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ORIGINAL INVESTIGATION

Repetitive transcranial magnetic stimulation (rTMS) for schizophrenia patients treated with clozapine

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ABSTRACT

Objectives: Biological strategies to improve treatment efficacy in clozapine-treated patients are urgently needed. Repetitive transcranial magnetic stimulation (rTMS) merits consideration as intervention for patients with persistent auditory hallucinations (AH) or negative symptoms (NS) not responding sufficiently to clozapine treatment.

Methods: Data from 10 international RCTs of rTMS for patients being treated with clozapine were pooled. Two levels of symptomatic response were defined: improvement of ≥20% and ≥50% on study-specific primary endpoint scales. Changes in the positive and negative syndrome scale (PANSS) from baseline to endpoint assessment were also analysed.

Results: Analyses of 131 patients did not reveal a significant difference for ≥20% and ≥50% response thresholds for improvement of AH, negative or total symptoms between active and sham rTMS groups. The number needed to treat (NNT) for an improvement in persistent AH was nine following active rTMS. PANSS scores did not improve significantly from baseline to endpoint between active and sham groups in studies investigating NS and AH.

Conclusions: rTMS as a treatment for persistent symptoms in clozapine-treated patients did not show a beneficial effect of active compared to sham treatment. For AH, the size of the NNTs indicates a possible beneficial effect of rTMS.

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Schizophrenia; meta-analysis; response; rTMS; clozapine

1. Introduction

Clozapine is an antipsychotic with superior effects on treatment-resistant positive symptoms among people with schizophrenia compared to other antipsychotics (Siskind et al. 2016). Nevertheless, treatment with clozapine is only effective in about 40% of these patients (Siskind et al. 2016) and the clinical need for add-on strategies for patients suffering from ongoing symptoms is highly prevalent. Finally, clozapine use for the indication of treatment-resistance is often delayed by several years (Howes et al. 2012), possibly due to barriers from prescribers and institutions (Verdoux et al. 2018). Thus, patients with delayed initiation of clozapine are at risk for poorer treatment outcomes (Shah et al. 2018). Evidence for add-on strategies specifically with regard to patients treated with clozapine is mainly available for patients with previously defined clozapine-resistance

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criteria, e.g. as suggested by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group (Howes et al. 2017). For these clinically defined clozapine-resistant schizophrenia (CRS) patients, pharmacological augmentation strategies show none or only minimal effects (Wagner et al. 2019). Addition of cognitive behavioural therapy (CBT) was shown to be negative in a high-quality trial by Morrison et al. (2018), but the number needed to treat (NNT) for a more than 50% PANSS improvement after 21 months was 15 suggesting that a small cohort of CRS patients might benefit from CBT. Of the neurostimulation treatment options, electroconvulsive therapy (ECT) shows promising results for clozapine-resistant positive symptoms (Lally et al. 2016; Siskind et al. 2018), but might be accompanied by a relatively higher rate of adverse events, such as anterograde and retrograde memory loss (Lally et al. 2016) when compared to other neurostimulation techniques (Arumugham et al. 2016). Repetitive transcranial magnetic stimulation (rTMS) represents another treatment option that is relatively safe (Arumugham et al. 2016), but the evidence for efficacy is still low in CRS due to a small number of trials applying clozapine-resistance criteria (de Jesus et al. 2011). According to meta-analytic data, rTMS treatment was superior and showed small up to moderate effect sizes for auditory hallucinations (AH) (Slotema et al. 2014; Kennedy et al. 2018) and negative symptoms (NS) (Aleman et al. 2018; Kennedy et al. 2018; Osoegawa et al. 2018) compared to sham, but also failed to show significant treatment effects (Huang et al. 2017). Since patients treated with clozapine show alterations in TMS neurophysiological responses, such as e.g. increased cortical inhibition (Daskalakis et al. 2008), clozapine might prime the likelihood for rTMS response. Moreover, for both rTMS (Huang et al. 2017) and clozapine (Konradi and Heckers 2001; Maeda et al. 2007) a plasticity enhancing effect has been proposed. Thus, one could hypothesise that the combination of both interventions may increase the likelihood for a plasticity-mediated treatment effect in schizophrenia patients.

Effects of rTMS on patients treated with clozapine have only been meta-analysed once with a small number of patients ($n = 17$) from one randomised-controlled trial (RCT) (de Jesus et al. 2011) and showed no difference in effects between active and sham rTMS for positive, negative and total symptoms (Siskind et al. 2018). On the other hand, results from a re-analysis of the largest rTMS trial for NS in schizophrenia (RESIS) (Wobrock et al. 2015) showed promising results for patients treated with clozapine and fulfilling CRS criteria (Wagner et al. 2019). To further investigate, rTMS response rates in schizophrenia patients treated with clozapine but still being symptomatic, we collected individual patient-level data of patients treated with clozapine who participated in RCTs that targeted either persistent AH or NS. The collected sample represents the largest database of schizophrenia patients being treated with clozapine and additionally with rTMS out of RCTs so far.

2. Methods

2.1. Selection of RCTs

Based on the most recent five meta-analyses (Slotema et al. 2014; Huang et al. 2017; Aleman et al. 2018; Kennedy et al. 2018; Osoegawa et al. 2018) including a total of 51 rTMS RCTs, we selected the source trials being used in our study by systematically contacting all corresponding authors and asking to extract clozapine patients datasets in the original datasets, if available. The strategy of identifying source data (here: RCTs) based on systematically developed meta-analyses is within the framework of national and international guideline development procedures. Our inclusion criteria were: (1) RCTs included in one of the five meta-analyses, (2) rTMS/sham intervention irrespective of the individual sample size, (3) availability of clozapine-treated patients and (4) availability of at least one outcome measure before and after intervention. The corresponding authors were contacted *via* mail in order to share anonymized datasets. Readers should be aware that due to the retrospective nature of this single-subject meta-analysis, CRS was not an inclusion criterion (see also discussion). Figure 1 presents a PRISMA-related (Moher et al. 2009) description of the selection process. In the end, 10 RCTs were included (Poulet et al. 2005; Novak et al. 2006; Cordes et al. 2010; Slotema et al. 2011; Blumberger et al. 2012; Klirova et al. 2013; Bais et al. 2014; Dlabac-de Lange et al. 2015; Wobrock et al. 2015; Koops et al. 2016) with a total number of $n = 152$ participants being treated with clozapine (31% of all participants). From these 152 participants, 21 were excluded due to missing data or diagnoses other than schizophrenia or schizoaffective disorder (Figure 1) resulting in a sample size of 131 for further analyses. The local ethics committee approved this project (*Reference number*: 19–307).

We included six trials using rTMS in patients with persistent AH targeting the left temporo-parietal cortex (TPC) (Poulet et al. 2005; Slotema et al. 2011; Blumberger et al. 2012; Klirova et al. 2013; Bais et al. 2014; Koops et al. 2016) and four trials using rTMS in

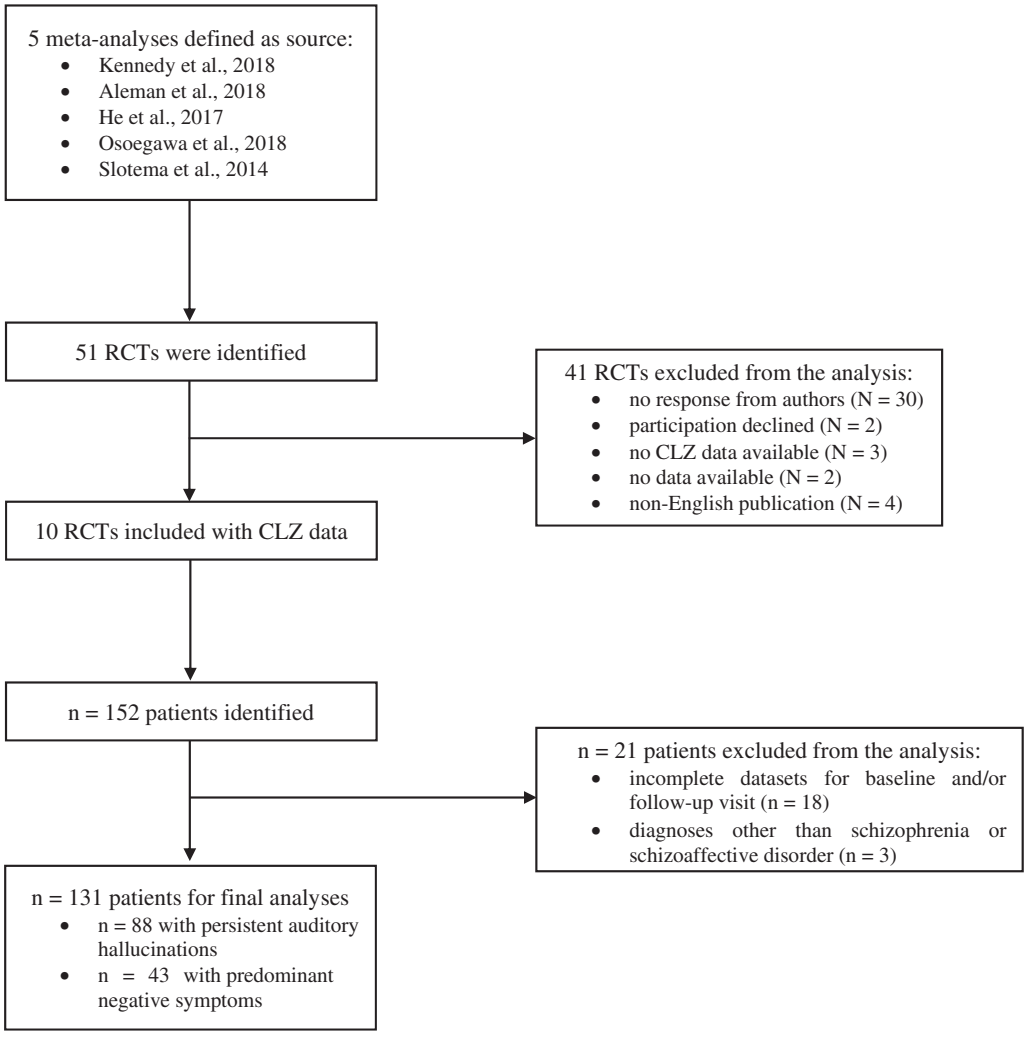

Figure 1. Overview of the data selection process. Identification and inclusion of RCTs with data of patients treated with clozapine. CLZ: clozapine; *N:* number of RCTs; *n:* number of patients.

patients with predominant NS targeting either the left dorsolateral prefrontal cortex (DLPFC) (Novak et al. 2006; Cordes et al. 2010; Wobrock et al. 2015) or both DLPFCs (Dlabac-de Lange et al. 2015) (Table 1). The individual trial characteristics are displayed in Table 1.

2.2. Endpoint definitions

To provide a measure with comparable characteristics across trials and outcome measures, we defined response as primary outcome measure. Response was in general defined as change of $\geq$20% and $\geq$50% after the intervention compared to baseline using the respective primary outcome scale (Samara et al. 2014) (Table 1). However, in one RCT, where P3 PANSS item was defined as primary outcome (Bais et al. 2014), we used the PANSS total score as primary endpoint of our analyses since we decided not to analyse single items. In another RCT, where the Clinical Global Impressions Scale (CGI) was the primary outcome (Cordes et al. 2010), we also used the PANSS total score as primary outcome since there is a high positive correlation between PANSS and CGI scores (Samara et al. 2014) and CGI is not primarily focussing on schizophrenia symptoms. PANSS was corrected for the established issue that the lowest possible score is not zero (Samara et al. 2014). For example, for PANSS total score, the relative change was computed as $1 - (PANSS_{total,\ endpoint} - 30)/(PANSS_{total,\ baseline} - 30)$.

The NNT was calculated by taking the inverse of the risk difference between active and sham rTMS (Laupacis et al. 1988). First, we assessed the primary outcome with regard to AH and NS studies. Then, in order to investigate overall effects of rTMS independent of the stimulation location, we analysed all patients in combined explorative analyses.

The secondary outcome measure was the PANSS total scale that has been the most frequently used

outcome measure across all 10 trials, irrespective of whether this scale was used as primary or secondary outcome. According to the procedure detailed above, we calculated response rates using PANSS total values. For relative change in PANSS total data, we corrected PANSS total data accordingly as described above. With regard to cross-over trials (Poulet et al. 2005; Klirova et al. 2013), we focussed on outcome data before the switch from sham to active or active to sham was performed.

2.3. Statistical analyses

Statistical analyses were carried out in SPSS version 25 (IBM, Armonk, NY), with a significance level of $\alpha = 0.05$. Baseline differences between groups (active *vs.* sham) were analysed using independent t-tests or *LR*-χ^2 tests. Response rates with $\geq$20% and $\geq$50% thresholds were compared using 2-sided Fisher's exact tests between groups. All analyses were separately performed for the group of patients with AH ($n = 88$), the group of patients with NS ($n = 43$) and the complete group ($n = 131$). Relative changes (post rTMS/baseline) in all PANSS scores between groups were analysed using independent t-tests. Next, a repeated measures analysis of variance (RM-ANOVA) with the within-subject factor TIME (pre- and post-intervention) and the between-subject factor GROUP (active *vs.* sham) was calculated for PANSS total, PANSS positive and PANSS negative raw values. Finally, we conducted sensitivity analyses for the different sham conditions by analysing the response rates with *LR* χ^2 tests in patients treated with active rTMS, sham rTMS with a sham coil and sham rTMS with a tilted active coil.

3. Results

3.1. rTMS parameters of included studies

3.1.1. AH studies

All studies were sham-controlled and except one single-blind study (Blumberger et al. 2012) all were double-blind. Three studies were using sham coil (Poulet et al. 2005; Bais et al. 2014; Koops et al. 2016) and three using tilted coil method (Slotema et al. 2011; Blumberger et al. 2012; Klirova et al. 2013) (Table 1).

3.1.2. NS studies

All studies were sham-controlled and double-blind. One study was using sham coil (Cordes et al. 2010) and three tilted coil method (Novak et al. 2006; Dlabac-de Lange et al. 2015; Wobrock et al. 2015) (Table 1).

3.2. Baseline characteristics

3.2.1. AH studies

Apart from a longer duration of illness in the sham group ($p = .028$), no significant baseline differences between groups were detected (Table 2).

3.2.2. NS studies

A significantly higher PANSS general score in the active group at baseline, but no other between-group differences, could be observed ($p = .033$) (Table 2).

3.2.3. AH and NS studies combined

No significant baseline differences between both intervention groups could be detected (Table 2).

3.2.4. AH vs. NS studies

Patients in the NS studies had significantly higher PANSS total ($t_{(109)} = -2.996$, $p = .003$), PANSS negative ($t_{(109)} = -8.046$, $p < .001$) and PANSS general scores ($t_{(109)} = -2.626$, $p = .010$) compared to AH studies. PANSS positive scores were significantly higher in AH studies than in NS studies ($t_{(108.48)} = 4.589$, $p < .001$).

3.3. Response rates

3.3.1. Symptomatic improvement $\geq$20% in the respective primary outcome

3.3.1.1. AH studies. Analyses showed no significant differences in response distribution between groups ($p = .295$) and a NNT of 9 patients (Table 3).

3.3.1.2. NS studies. No significant group differences between active and sham rTMS could be revealed ($p = .745$) with a NNT of 19 patients (Table 3).

3.3.1.3. AH + NS studies combined. Comparisons between all patients did also not show significant differences in the distribution of responders ($p = .303$) with a NNT of 12 (Table 3).

3.3.2. Symptomatic improvement $\geq$ 50% in the respective primary outcome

3.3.2.1. AH studies. Analyses showed no significant differences between groups ($p = .298$) and a NNT of 19 patients (Table 3).

3.3.2.2. NS studies. No significant differences between groups ($p = 1.000$) with a NNT of 28 patients could be found (Table 3).

3.3.2.3. AH + NS studies combined. Comparisons between all patients did not show significant

Table 1. Characteristics of the included studies.

Trial (author and year)	Design, blinding	Patients in active condition	Patients in sham condition	Target	Number of sessions	Total number of rTMS stimuli	Frequency rTMS (Hz)	Primary outcome measure(s)	CLZ patients included (active)	CLZ patients included (sham)
Bais et al. (2014)[1,a]	Par, DB	16 left TMS, 15 bilateral TMS	16	Left and bilateral TPC	12	14,400	1	**PANSS item P3**, PANSS total, AHRS	12	6
Blumberger et al. (2012)[2,a]	Par, SB	17 standard, 17 priming	17	Left TPC	20	24,000	1 (standard), 6 and 1 (priming)	**PSYRATS**	9	6
Cordes et al. (2010)[3,b]	Par, DB	18	14	Left DLPFC	10	10,000	10	**PANSS total**, CGI	5	2
Dlabac-de Lange et al. (2015)[b]	Par, DB	16	14	Bilateral DLPFC	30	20,000	10	**SANS,** PANSS	6	6
Klirova et al. (2013)[a]	Cro, DB	6	9	Left TPC	10	10,800	0.9	**AHRS**, PANSS	1	4
Koops et al. (2016)[a]	Par, DB	37	34	Left TPC	10	9000	cTBS	**AHRS**, PANSS	19	11
Novak et al. (2006)[b]	Par, DB	8	8	Left DLPFC	10	20,000	20	**PANSS negative**	1	2
Poulet et al. (2005)[a]	Cro, DB	10	10	Left TPC	10	10,000	1	**AHRS**, SAPS	2	1
Slotema et al. (2011)[4,a]	Par, DB	20 fMRI, 22 T3P3	20	fMRI-targeted/ EEG10-20 left TPC	15	18,000	1	**AHRS**, PANSS, PSYRATS	13	4
Wobrock et al. (2015)[5,b]	Par, DB	76	81	Left DLPFC	15	15,000	10	**PANSS negative**	11	10

[1]From 12 clozapine patients in the active condition, 5 received left TPC rTMS and 7 bilateral TPC rTMS.
[2]From 9 clozapine patients in the active condition, 4 received standard rTMS and 5 priming before standard rTMS over the left TPC.
[3]Two additional cases were identified as part of the selection process in our project.
[4]From 13 clozapine patients in the active condition, 4 were in the fMRI group and 9 in the non-guided rTMS group. In the fMRI-guided group and the sham group, fMRI targeted the area of maximal hallucinatory activation within left TPC; in the nonguided rTMS group, the 10–20 electrode placement system was used to localise T3P3 electroencephalogram electrode sites.
[5]One CLZ patient was excluded from the analyses beforehand, since CLZ was given first at Treat 0.
[a]Medication-resistant.
[b]Not specified if medication-resistant.
In bold print, the primary endpoints (=end of treatment intervention) of the respective RCTs used in our analyses are displayed.
DB: double-blind; SB: single-blind; cTBS: continuous theta burst stimulation; rTMS: repetitive transcranial magnetic stimulation; Hz: hertz; CLZ: clozapine; Par: parallel; Cro: cross-over trial; T3P3 = exact localisation of electrode placement at the temporoparietal cortex; fMRI: functional magnetic resonance imaging; PSYRATS: the psychotic symptom rating scale; PANSS: positive and negative syndrome scale; AHRS: auditory hallucination rating scale; SAPS: scale for the assessment of positive symptoms; SANS: scale for the assessment of negative symptoms; CGI: the clinical global impressions scale; TPC: temporoparietal cortex; DLPFC: dorsolateral prefrontal cortex; SD: standard deviation.

Table 2. Baseline characteristics.

	Active			Sham			Group comparisons		
	n	mean	SD +/−	*n*	mean	SD +/−		df	*p*
Persistent AH[a]	56	–	–	32	–	–			
							LR		
Gender (m:f)	39:17	–	–	19:13	–	–	0.946	1	.331
							t		
Age (years)	56	35.2	11.1	32	37.6	11.6	−0.957	86	.341
Duration of illness (years)	56	12.1	10.5	32	18.2	14.9	−2.241	86	**.028**
Clozapine dose (mg)	39	357.7	198.4	26	362.5	212.0	−0.093	63	.926
Motor Threshold	42	54.7	9.4	14	57.7	7.1	−1.106	54	.274
PANSS total	41	66.4	15.9	27	68.9	22.0	−0.507	43.66	.615
PANSS positive	41	18.0	5.4	27	17.9	5.5	0.074	66	.941
PANSS negative	41	15.8	4.9	27	17.0	7.0	−0.767	42.79	.447
PANSS general*	41	32.6	8.5	27	34.0	11.4	−0.579	66	.564
Persistent NS[b]	23	–	–	20	–	–	–	–	–
							LR		
Gender (m:f)	17:6	–	–	15:5	–	–	0.007	1	.935
							t		
Age (years)	23	38.6	10.6	20	36.6	8.9	0.654	41	.517
Duration of illness (years)	14	14.6	10.7	17	12.0	6.9	0.799	21.29	.433
Clozapine dose (mg)	23	363.6	149.1	20	333.8	155.2	0.642	41	.524
Motor Threshold	15	51.7	10.8	9	45.1	14.7	1.262	22	.220
PANSS total	23	80.9	13.7	20	72.9	13.0	1.974	41	.055
PANSS positive	23	14.5	4.1	20	13.4	3.0	1.037	39.87	.306
PANSS negative	23	26.0	5.8	20	24.4	5.7	0.938	41	.354
PANSS general*	23	40.4	7.5	20	35.1	8.2	2.203	41	**.033**
All patients	79	–	–	52	–	–	–	–	–
							LR		
Gender (m:f)	56:23	–	–	34:18	–	–	0.439	1	.508
							t		
Age (years)	79	36.2	11.0	52	37.2	10.5	−0.534	129	.594
Duration of illness (years)	70	12.6	10.5	49	16.0	13.0	−1.597	117	.113
Clozapine dose (mg)	62	359.9	180.4	46	350.0	188.0	0.276	106	.783
Motor Threshold	57	53.9	9.8	23	52.8	12.1	0.422	78	.674
PANSS total	64	71.6	16.6	47	70.6	18.6	0.310	109	.757
PANSS positive	64	16.7	5.2	47	16.0	5.0	0.774	109	.441
PANSS negative	64	19.5	7.2	47	20.1	7.4	−0.472	109	.638
PANSS general*	64	35.4	8.9	47	34.5	10.1	0.517	109	.606

[a]Included trials: Blumberger et al. (2012), Poulet et al. (2005), Bais et al. (2014), Koops et al. (2016), Slotema et al. (2011), Klirova et al. (2013).
[b]Included trials: Cordes et al. (2010), Novak et al. (2006), Dlabac-de Lange et al. (2015), Wobrock et al. (2015).
*In some RCTs, PANSS general data was not available and was calculated from available PANSS total, PANSS positive and PANSS negative data.
AH: auditory hallucinations; BL: baseline; NS: predominant negative symptoms; LR: likelihood ratio; T=*t*-value; SD: standard deviation; *n:* number of cases; significant results ($p < .05$) in bold.

Table 3. Response patterns of the different domains.

	Active		Sham		Group comparisons	
a) Primary outcome	≥20 % response	<20 % response	≥20 % response	<20 % response	*p**	NNT
AH[1]	15	41	5	27	.295	9
NS[2]	7	16	5	15	.745	19
All	22	57	10	42	.303	12
	≥50 % response	<50 % response	≥50 % response	<50 % response	*p**	NNT
AH[1]	3	53	0	32	.298	19
NS[2]	2	21	1	19	1.000	28
All	5	74	1	51	.402	23
b) PANSS total	Active		Sham		Group comparisons	
	≥20 % response	<20 % response	≥20 % response	<20 % response	*p**	NNT
AH[1]	12	29	7	20	1.000	30
NS[2]	7	16	6	14	1.000	230
All patients	19	45	13	34	.836	50
	≥50 % response	<50 % response	≥50 % response	<50 % response	*p**	NNT
AH[1]	1	40	0	27	1.000	41
NS[2]	1	22	0	20	1.000	23
All	2	62	0	47	.507	32

a) Symptomatic response (defined as ≥20% and ≥50% improvement of the primary outcome of the respective study) for RCTs with TPC (positive symptoms, e.g. auditory hallucinations) and DLPFC (negative symptoms) as stimulation locus and for all patients independent of the stimulation locus and b) PANSS total as available primary or secondary outcome in the trials with regard to symptomatic response (defined as ≥20% and ≥50% improvement of the primary outcome of the respective study).
The numbers for response represent the respective number of cases (*n*).
[1]included trials: Blumberger et al. (2012), Poulet et al. (2005), Bais et al. (2014), Koops et al. (2016), Slotema et al. (2011), Klirova et al. (2013).
[2]included trials: Cordes et al. (2010), Novak et al. (2006), Dlabac-de Lange et al. (2015), Wobrock et al. (2015).
*Fisher's exact test (2-sided).
AH: auditory hallucinations; NS: negative symptoms; NNT: number needed to treat.

Table 4. Relative changes between baseline and endpoint scores of PANSS total, PANSS positive, PANSS negative and PANSS general scores.

	Active			Sham			Group comparisons		
PANSS total	*n*	mean	SD	*n*	mean	SD	*t*	df	*p*
AH[a]	41	0.059	0.306	27	−0.214	1.569	1.087	66	.281
NS[b]	23	0.153	0.165	20	0.119	0.178	0.648	41	.521
All	64	0.093	0.266	47	−0.072	1.197	1.070	109	.287
PANSS positive									
AH[a]	41	0.052	0.314	27	−0.014	0.421	0.744	66	.460
NS[b]	23	0.163	0.388	20	0.064	0.552	0.691	41	.493
All	64	0.092	0.344	47	0.019	0.477	0.939	109	.350
PANSS negative									
AH[a]	41	−0.081	0.674	27	0.143	0.271	−1.641	66	.106
NS[b]	23	0.186	0.206	20	0.190	0.161	−0.059	41	.953
All	64	0.015	0.566	47	0.163	0.230	−1.692	109	.093
PANSS general									
AH[a]	41	0.157	0.309	27	0.183	0.395	−0.304	66	.762
NS[b]	23	0.101	0.175	20	0.015	0.308	1.139	41	.261
All	64	0.137	0.268	47	0.111	0.367	0.418	109	.677

[a]Included trials: Blumberger et al. (2012), Poulet et al. (2005), Bais et al. (2014), Koops et al. (2016), Slotema et al. (2011), Klirova et al. (2013).
[b]Included trials: Cordes et al. (2010), Novak et al. (2006), Dlabac-de Lange et al. (2015), Wobrock et al. (2015).
AH: auditory hallucinations; NS: negative symptoms; SD: standard deviation; *n:* number of patients.

differences in the distribution of responders ($p = .402$). The NNT was 23 (Table 3).

3.3.3. Relative changes in PANSS scores from baseline to endpoint

3.3.3.1. AH studies. No significant differences in PANSS total scores were detected between active and sham groups for PANSS total symptoms ($p = .281$). No significant differences in PANSS positive, negative and general scores for AH studies between active and sham groups were detected (Table 4).

3.3.3.2. NS studies. No significant differences in PANSS total scores were detected between active and sham groups for PANSS total ($p = .521$). No significant differences in PANSS positive, negative and general scores for NS studies between active and sham groups were detected (Table 4).

3.3.3.3. AH + NS studies combined. No significant differences in PANSS total ($p = .287$) and other PANSS scores were detected between active and sham groups for all patients (Table 4).

3.3.4. Symptomatic improvement ≥20% in PANSS total scores

3.3.4.1. AH studies. No significant group differences were detected ($p = 1.000$) with a NNT of 30 (Table 3).

3.3.4.2. NS studies. No significant group differences were detected ($p = 1.000$) with a NNT of 230 (Table 3).

3.3.4.3. AH + NS studies combined. For all patients ($n = 111$), no significant differences could be observed between the groups ($p = .836$). The NNT was 50 (Table 3).

3.3.5. Symptomatic improvement ≥ 50% in PANSS total scores

3.3.5.1. AH studies. In the analysis of patients in AH studies, no significant group differences were detected ($p = 1.000$) with a NNT of 41 (Table 3).

3.3.5.2. NS studies. In the analysis of patients in NS studies, no significant group differences were detected ($p = 1.000$) with a NNT of 23 (Table 3).

3.3.5.3. AH + NS studies combined. For all patients ($n = 111$), no significant group differences were detected ($p = .507$) with a NNT of 32 (Table 3).

3.3.6. Time course of PANSS changes

3.3.6.1. AH studies. With regard to PANSS total scores, RM-ANOVA showed a significant main effect of TIME ($F_{(1,\ 66)} = 6.280$, $p = .015$), but no TIME x GROUP interaction ($F_{(1,\ 66)} = 0.266$, $p = .608$) and no main effect of GROUP ($F_{(1,\ 66)} = 0.182$, $p = .671$).

With regard to PANSS positive, RM-ANOVA showed no significant main effect of TIME ($F_{(1,66)} = 3.460$, $p = .067$), no TIME × GROUP interaction ($F_{(1,66)} = 0.031$, $p = .862$) and no main effect of GROUP ($F_{(1,66)} = 0.001$, $p = .981$).

3.3.6.2. NS studies. With regard to PANSS total scores, RM-ANOVA showed a significant main effect of TIME

($F_{(1,\ 41)} = 33.100$, $p < .001$), but no TIME × GROUP interaction ($F_{(1,\ 41)} = 1.264$, $p = .267$) and no main effect of GROUP ($F_{(1,\ 41)} = 3.042$, $p = .089$).

With regard to PANSS negative, RM-ANOVA showed a significant main effect of TIME ($F_{(1,\ 41)} = 41.792$, $p < .001$), but no TIME × GROUP interaction ($F_{(1,\ 41)} = 0.302$, $p = .586$) and no main effect of GROUP ($F_{(1,\ 41)} = 0.753$, $p = .390$).

3.3.6.3. AH + NS studies combined. With regard to PANSS total scores, RM-ANOVA showed a significant main effect of TIME ($F_{(1,\ 109)} = 26.259$, $p < .001$), but no TIME × GROUP interaction for all patients ($F_{(1,\ 109)} = 0.002$, $p = .961$) and no main effect of GROUP ($F_{(1,\ 109)} = 0.095$, $p = .759$).

3.3.7. Sensitivity analyses

3.3.7.1. AH studies. For sensitivity analyses differing sham-coil ($n = 7$) vs. tilted coil ($n = 25$) vs. active ($n = 56$) stimulation, analyses were also non-significant in response rates defined as ≥20% ($LR\ \chi^2_{(2)} = 2.522$, $p = .283$) and ≥50% ($LR\ \chi^2_{(2)} = 2.772$, $p = .250$).

Correlation analyses between age and the relative changes in PANSS total score in the active rTMS group did not show significant correlations ($r = -0.061$, $p = .703$, $n = 41$).

Correlation analyses between clozapine dose and the relative changes in PANSS total score in the active group were negative ($r = -0.140$, $p = .409$, $n = 37$). Also for sham rTMS, no correlations between age and relative changes in PANSS total score ($p = .564$) or between clozapine dose and relative changes in PANSS total score ($p = .280$) could be observed.

3.3.7.2. NS studies. For sensitivity analyses differing sham-coil ($n = 2$) *vs.* tilted coil ($n = 18$) vs. active ($n = 23$) stimulation, analyses were non-significant for response rates defined as ≥20% ($LR\ \chi^2_{(2)} = 1.381$, $p = .501$) and ≥50% ($LR\ \chi^2_{(2)} = 0.447$, $p = .800$).

Correlation analyses between age and the relative changes in PANSS total score in the active group did not show significant correlation for patients ($r = -0.076$, $p = .729$, $n = 23$).

Correlation analyses between clozapine dose and the relative changes in PANSS total score were negative ($r = -0.223$, $p = .306$, $n = 23$) in patients treated with active rTMS. Also for sham rTMS, no correlations between age and relative changes in PANSS total score ($p = .888$) or between clozapine dose and relative changes in PANSS total score ($p = .524$) could be observed.

3.3.7.3. AH + NS studies combined. Non-significant differences were obtained with regard to response rates defined as ≥20% change for all patients differing sham-coil ($n = 9$) *vs.* tilted coil ($n = 43$) *vs.* active ($n = 79$) ($LR\ \chi^2_{(2)} = 1.349$, $p = .509$) and ≥50% change ($LR\ \chi^2_{(2)} = 1.946$, $p = .378$).

Correlation analyses between age and the relative changes in PANSS total score did not show significant correlation in the complete group ($r = -0.043$, $p = .735$, $n = 64$) treated with active rTMS.

Correlation analyses between clozapine dose and the relative changes in PANSS total score were negative in the complete group ($r = -0.152$, $p = .245$, $n = 60$) treated with active rTMS. Also for sham rTMS, no correlations between age and relative changes in PANSS total score ($p = .547$) or between clozapine dose and relative changes in PANSS total score ($p = .224$) could be observed.

4. Discussion

We present the first pooled individual patient-level analysis that investigates the effects of rTMS on severity of AH and NS in schizophrenia patients with remaining symptoms treated with clozapine. Thus, our sample constitutes the largest available cohort of clozapine patients treated with rTMS to date. Our results did not show a significant superior effect of active rTMS compared to sham for AH (stimulation of TPC) and NS studies (stimulation of DLPFC) when applied to augment an unsuccessful treatment with clozapine when response rates or symptomatic changes were analysed. Nonetheless, subsequent analyses showed a NNT of 9 for a ≥ 20% improvement of AH and of 12 when all patients were analysed. However, the general pattern of our findings indicates that the intervention with rTMS in patients with remaining symptoms despite clozapine treatment, irrespective whether hallucinations or NS were the target symptoms, does not offer a benefit.

Baseline PANSS total scores were high despite clozapine treatment, suggesting that this population was at least in part refractory to current clinical interventions. Higher PANSS total scores of patients at baseline in the NS studies compared to AH studies could be due to significantly higher PANSS general scores of patients in NS studies compared to patients in AH studies with a higher prevalence of e.g. depressive symptoms increasing PANSS general scores in patients with predominant NS. Furthermore, the overall long duration of illness in both groups suggests a cohort of chronically affected patients. Thus, despite the

situation that we do not have the information whether our sample was treatment-resistant or not, the fact that patients were treated with clozapine and had relevant symptoms indicates that this population had a need for an add-on therapeutic strategy. This argument is supported by the observation that as soon as CRS is established, evidence for the efficacy of pharmacological and psychosocial augmentation strategies is sparse (Wagner et al. 2019). In a recent systematic meta-review investigating treatment options of CRS, the highest recommendation level (Grade B according to SIGN criteria (Scottish Intercollegiate Guidelines Network (SIGN) 2013)) was given to clozapine add-on treatment with first- or second-generation antipsychotics and ECT for clozapine-resistant positive symptoms, and clozapine add-on treatment with first- or second-generation antipsychotics and certain antidepressants (fluoxetine, duloxetine and citalopram) for clozapine-resistant NS (Wagner et al. 2019). For rTMS as CRS augmentation strategy, a recommendation level Grade C was defined due to a lack of evidence from RCTs (Wagner et al. 2019). So far, proof-of-concept rTMS trials with clozapine patients as target population focussed on refractory positive symptoms (e.g. AH) (Rosa et al. 2007; de Jesus et al. 2011). In the trial from de Jesus et al. schizophrenia patients ($n = 17$) received active 1-Hz rTMS compared with sham 1-Hz for 20 d applied to the left TPC (de Jesus et al. 2011) and a significant reduction in Brief Psychiatric Rating Scale (BPRS) scores was found in the active group compared to sham. No significant difference was found in the auditory hallucinations rating scale (AHRS). In the RCT by Rosa et al. (2007) ($n = 11$) no significant reduction in AH was reported. In a secondary analysis of clozapine patients participating in a RCT where rTMS was applied to the left DLPFC to improve predominant NS (Wagner et al. 2019), time-$\times$group interactions were significant in the PANSS positive, general and total scale), but not the PANSS negative subscale (primary endpoint of the RESIS trial), when all PANSS measurements from screening to the end of the study were included (Wagner et al. 2019). In published meta-analyses of active *vs.* sham rTMS for positive or NS in schizophrenia to date, patients on clozapine were not specifically investigated (Slotema et al. 2014; Huang et al. 2017; Aleman et al. 2018; Kennedy et al. 2018; Osoegawa et al. 2018).

ECT seems to be an effective non-pharmacological augmentation strategy for clozapine-resistant positive symptoms (Wang et al. 2018). Wang et al. found adjunctive ECT being superior to clozapine-monotherapy regarding symptomatic improvement at post-ECT and endpoint assessment (Wang et al. 2018). Evidence is still hampered since the number of high-quality studies in this field remains low and none of the RCTs used sham-ECT. Nonetheless, the only high-quality RCT to date from Petrides et al. ($n = 39$) showed a high efficacy of ECT as clozapine augmentation strategy in patients with ultra-treatment-resistance (Petrides et al. 2015).

The evidence for other non-pharmacological clozapine augmentation strategies remains sparse with negative results for CBT in a recent high-quality RCT ($n = 487$) (Morrison et al. 2018). Even though we found no significant superior effect of active rTMS *vs.* sham rTMS in the primary analyses with both $\geq$20% and $\geq$50% response thresholds, the NNT of 9 patients for $\geq$20% improvement of AH for RCTs with TPC as stimulation locus is comparable to CBT as clozapine add-on (Morrison et al. 2018). The RCT from Morrison et al. did not show benefit of CBT among CRS patients with regard to PANSS total score after 9 months as primary outcome (Morrison et al. 2018). Nonetheless, the trial showed that some CRS patients might benefit from CBT with a NNT of 15 to achieve a $>$50% PANSS improvement after 21 months. Even though overall intervention periods were shorter in our pooled analysis, some patients, especially with persistent positive symptoms (e.g. AH), might equally benefit from rTMS applied to the TPC as an alternative non-pharmacological clozapine augmentation strategy.

As a limitation, our pooled secondary analysis included studies with heterogenous parameters (Figure 1) and with primarily negative primary outcome results (Novak et al. 2006; Cordes et al. 2010; Slotema et al. 2011; Blumberger et al. 2012; Bais et al. 2014; Wobrock et al. 2015; Koops et al. 2016). One out of 10 studies showed significant treatment effects in AH (Poulet et al. 2005) and two out of 10 showed non-significant findings in PANSS and significant treatment effects in SANS (Dlabac-de Lange et al. 2015) or AHRS (Klirova et al. 2013). Seven out of 10 showed non-significant findings whatsoever. Most clozapine patients ($>$10 per study) are from four studies with only negative findings (Slotema et al. 2011; Bais et al. 2014; Wobrock et al. 2015; Koops et al. 2016). Subtracting sub-samples from mainly those studies is a potential bias for our secondary analyses and the lack of beneficial effect of rTMS on patients treated with clozapine might reflect the bias of non-significant rTMS effects. A visual inspection of the forest-plots of the included meta-analyses (Slotema et al. 2014; Huang et al. 2017; Aleman et al. 2018; Kennedy et al. 2018; Osoegawa et al. 2018) displays in more than a

half of the respectively included studies no positive effect of active rTMS. Thus, the lack of beneficial effects of rTMS on patients treated with clozapine reported here may reflect a potential bias of non-significant rTMS effects from the included source studies.

Unfortunately, 30 authors did not respond to our request and two authors declined to participate – this observation of a reduced likelihood to receive requested data has been frequently reported in the literature (Savage and Vickers 2009; Wicherts et al. 2011) and, thus, is an inherent limitation of all pooled-analyses approaches.

Moreover, our analyses involved rTMS as an add-on treatment to clozapine, but that does not imply that our included patients met TRRIP criteria for CRS (Howes et al. 2017), as the included studies were conducted prior to the publication of the TRRIP guidelines. We cannot clearly define at this stage whether patients received clozapine due to treatment-resistance, as an augmentation strategy of an ongoing antipsychotic treatment or e.g. off-label to manage tardive dyskinesia or suicidality. Thus, our approach investigated rTMS as add-on strategy to an ongoing clozapine treatment rather than as an CRS augmentation strategy. Single PANSS items scores were not available in 70% of the included studies. Thus, CRS criteria were not assessed for our cohort retrospectively and our findings cannot answer the question whether adding rTMS in cases of CRS is effective or not. However, as detailed above, the PANSS values at baseline indicate that the patients were still symptomatic. Meta-analyses focussing on NS and AH established a relationship between shorter duration of illness or younger age with better response to rTMS (Aleman et al. 2018; Koops et al. 2018). This is principally consistent with the observation that rTMS-induced motor-cortical plasticity is also related to younger age, but also to other factors like neuroactive medication (Ridding and Ziemann 2010). However, in our analyses neither age nor clozapine dose correlated with the symptomatic improvement. Finally, the number of patients included in the sham-group of the sensitivity-analysis of the sham conditions was low. Assuming that rTMS induces a plastic response and that plastic responses need time to emerge, one could speculate that differences between active and sham rTMS might not be disentangled immediately after the end of the stimulation (endpoints analyses in this work), but during longer follow-up periods. However, the available rTMS trials with longer follow-up intervals for AH (e.g. Koops et al. 2016) and for NS (e.g. Dlabac-de Lange et al. 2015; Wobrock et al. 2015) were negative, both immediately after the treatment period as well as at the end of follow-up intervals within the range of 1–3 months.

Hence, for schizophrenia patients receiving plasticity-inducing rTMS add-on to clozapine, neuroplastic changes inducing (Konradi and Heckers 2001; Morais et al. 2017) neurophysiological and biological predictors of response (such as cortical silent period, short-interval cortical inhibition, grey matter density among others) should be investigated in future trials in order to delineate potential rTMS responders with remaining symptoms under clozapine therapy. Moreover, physiological studies using the motor-cortex model clearly show high intraindividual response variability to rTMS and other transcranial non-invasive brain stimulation techniques (Huang et al. 2017) and it is very likely that rTMS to the TPC or DLPFC is also subject to such physiological variability effects. Thus, strategies to overcome this inherent limitation of the methods are urgently needed. In this context, recent work using advanced statistical methods indicate that baseline structural MRI has the potential to predict response to ECT (Redlich et al. 2016) or rTMS (Koutsouleris et al. 2018) on a single-subject level. In the absence of an overall group effect in our analyses, such approaches could help to identify those schizophrenia patients receiving clozapine who may benefit for an augmentation treatment with rTMS.

In conclusion, our results do not support the application of low- or high-frequency rTMS specifically for schizophrenia patients with persistent AH or NS who receive clozapine treatment. However, based on the observed NNT further research regarding a prospective multicentric RCT of rTMS with clozapine and a control group using non-clozapine antipsychotics as well as the development of single-subject predictors in schizophrenia patients fulfilling ultra-treatment-resistance criteria are warranted.

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