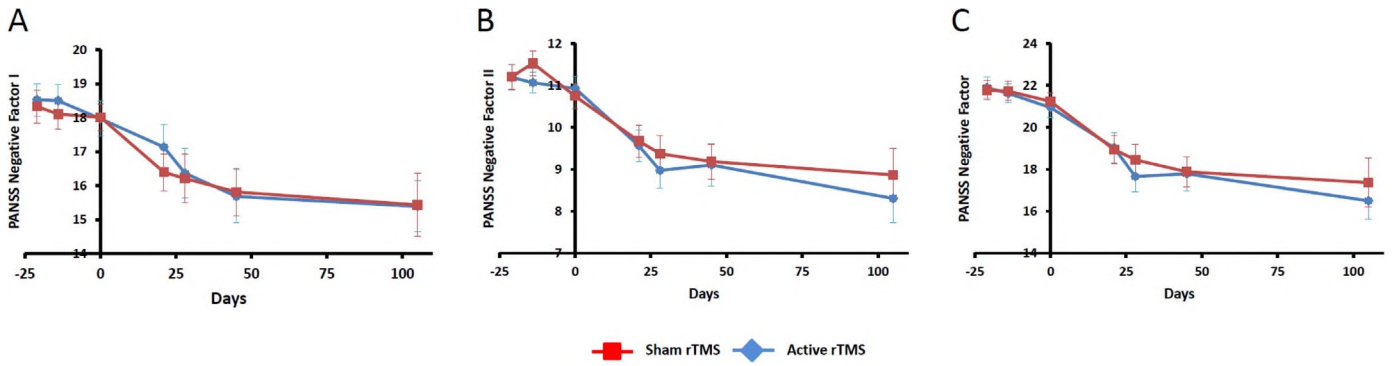

Fig. 1. Represent the data for PANSS negative factor 1 and 2 according to Liemburg et al. (2013) and PANSS negative factor according to Wallwork et al. (2012) between screening and day 105. PANSS negative factor 1 (A) consists of PANSS N1 + N3 + N6 + G5 + G7 + G13 and the following *N* were used for analyses: Verum: Screening: $N = 72$, Baseline: $N = 72$, Treat 0: $N = 71$, Treat 21: $N = 60$, FU 28: $N = 41$, FU45: $N = 38$, FU105: $N = 36$; Sham: Screening: $N = 76$, Baseline: $N = 76$, Treat 0: $N = 75$, Treat 21: $N = 61$, FU 28: $N = 48$, FU45: $N = 43$, FU105: $N = 30$. PANSS negative factor 2 (B) consists of PANSS N2 + N4 + 16 and the following *N* were used for analyses: Verum: Screening: $N = 72$, Baseline: $N = 72$, Treat 0: $N = 71$, Treat 21: $N = 60$, FU 28: $N = 41$, FU45: $N = 38$, FU105: $N = 36$; Sham: Screening: $N = 76$, Baseline: $N = 77$, Treat 0 $N = 75$, Treat 21: $N = 62$, FU 28: $N = 48$, FU45: $N = 43$, FU105: $N = 30$. PANSS negative factor (Wallwork) (C) consists of PANSS N1 + N2 + N3 + N4 + N6 + G7 and the following *N* were used for analyses: Verum: Screening: $N; = 72$, Baseline: $N = 72$, Treat 0: $N = 71$, Treat 21: $N = 60$, FU 28: $N = 41$, FU45: $N = 38$, FU105: $N = 36$. Sham: Screening: $N = 76$, Baseline: $N = 77$, Treat 0: $N = 75$, Treat 21: $N = 61$, FU 28: $N = 48$, FU45: $N = 43$, FU105: $N = 30$. Error bars represents standard errors of the mean.

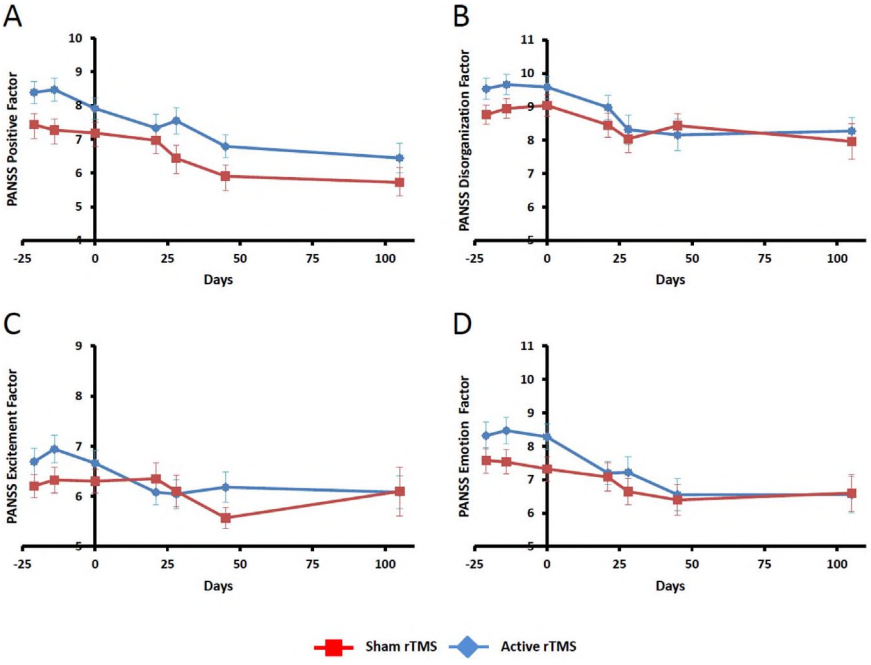

Fig. 2. Represent the data for PANSS positive, disorganization, excitement and emotion factors from the Wallwork PANSS factors between screening and day 105. A to D are calculated according to Wallwork et al. (2012). PANSS positive factor (A) consists of PANSS P1 + P3 + P5 + G9 and the following *N* were used for analyses: Verum: Screening: $N = 72$, Baseline: $N = 72$, Treat 0: $N = 70$, Treat 21: $N = 60$, FU 28: $N = 40$, FU45: $N = 38$, FU105: $N = 36$; Sham: Screening: $N = 76$, Baseline: $N = 77$, Treat 0: $N = 74$, Treat 21: $N = 62$, FU 28: $N = 48$, FU45: $N = 43$, FU105: $N = 29$. PANSS excitement factor (B) consists of PANSS P4 + P7 + G8 + G14 and the following N were used for analyses: Verum: Screening: $N = 72$, Baseline: $N = 72$, Treat 0: $N = 71$, Treat 21: $N = 60$, FU 28: $N; = 41$, FU45: $N = 38$, FU105: $N = 36$; Sham: Screening: $N; = 76$, Baseline: $N = 76$, Treat 0: $N = 75$, Treat 21: $N = 62$, FU 28: $N = 48$, FU45: $N = 42$, FU105: $N = 30$. PANSS disorganization factor (C) consists of PANSS P2 + N5 + G11 and the following *N* were used for analyses: Verum: Screening: $N = 72$, Baseline: $N = 72$, Treat 0: $N = 71$, Treat 21: $N = 59$, FU 28: $N = 41$, FU45: $N = 38$, FU105: $N = 36$; Sham: Screening: $N = 76$, Baseline: $N = 77$, Treat 0: $N = 75$, Treat 21: $N = 61$, FU 28: $N = 47$, FU45: $N = 41$, FU105: $N = 39$. PANSS emotion factor (D) consists of PANSS G2 + G3 + G6 and the following *N* were used for analyses: Verum: Screening: $N = 72$, Baseline: $N = 72$, Treat 0: $N = 71$, Treat 21: $N = 59$, FU 28: $N = 41$, FU45: $N = 38$, FU105: $N = 36$; Sham: Screening: $N = 76$, Baseline: $N = 77$, Treat 0: $N = 74$, Treat 21: $N = 62$, FU 28: $N = 48$, FU43: $N = 42$, FU105: $N = 30$. Error bars represents standard errors of the mean.

there was only a trend for time · group interaction for the PANSS excitement factor ($F_{(6,\ 99.8)} = 2.1$, $p = 0.055$). While in the active rTMS group, the PANSS excitement factor at follow-up remained approximately at the level of day 21, in the sham group, the PANSS excitement factor improved from day 21 to day 45, ranging even at a better level than active rTMS patients at this time, however at the end of the study the PANSS excitement factor was at about the same level in both groups. (Please see Table 2 for more details and Fig. 2 for a visualization of the time course and its legend for the sample size per time point.)

4. Discussion

This is the first analysis of the effects of high frequency rTMS applied to the left DLPFC on different PANSS factors in large sample of schizophrenia patients suffering from predominant negative symptoms. Our results confirm and extend our previously reported negative findings on psychopathological outcomes in the RESIS sample (Wobrock et al., 2015). In the original intention-to-treat analysis, we could not establish a superiority 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) (Wobrock et al., 2015). Our new analyses using the two-factor PANSS approach to investigate negative symptoms (Liemburg et al., 2013) and the literature based five-factor consensus PANSS model (Wallwork et al., 2012) confirmed no beneficial impact of active rTMS on other negative symptom dimensions and supports our initial negative finding. However, our new analysis showed that the PANSS excitement factor improved in the active rTMS group significantly more than in the sham group, but this finding did not persist if follow-up data were taken into account.

The two-factor PANSS model (core negative symptoms and social emotive withdrawal) (Liemburg et al., 2013) and other related two-factor models (Jang et al., 2016) have been discussed to be superior to any single-factor analysis of negative symptoms. For pharmacological trials addressing negative symptoms, the original PANSS negative subscale (N1 to N7) has been discussed not to provide an adequate

representation of negative symptoms in clinical trials and that the corresponding PANSS data should be analyzed in accordance with the available factor models for negative symptoms (Marder et al., 2011). Several rTMS studies (Dlabac-de Lange et al., 2015; Prikryl et al., 2007; Prikryl and Kucerova, 2013) applied the SANS and the PANSS to assess the change in negative symptoms and showed a positive effect of rTMS exclusively on the SANS (Dlabac-de Lange et al., 2015; Prikryl et al., 2007; Prikryl and Kucerova, 2013). SANS and PANSS do correlate (Lyne et al., 2012; Rabany et al., 2011) and it is possible to convert symptom ratings between SANS and PANSS (van Erp et al., 2014). However, despite being related and measuring similar constructs (Rabany et al., 2011), both scales have differences and not all items of the SANS are covered by the PANSS negative symptom subscale. Some SANS-items are exclusively found in the general psychopathology scale of the PANSS (e.g. the SANS item "attention" corresponds to "poor attention" (G11) of the PANSS). Therefore, different effects of rTMS on negative symptoms assessed by SANS or PANSS (Dlabac-de Lange et al., 2015; Prikryl et al., 2007; Prikryl and Kucerova, 2013) may be due to the finer structure of SANS. Therefore, the calculation of specific PANSS factor models, as presented here, has been proposed for an improved assessment of negative symptoms. One could speculate, that studies which have used the PANSS as an outcome measure and found no effects on negative symptoms, may show effects when the data is re-analyzed (e.g. with a factor analysis).

In our new analyses, both PANSS negative factors (Liemburg et al., 2013) improved over time irrespective whether patients were randomized to the active or sham rTMS group. As the here used PANSS negative symptom factors include several items from the PANSS general symptom subscale and allow to differentiate between expressive deficits and social amotivation (Liemburg et al., 2013), our results confirm that the initial negative finding cannot be explained by the use of the original PANSS negative subscale, but seems to represent a relevant lacking effect of prefrontal rTMS on different negative symptom dimensions in this sample. Moreover, the negative factor derived from the alternative five-factor model (Wallwork et al., 2012) also confirmed the previously described findings. In this context, the inclusion of motor retardation (G7) and active social avoidance (G16) and the exclusion of difficulty in abstract thinking (N5) and stereotyped thinking (N7) focus the analyses on core elements of schizophrenia negative symptoms.

In a second exploratory step, we extended our analyses using the PANSS five-factor consensus model (Wallwork et al., 2012) and we were not able to show a difference between active and sham rTMS for the PANSS positive factor, the PANSS negative factor (see also discussion above), the PANSS disorganization factor and the PANSS emotion/depression factor. This finding is in line with the original RESIS publication where we were not able to show group differences for PANSS general or depression scales (Wobrock et al., 2015). The previously published analyses showed a small, but unexpected improvement in positive symptoms exclusively in the active rTMS group that could only be explained in parts by a significant baseline difference (Wobrock et al., 2015). It is remarkable that the PANSS positive factor used in our analyses did not confirm this effect of PANSS positive subscale. The PANSS positive factor consists of P1 (delusions), P3 (hallucinatory behavior), P5 (grandiosity) and G9 (unusual thought content) and these 'positive symptoms' items are unlikely to be modulated by prefrontal rTMS, but may be responsive to temporal lobe rTMS (He et al., 2017; Lefaucheur et al., 2014). Interestingly, our new analyses showed that active, but not sham rTMS improved the PANSS excitement factor that consists of P4 (excitement), P7 (hostility), G8 (uncooperativeness) and G14 (poor impulse control). However, the PANSS excitement factor scores consisting of 4 PANSS items were rather low (< 7) already before the intervention and this finding would not survive correction for multiple comparisons. In a subsequent analysis we intended to discover, which of the four items of the PANSS excitement accounted for the time x group interactions. These analyses revealed only trends for interactions between group and time for the hostility score (P7, $p = 0.062$) and for the uncooperativeness score (G8, $p = 0.058$) towards a higher improvement in the active rTMS group. This was the case as the variance for the single PANSS items was larger than for the PANSS factors consisting of several items. For items P4 and G14 no significant for group $\times$ time interactions were observed. The PANSS excitement finding only persists for the data comparison between day 0 and day 21. When taking the follow-up data into account, the interaction between time and group was not significant. Especially at day 45 the processing of the PANSS excitement factor was changing with even smaller PANSS excitement scores for the sham compared to the active rTMS group. At day 105 the PANSS excitement factor scores were at the same level for active und sham rTMS. Therefore, the relevance of the reported PANSS excitement finding is limited.

As displayed in the figures and in Table 2, not only the active rTMS group but also the sham group showed a substantial improvement in most of the analyzed PANSS factors. Unspecific placebo (sham) effects related to the participation in a clinical trial, but also the everyday psychosocial care provided by study assistants during the intervention may have had a therapeutic effect on negative symptoms. One could speculate that the social stimuli related to the participation in the trial had such an impact on the negative symptoms that a potential effect of active rTMS disappeared in the statistical analyses.

This secondary analysis of the RESIS trial has several limitations. First of all, the analysis of the primary endpoint was negative (Wobrock et al., 2015) and all subsequent secondary analyses showing a positive effect of the intervention (here: change in PANSS excitement factor) are of limited statistical power and therefore subject to uncertainty. On the other hand, our analyses confirm the negative finding of the original publication and extend this finding to a broader negative symptom definition. Moreover, the new analyses provide a possible, but hypothetical explanation for the previously described effect of active rTMS on PANSS positive subscale. Of course, many other PANSS factor models are available and in pharmacological research the Marder factors (Janicak et al., 2009; Marder et al., 1997) have particular significance. However, the here used five-factor consensus model (Wallwork et al., 2012) includes the Marder factor results and our negative symptom factors overlaps with those factors. Another limitation is that it may be possible that our sham stimulation (coil tilted over one wing at an angle of 45° (Wobrock et al., 2015)) may still have been slightly biologically active as discussed elsewhere (Wobrock et al., 2015).

5. Conclusions

In summary, we applied two alternative approaches to analyze PANSS data in schizophrenia rTMS trials and the results support the findings of the original RESIS publication. Based on these secondary analyses, we can conclude that in our large multi-site clinical trial including schizophrenia patients with predominant negative symptoms, high-frequency active rTMS is not superior to sham rTMS in improving negative symptoms. Future trials should implement and combine more specific assessments for negative symptoms like the BNSS (Kirkpatrick et al., 2011), CAINS (Kring et al., 2013), SANS (Andreasen, 1982) or use reliable PANSS factors beyond the established PANSS subscales to stratify inclusion criteria and outcome as recently shown in pharmaceutical research (Nemeth et al., 2017).

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Conflict of interest

M. Hansbauer 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. 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, AstraZeneca, Eli Lilly, Bristol Myers-Squibb, Lundbeck, Pfizer, Bayer Vital, SmithKline Beecham, Wyeth, and Essex. During the last 5 years, but not presently, he was a member of the advisory boards of Janssen-Cilag, AstraZeneca, Eli Lilly, and Lundbeck. A. Hasan has been invited to scientific meetings by Lundbeck, Janssen-Cilag, and Pfizer, and he received paid speakerships from Desitin, Janssen-Colag, Otsuka and Lundbeck. He was member of Roche and Janssen-Cilag advisory boards.

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