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Original article

Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have shown promise in the treatment of schizophrenia.
Objective: To quantify the efficacy of double-blind randomized controlled trials (RCT) of tDCS and rTMS for the positive and negative symptoms of schizophrenia and identify significant moderators relating to patient-related features and stimulation parameters.
Methods: Systemic review and meta-analyses of the relevant literature published until February 1st, 2017 to assess treatment efficacy and quantify the contribution of potential moderator variables.
Results: We identified 7 RCTs on tDCS (involving 105 participants) and 30 RCTs on rTMS (involving 768 participants). Compared to sham, tDCS improved all symptom dimensions but the effect reached significance for negative symptoms (Hedge's $g = -0.63$, $p = 0.02$). Efficacy for positive but not negative symptoms was linearly associated with cumulative tDCS stimulation. Compared to sham, rTMS improved hallucinations (Hedge's $g = -0.51$, $p < 0.001$) and negative symptoms (Hedge's $g = -0.49$, $p = 0.01$) but was associated with modest, non-significant worsening of positive symptoms (Hedge's $g = 0.28$, $p = 0.13$). Higher pulse frequency (>10 Hz), motor threshold intensity of 110%, left prefrontal cortical treatment site and trial duration over 3 weeks were associated with improvement in negative symptoms and worsening in positive symptoms (all $p < 0.03$).
Conclusions: The symptom dimensions in schizophrenia may respond differently to brain stimulation interventions in a way that may reflect the interaction between disease- and treatment-related mechanisms. Our findings underscore the need for further research into patient selection prior to treatment assignment and greater refinement of stimulation protocols.

1. Introduction

Schizophrenia is a severe and complex disorder presenting with positive (hallucinations, delusions, disorganized thinking and agitation) and negative (affective flattening, amotivation, and alogia) symptoms [1]. Approximately 10% of patients are resistant to standard treatments at disease onset and this proportion increases to around 40% with chronicity [2–6]. In response, there is increased interest in the therapeutic potential of novel approaches involving noninvasive neuromodulation, and particularly repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS involves the use of a rapidly fluctuating electrical current to generate a magnetic field which, when applied to the scalp, can influence neuronal excitability to a depth of approximately 2 cm below the skull [7,8]. Randomized controlled trials (RCTs) in schizophrenia suggest that rTMS is moderately effective in the treatment of auditory hallucinations [9] and negative symptoms [10,11]. These studies also report that duration of illness and stimulation parameters relating to target region, pulse frequency and motor threshold as well as overall treatment duration were significant moderators of efficacy [9–11]. tDCS involves the application of weak electrical currents (typically 2 mA) that flow through the brain from anodal to cathodal scalp electrodes. These weak electrical currents are thought to modulate the resting membrane potentials of neurons, reducing (cortical) excitability at the cathode while increasing it at the anode [12]. tDCS in schizophrenia has been evaluated mostly in connection to auditory hallucinations; the results have been mixed and the role of moderator variables remains unclear [13–19].

This study addresses two key knowledge gaps. First, we used quantitative meta-analysis to evaluate the efficacy of rTMS and tDCS on the positive, negative and general symptoms of schizophrenia using data from the available RCTs. Second, we

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quantified the moderator effects relating to patient-related characteristics (sex, age, duration of illness and antipsychotic dose) and stimulation parameters. The stimulation parameters considered were target brain regions, trial duration, electrical current amplitude (for tDCS trials only), pulse frequency and motor threshold (for rTMS trials only) and cumulative stimulation, new composite measure of stimulation "dose". In addition, we provide an online, freely accessible and searchable database listing the variables used in this study to enable future work by other researchers.

2. Materials & methods

2.1. Search strategy and selection criteria

We conducted a systematic search of the major electronic databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [20] to identify studies published between January 1 st 1996 and February 1st 2017. Our start date was determined by the first publication of an RCT using rTMS in schizophrenia and was extended by 3 years to include any other reports. Selection criteria were: (a) Peer-reviewed, original studies of patients with schizophrenia and related psychoses diagnosed according to standardized criteria; (b) Double-blind randomized sham controlled design; (c) Symptom ratings using the Auditory Hallucinations Rating Scale (AHRS) [21] and/or the Positive and Negative Syndrome Scale (PANSS) [22]; (d) Sufficient data to calculate effect size using Hedges' g; (e) information about study drop-outs/withdrawals. Based on the criteria set-out by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group (http://www.gradeworkinggroup.org/) the studies selected would be rated as 4 (highest rating). Conference abstracts, open label trials, case reports and case series were not included. Details of the search strategy and the study selection process are provided in supplemental material (PRISMA flowcharts Figs. S1 and S2), supplemental datasheet and Fig. S3.

2.2. Data extraction and database construction

We extracted the following variables from each study: treatment modality (tDCS or rTMS), sample size per treatment condition (active or sham), sex, age, duration of illness, antipsychotic dose (converted into chlorpromazine equivalent milligrams; CPZE), frequency of treatment administration, trial duration and stimulation parameters (electrode montage and current amplitude for tDCS, target brain region, motor threshold and pulse frequency for rTMS), time point of data collection, raw difference in mean and standard deviation of pre- and post-treatment symptom scores in the active and sham condition, difference in means with associated p value and 95% confidence intervals, or exact *F* or *t* values, and number of dropouts and side-effects.

2.3. Statistical analysis

All analyses were conducted using the Comprehensive Meta-Analysis (CMA) v3.3.070 software (Biostat, Englewood, NJ, USA). Because of the imbalance in the number of studies reporting on tDCS and rTMS, data for each neuromodulation modality were analyzed separately using identical methodology. The outcomes considered were (a) reduction in auditory hallucinations as measured by a composite score derived from the AHRS and the PANSS auditory hallucination subscale computed using the "which procedure" in the CMA software; (separate confirmatory meta-analyses using the AHRS alone are reported in supplemental material); (b) reduction in positive symptoms as measured by the positive symptoms subscale of the PANSS; (c) reduction in negative symptoms as measured by the negative symptoms subscale of the PANSS; (d) reduction in overall symptom severity as measured by the PANSS total score; (e) number of dropouts; (f) type and number of side-effects.

For each outcome, we calculated weighted standardized mean differences (Hedges' g) between active and sham conditions using a DerSimonian and Laird's random effects model [23]. Studies were weighted by sample size as calculated by the Mantel-Haenszel method [24]. Effect sizes were considered small (<0.20), medium and large (>0.80) in accordance with conventional guidelines [25]. When trials comparing effects of multiple stimulation parameters were reported in the same article, we treated each trial as an independent dataset. In four studies that employed a crossover design [26–29] we used the clinical scores at initial randomization as baseline. We considered only outcome data recorded on completion of the clinical trial and not at other timepoints.

Heterogeneity was quantified using the I^2 statistic which accommodates small numbers of studies. Conventionally, an $I^2 < 25\%$ is considered as likely unimportant while an $I^2 > 50\%$ is indicative of substantial heterogeneity requiring cautious interpretation of the results [30]. A random effects model was applied to all analyses where the $I^2 \geq 25\%$. The threshold for statistical significance was set at $p < 0.002$, following Bonferroni correction considering the 4 clinical efficacy outcomes examined per modality.

For each modality, we considered moderator effects relating to patient-related characteristics and stimulation parameters. Patient-related characteristics comprised sex (expressed as the percentage of male patients within each study), age, duration of illness and antipsychotic dose (in CPZE). The stimulation parameters considered for both modalities were target brain regions and trial duration. Additional moderators were electrical current amplitude for tDCS trials and pulse frequency and motor threshold for rTMS studies. We also evaluated the usefulness of "cumulative stimulation" as composite measure of "dose" defined as:

$$\begin{aligned}(\text{tDCS cumulative stimulation}) = {} & (\text{density of administration}) \\ & \times (\text{individual session duration}) \\ & \times (\text{current amplitude})\end{aligned}$$

$$\begin{aligned}(\text{rTMS cumulative stimulation}) = {} & (\text{density of administration}) \\ & \times (\text{individual session duration}) \\ & \times (\%\text{motor threshold}) \\ & \times (\text{pulse frequency})\end{aligned}$$

For both tDCS and rTMS, administration density was defined as the ratio of total number of treatment sessions over the duration of the treatment trial. Regression analyses were used to assess the independent contribution of each continuous moderator to change in clinical outcomes based on the regression coefficient, 95% confidence interval (CI) and the R^2 statistic. Subgroup analyses were used to assess effect size for categorical variables. We retained the conventional statistical threshold of $p < 0.05$ as we considered these analyses potentially informative for future detailed examination. For each modality, we assessed tolerability by calculating the odds ratio (OR) of dropout and side-effect rates between the active versus sham condition across all studies.

3. Results

3.1. Dataset

The final dataset comprised 7 tDCS and 30 rTMS studies (Tables 1 and 2 and Tables S1 and S2). We found no evidence of publication bias (Fig. S4). For both modalities, the study samples comprised patients with persistent symptoms despite adequate

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Table 1
List of tDCS studies included in the meta-analysis with details of stimulation parameters.

Study (First Author, Year)	Patients in the active condition (n)	Patients in the sham condition (n)	Anode placement[1]	Cathode placement[1]	Current Amplitude (mA)	Electrode surface area (cm^2)	Number of sessions	Frequency of treatment	tDCS Cumulative Stimulation[2]	tDCS Density of Session Administration	Outcome measures included in *meta*-analysis
Brunelin 2012 [18]	15	15	L F3/Fp1	L T3/P3	2	35 cm^2	10	Twice daily	80	2	AHRS, PANSS
Fitzgerald[3] 2014 [17]	24	24	L F3 or F3/4	L TP3 or TP3/4	2	35 cm^2	15	Once daily	28.4	0.71	PANSS
Frohlich 2016 [15]	13	15	L F3/Fp1	L T3/P3	2	35 cm^2	5	Once daily	40	1	AHRS, PANSS
Gomes 2015 [19]	7	8	L F3	R F4	2	Not reported	10	Once daily	28.4	0.71	PANSS
Mondino 2016 [14]	11	12	L F3/Fp1	L T3/P3	2	35 cm^2	10	Twice daily	80	2	AHRS, PANSS
Palm 2016 [13]	10	10	L F3	R Fp2	2	35 cm^2	10	Once daily	28.4	0.71	PANSS
Smith 2015 [16]	17	16	L F3	R Fp2	2	2 in^2	5	Once daily	40	1	AHRS, PANSS

AHRS = Auditory Hallucinations Rating Scale; L = Left; PANSS = Positive and Negative Syndrome Scale; PSYRATS = Psychotic Symptoms Rating Scale; R = Right; tDCS = Transcranial Direct Current Stimulation.
[1] Electrode placement according to the International 10–20 system.
[2] Cumulative density is in mAmin.
[3] This study used two different electrode montages without specifying how many patients were assigned in each.

antipsychotic treatment. Of the seven tDCS studies, two had significantly overlapping samples of patients [31,18]. We conducted the analyses while including either both or the largest of the two studies [18]. The outcome remained comparable to the point that we decided to include both studies in the results presented here.

3.2. Efficacy of tDCS in schizophrenia

Details of the 7 studies included in the meta-analyses are shown in Tables 1 and S1. We did not examine the effect of duration of illness and medication dose (due to insufficient data) and of montage and current amplitude (due to limited inter-study variability) (Table 1). The main findings are presented in Table 3 and Fig. 1 and further details are provided in supplemental material Section 2 and Table S3.

3.2.1. Auditory hallucinations

We analyzed data from 5 studies based on the composite hallucinations score derived from 80 patients allocated to active tDCS and 63 patients allocated to the sham condition [15–18,31]. Although active tDCS was associated with symptom reduction, the effect was not significant (Hedge's $g = -0.28$, $p = 0.38$) with evidence of substantial heterogeneity ($I^2 = 77.11\%$). The efficacy of active tDCS increased significantly with greater cumulative stimulation (coefficient = −0.02, $p = 0.01$). No other moderator variable showed a significant contribution ($p > 0.10$) (Table S3).

3.2.2. Positive psychotic symptoms

We analyzed data from 7 tDCS studies based on the PANSS positive symptoms subscale score derived from 97 patients allocated to active tDCS and 93 patients allocated to the sham condition [13,15–19,31]. There was a non-significant reduction in symptoms (Hedge's $g = -0.10$, $p = 0.59$) which was linearly associated with cumulative stimulation but this effect was also not significant ($p = 0.13$) (Table S3). No moderator variable made a significant contribution ($p > 0.40$) (Table S3).

3.2.3. Negative symptoms

We used data from the same 7 studies as for the positive symptoms but analyzed changes in the PANSS negative symptoms subscale score [13,15–19,31]. We found a significant effect of treatment (Hedge's $g = -0.63$, $p = 0.02$) and evidence of significant heterogeneity ($I^2 = 69.70\%$). The contribution of cumulative stimulation was minimal and not significant ($p = 0.97$).None of the other moderator variables were significantly associated with response to active treatment ($p > 0.11$) (Table S3).

3.2.4. Overall symptom severity

We included 6 studies that provided data on the PANSS total score derived from 86 patients allocated to active tDCS and 77 patients allocated to the sham condition [13,15,16,18,19,31]. There was no significant effect of treatment (Hedge's $g = -0.48$, $p = 0.12$) or of the moderator variables ($p > 0.28$) (Table S3).

3.3. Efficacy of rTMS in schizophrenia

Details of the 30 studies considered are shown in Tables 2 and S2. The most common treatment sites were the temporo-parietal junction (TPJ) (n=17) and dorsal PFC (n=11); studies varied in pulse frequency (1–50 Hz), number of sessions (4 to 30) and trial duration (2 days to 4 weeks) (Table 2). The main findings are presented in Table 3 and Fig. 2 and further details are provided in supplemental material section 3 and Tables S4 and S5.

3.3.1. Auditory hallucinations

We analyzed data from 14 studies using the composite hallucination score derived from 340 patients allocated to active rTMS and 238 patients allocated to the sham condition [26–29,32–42]. There was a significant effect of treatment (Hedge's $g = -0.51$, $p = 0.0001$) with evidence of moderate heterogeneity ($I^2 = 58.81\%$). Older age was associated with small reduction in response to the active (coefficient = 0.08, $p = 0.03$) and the sham condition (coefficient = 0.14, $p < 0.0001$). Higher antipsychotic dose was also associated with a small but significant reduction in response in the active condition (coefficient = 0.003, $p = 0.03$). The effect of other patient-related variables was not significant ($p > 0.22$) (Table S4). There was little inter-study variability in terms of motor threshold intensity (all 110%), pulse frequency and treatment site but reductions in the composite hallucinations scores was associated with short trial duration (<3weeks) (Hedges' $g = -6.03$, $p = 0.001$) (Table S5).

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Table 2
List of rTMS studies included in the meta-analysis with details of stimulation parameters.

Study (First Author, Year)	Number of patients in the active condition	Number of patients in the sham condition	Target	Stimulation frequency Hz	Number of sessions	Frequency of treatment	rTMS Cumulative Stimulation	rTMS Density of Session Administration	Sham angle	Outcome measures included in *meta*-analysis
Barr 2012 [43]	13	14	Bilateral DLPFC	20	20	Once daily	1065	0.71	90°	PANSS
Blumberger 2012 [32]	17 standard, 17 priming	17	L TPJ	1/6-1	20	Once daily	852 2982	0.71 0.71	90°	AHRS, PANSS
Brunelin 2006 [33]	14	10	L TPJ	1	10	Twice daily	2860	1.43	Nonmagnetic coil	AHRS
de Jesus 2011 [34]	8	9	L TPJ	1	20	Once daily	852	0.71	45°	AHRS
Dlabac-de Lange 2015 [44]	16	14	Bilateral DLPFC	10	30	Twice daily	2860	1.43	90°	PANSS
Fitzgerald 2005 [35]	17	16	L TPJ	1	10	Once daily	633	0.71	45°	PANSS
Fitzgerald 2008 [45]	10	10	Bilateral DLPFC	10	15	Once daily	1065	0.71	90°	PANSS
Garg 2016 [46]	20	20	Cerebellar vermis	5/6/7	10	Once daily	498	0.8	45°	PANSS
Hoffman 2005 [36]	27	23	L TPJ	1	9	Once daily	880	1	45°	PANSS, AHRS
Hoffman 2013 [37]	55	28	BL TPJ	1	15	Once daily	681.6	0.71	45°	AHRS
Holi 2004 [47]	11	11	L DLPFC	10	10	Once daily	710	0.71	90°	PANSS
Kimura 2016 [38]	16	14	L TPJ	20	4	Twice daily	5200	2	Nonmagnetic coil	AHRS
Klein 1999 [48]	18	17	R DLPFC	1	10	Once daily	85.2	0.71	90°	PANSS
Klirova 2013 [28]	15	Crossover design	L TPJ	0.9	10	Once daily	766.8	0.71	90°	AHRS, PANSS
Koops 2016 [39]	37	34	L TPJ	50	10	Twice daily	90000	2	Nonmagnetic coil	AHRS, PANSS
Lee 2005 [40]	13 L/ 12 R	14	TPJ	1	10	Once daily	852	0.71	90°	AHRS, PANSS,
Li 2016 [56]	25	22	L DLPFC	10	20	Once daily	1065	0.71	Nonmagnetic coil	PANSS
McIntosh 2004 [29]	16 Crossover design	16 Crossover design	L TPJ	1	4	Once daily	2400	1	45°	PANSS
Poulet 2005 [26]	10 Crossover design	10 Crossover design	L TPJ	1	10	Once daily	710	0.71	Nonmagnetic coil	AHRS
Prikryl 2007 [49]	11	11	L DLPFC	10	15	Once daily	1071	0.71	90°	PANSS
Prikryl 2014 [50]	18	17	L DLPFC	10	21	Once daily	2000	1	Nonmagnetic coil	PANSS
Quan 2015 [51]	78	39	L DLPFC	10	10	Once daily	381	0.48	90°	PANSS
Rabany 2014 [55]	20	10	L DLPFC	20	20	Once daily	1200	0.71	Not reported	PANSS
Rosa 2007 [52]	6	5	L TPJ	1	10	Once daily	685	0.71	Nonmagnetic coil	PANSS
Rosenberg 2012 [66]	9	9	L TPJ	1	10	Once daily	428.4	0.71	Nonmagnetic coil	AHRS
Saba 2006 [27]	8	8	L TPJ	1	10	Once daily	214	0.71	Nonmagnetic coil	PANSS
Slotema 2011 [41]	20/22	20	L TPJ	1	15	Once daily	856.8	0.71	90°	AHRS, PANSS
Vercammen 2009 [42]	24	12	L TPJ	1	12	Twice daily	1800	1.5	Nonmagnetic coil	AHRS, PANSS
Wobrock 2015 [53]	76	81	L DLPFC	10	15	Once daily	710	0.71	45°	PANSS
Zhao 2014 [54]	72	24	L DLPFC	10 Hz, 20 Hz, Theta burst	20	Once daily	1065, 2130, 1704	0.71	180°	PANSS

AHRS = Auditory Hallucinations Rating Scale; BL = Bilateral; DLPFC = dorsolateral prefrontal cortex; L = Left; PANSS = Positive and Negative Syndrome Scale; R = Right; rTMS – repetitive transcranial magnetic stimulation; TPJ = Temporo-parietal junction.

3.3.2. Positive psychotic symptoms

We analyzed data from 22 studies reporting PANSS positive subscale scores from 585 patients undergoing active rTMS treatment and 414 patients allocated to sham treatment [26–28,32,35,36,40–54]. There was no significant effect of treatment (Hedge's $g = 0.28$, $p = 0.13$) with evidence of substantial heterogeneity ($I^2 = 87.87\%$). Older age was associated with a small increase in positive symptom scores regardless of condition ($p < 0.006$) but the effect of the other patient-related variables was not significant ($p > 0.08$) (Table S4). It is noteworthy that the direction of change, albeit not significant in this dataset, suggests that rTMS may be associated with worsening of positive

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Table 3
Summary of the results of meta analyses of the efficacy of tDCS or rTMS in the treatment of auditory hallucinations, positive, negative and overall symptoms in patients with schizophrenia.

tDCS vs sham									
Outcome	Hedge's g effect size	P Value	I^2 statistic	Q value	Q degrees freedom	Tau^2	Number of datasets	Number of patients in the active condition	Number of patients on sham condition
Composite Hallucinations	−0.28	0.38	77.11	17.47	4	0.42	5	80	61
PANSS Positive	−0.10	0.59	42.30	10.39	6	0.10	7	97	93
PANSS Negative	−0.63	0.02	69.70	19.80	6	0.35	7	97	93
PANSS Total	−0.48	0.12	72.94	18.48	5	0.40	6	86	77

rTMS vs sham									
Outcome	Hedge's g effect size	P Value	I^2 statistic	Q statistic	Q degrees freedom	Tau^2	Number of datasets	Number of patients in the active condition	Number of patients on sham condition
Composite Hallucinations	−0.51	0.0001	58.81	41.26	17	0.18	18	340	238
PANSS Positive	0.28	0.13	87.87	214.44	26	0.81	27	585	414
PANSS Negative	−0.49	0.01	86.60	149.28	20	0.72	21	496	373
PANSS Total	−0.29	0.06	78.63	93.59	20	0.38	21	467	350

PANSS = Positive and Negative Syndrome Scale; rTMS = Repetitive Transcranial Magnetic Stimulation, tDCS = Transcranial Direct Current Stimulation; the composite hallucinations score derived from ratings using the Auditory Hallucinations Rating Scale and the PANSS auditory hallucination score.

symptoms. This is further supported by the association between worsening of positive symptoms and rTMS stimulation parameters; specifically higher positive symptom scores were associated with high frequency stimulation (over 20 Hz) (Hedge's g = 0.64, p = =0.0008), 110% motor threshold intensity (Hedge's g = 1.13, p = 0.001), trials lasting over 3 weeks (Hedge's g = 0.70, p = 0.01) and treatment site over the prefrontal cortex (PFC) (Hedge's g = 0.84, p = 0.006) (Table S5).

3.3.3. Negative symptoms

We analyzed data from 19 studies reporting on changes in the PANSS negative symptoms subscale score from 496 patients undergoing active rTMS treatment and 373 patients undergoing sham treatment [27,29,35,39,40,42–55]. There was a significant effect of treatment (Hedges' g = −0.49, p = 0.01) with evidence of considerable heterogeneity (I^2 = 86.60%). Older age predicted greater symptom reduction (active treatment coefficient = −0.09, p = 0.001; sham treatment coefficient = −0.09, p = 0.004) in both treatment groups but the opposite was the case for male sex (coefficient = 0.03, p = 0.03). No other patient-related characteristic had a significant effect (p > 0.06) (Table S4). Greater reduction in negative symptoms was associated with using pulse frequency of 20–50 Hz (Hedge's g = −0.93, p = 0.03), motor threshold intensity of 110% (Hedge's g = −1.07, p = 0.0005), trial duration over 3 weeks (Hedge's g = −0.90, P = 0.001) and treatment site over the left PFC (Hedge's g = −0.72, P = 0.007) (Table S5).

3.3.4. Overall symptom severity

We analyzed data from 18 studies reporting PANSS total scores derived from 467 patients receiving active rTMS and 350 patients receiving sham treatment [27,28,32,34,35,39,46–57]. There was no significant effect of treatment (Hedge's g = −0.29, p = 0.06) and the level of heterogeneity was high (I^2 = 78.63%). Older age was associated with marginally greater symptoms reduction in the sham group (coefficient = −0.06, p = 0.02). No other patient-related characteristic had a significant effect (p > 0.07) (Table S4). Greater reductions in general psychopathology were associated with pulse frequency of 20–50 Hz (Hedge's g = −0.97, p = 0.002), motor threshold intensity of 110% (Hedge's g = −0.53, p = 0.02), trail duration over 3 weeks (Hedge's g = −0.50, P = 0.01) and treatment site over the PFC (Hedge's g = −0.50, p = 0.02) (Table S5).

3.4. Safety and tolerability

Details of the safety and tolerability of tDCS and rTMS are shown in supplemental Tables S6 and S7. In tDCS, the most commonly reported adverse event was itchiness under the electrode; there were no dropouts and no effect of treatment condition on the rates of reported side-effects. In rTMS, dropouts in the active (n = 56) or sham condition (n = 44) were comparable (OR = 1.06, 95% CI 0.70–1.60, z = 0.29, p = 0.76). A significantly higher number of side effects (OR = 1.6, 95% CI 1.28–2.11, z = 3.96, p = 0.0001) was reported for the active rTMS (n = 245) than for the sham (n = 145) condition. The most common adverse event was headache which was also significantly more prevalent in the active treatment group (OR = 3.15, 95% CI 1.65–5.99, z = 3.50, p = 0.0005).

4. Discussion

We conducted a systematic review and quantitative meta-analyses of RCTs that compared tDCS or rTMS to sham treatment in patients with schizophrenia. Meta-analyses are inherently limited by the design and availability of the primary studies. We note that the sample size of each primary study was small and the total number of studies, especially for tDCS, was also small. Nevertheless, we were able to provide new information regarding the efficacy of tDCS and rTMS across multiple symptom domains and quantify the contribution of variables pertaining to patient- and protocol-related features. The results regarding the clinical efficacy of tDCS and rTMS in schizophrenia encourage therapeutic optimism particularly since the patients enrolled in the RCTs were selected on the basis of their inadequate response to antipsychotic medication. At the same time, our results suggest that neuromodulation interventions affect symptom dimensions differently in a way that may reflect the interaction between disorder- and treatment-related mechanisms.

First it is worth noting that demographic and clinical variables made minimal contributions to efficacy (Tables S3 and S4), suggesting that tDCS and rTMS may benefit patients regardless of sex, age and disease stage. Concomitant antipsychotic medication had some effect on the efficacy of rTMS but the data were not sufficient to draw conclusions for tDCS. Also, the tolerability profile of both modalities was very favorable (Tables S6 and S7). In the

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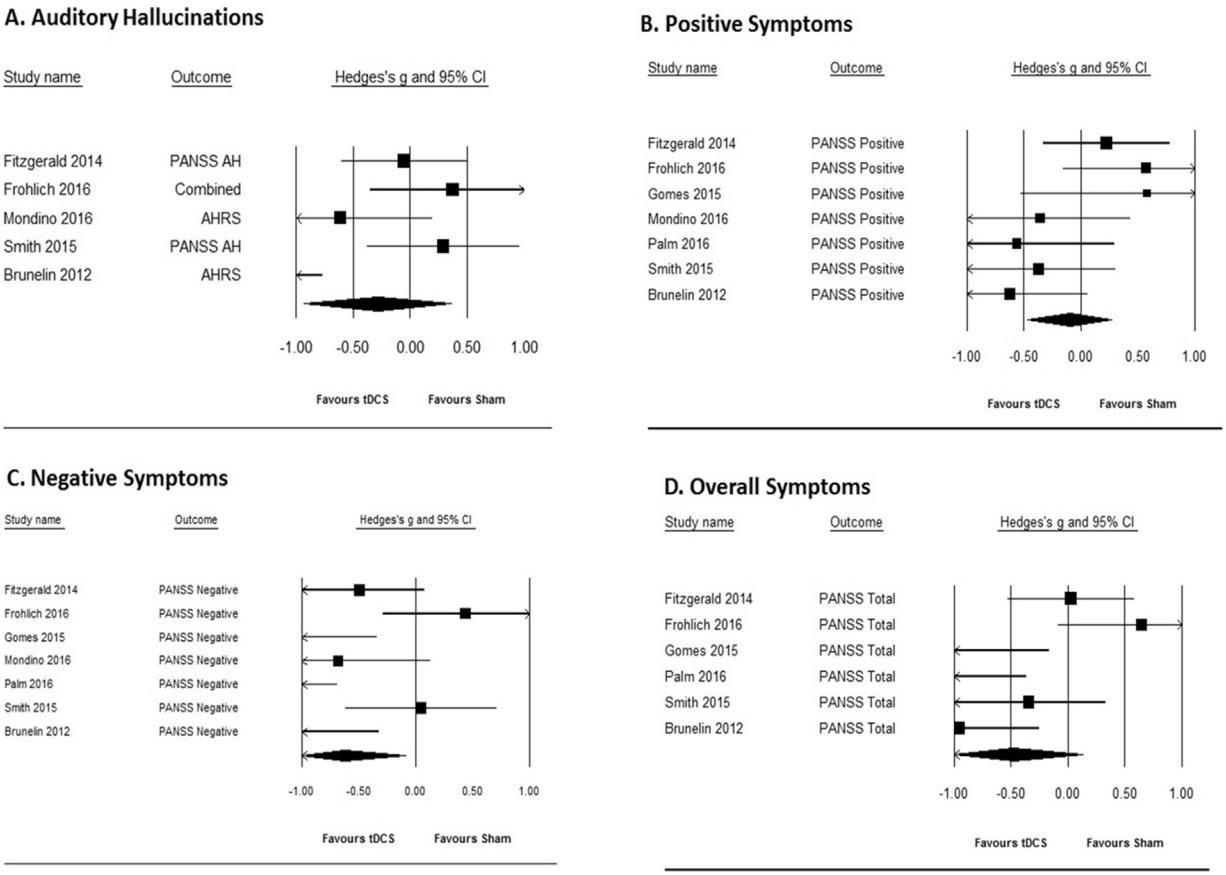

Fig. 1. Forest of plots the Hedges' g effect size comparing transcranial direct current stimulation (tDCS) to sham on auditory hallucinations, positive, negative and overall symptoms.

context of the stimulation parameters employed in the studies examined, tDCS was associated with fewer and less clinically significant adverse events.

The evidence-base regarding the efficacy of tDCS in schizophrenia is currently limited. It is encouraging to note that active tDCS was associated with reduction in every symptom dimension examined, with effect sizes ranging from 0.10 to 0.63. In the case of the AHRS for example, these reductions would correspond to an average drop of 2 to 9 points. On the data available, a significant treatment effect was present only for negative symptoms. The effect of active tDCS on hallucinations did not reach significance but this should to be considered in the context of the moderator effects of "dose". Higher cumulative stimulation was associated with increased reduction in auditory hallucinations. A trend in the same direction was also present for positive symptoms. These findings may account for the between-study variability observed in the efficacy of tDCS on hallucinations and the lack of a significant overall effect in this meta-analysis for hallucinations and positive symptoms. Our results suggest that current protocols may be affected by "underdosing" which could be improved by increasing current amplitude or frequency of treatment administration. However tDCS "dose" showed a minimal and non-significant association with improvement in negative symptoms. Differences in the neural correlates of the different symptom dimensions of psychosis may account for this finding. Negative symptoms are closely linked to PFC hypofunction [58–60] while auditory hallucinations are often considered in terms of a dual pathology involving prefrontal hypofunction coupled with hyperactivation in temporo-parietal regions involved in auditory and speech processing [61,62]. A plausible and testable hypothesis is that changes in PFC function conducive to improvement in negative symptoms may require lower overall stimulation levels and are thus less sensitive to tDCS stimulation parameters. Reduction in auditory hallucinations on the other hand may rely on "dose-dependent" hyperpolarization of auditory/speech-related regions under the cathode. Computational modeling of the spatial distribution of electric fields induced by tDCS would be a fruitful way forward in linking "dose" and efficacy. It was not possible to examine this here because the limited inter-study variability in tDCS montages. This represents a limitation for this study and for the field. In addition, we are not able to find computational modeling studies of tDCS for auditory hallucinations in the literature. There are several groups [63–67] including our own [68,69] that are developing pipelines for the quantification of electric fields generated by tDCS that could be usefully implemented in future clinical trials to evaluate targeting of specific brain regions with various stimulation parameters (e.g., the electrode/coil configuration, current amplitude, pulse width, frequency, number of pulse). Knowing the resulting distribution of the electric field is instrumental yet no easy conclusions can be drawn in terms of the resulting location-dependent changes in neuronal activity due to potentially quite different responses shaped by area-specific neurophysiology.

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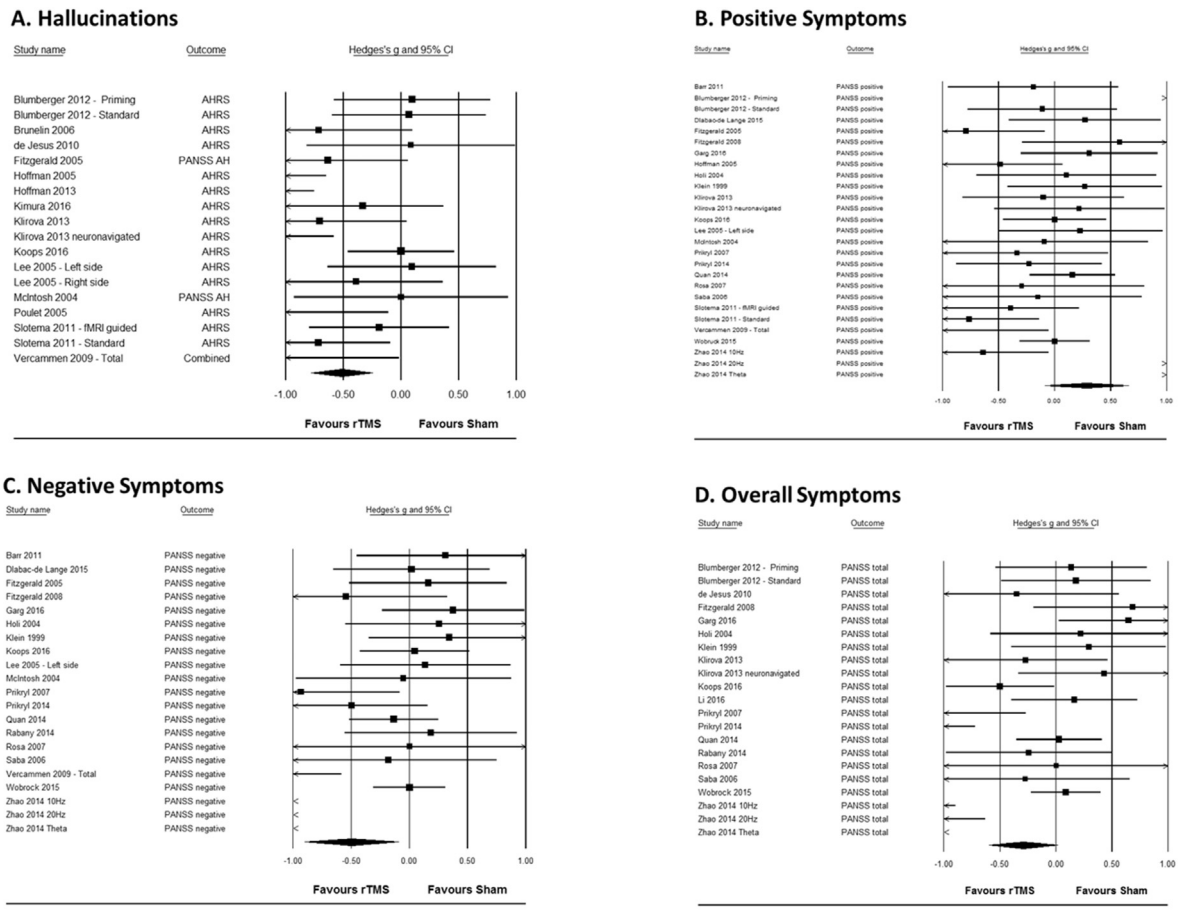

Meta-analyses conducted using a random effect model; the severity of auditory hallucinations was assessed using a composite score derived from the Auditory Hallucinations rating Scale (AHRS) and Positive and Negative Syndrome Scale (PANSS) hallucination score

Fig. 2. Forest of plots the Hedges' g effect size comparing repetitive transcranial magnetic stimulation (rTMS) to sham on auditory hallucinations, positive, negative and overall symptoms.

The relationship between rTMS efficacy and stimulation parameters showed a much more complex pattern that was not linearly associated with cumulative dose. Our analyses suggests that rTMS is effective in the treatment of hallucinations and negative symptoms, thus confirming and extending earlier meta-analyses [9–11]. The effect sizes reported here are also in line with previous literature [9–11]. As the majority of rTMS studies that focused on hallucinations targeted the left TPJ using low pulse frequencies (<10 Hz) we were not able to examine the moderator effect of stimulation parameters because of the limited inter-study variability. In terms of negative symptoms however, we confirmed previous findings that rTMS-induced improvement is associated with higher pulse frequencies (>20 Hz), motor threshold intensity of 110%, treatment site at the left PFC and trial duration of at least 3 weeks [10,11].

A novel but tentative finding concerns the effect of rTMS on the overall severity of positive symptoms, where a deterioration was noted. This is consistent with reports of worsening psychotic symptoms in the primary studies (Supplemental Table S6). Moreover, stimulation parameters (pulse frequency, motor threshold intensity, treatment site and trial duration) that predicted improvement in hallucinations were also significantly associated with worsening of overall positive symptoms. Pulse frequencies over 5 Hz are thought increase cortical excitability and dopamine release in subcortical regions including the basal ganglia [70,71]. It is possible that in a sizeable number of patients, rTMS stimulation at higher frequencies over the PFC may increase dopaminergic neurotransmission and/or disrupt the balance of inhibition and excitation with detrimental effects for positive symptoms. Testing this hypothesis in future studies would be important in refining rTMS applications in patients with psychosis.

In summary, the current study suggests that hallucinations may be particularly responsive to neuromodulation techniques that specifically reduce cortical excitability over auditory and language related regions. Current rTMS protocols yield more consistent reduction in hallucinations than current tDCS protocols. Arguably, the most significant limitation of the tDCS research at the moment is the lack of large RCTs, which should be priority in moving forward. Specifically for tDCS, changes in other parameters of study design may also be necessary including improved assessment of blinding and standardization of the environment in which tDCS takes place [72]. Further improvement may also be achieved by increasing stimulation parameters relating to current amplitude or administration density. Both neuromodulation methods improved negative symptoms largely to the same degree. In addition, our data raise the possibility that the hypothesized increased in PFC excitability may be difficult to titrate at the level of individual patients and may lead to worsening of positive symptoms in rTMS

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trials. The evidence for this would require further assessment and validation. The differential effect of tDCS and rTMS on symptom dimensions justifies their separate examination as joint analyses may obscure nuanced differences between the two that are informative in terms of the interactions between disease and therapeutic mechanisms. Our study enriches our understanding of the factors associated with the clinical efficacy of neuromodulation interventions in schizophrenia and identifies specific new directions for future research.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eurpsy.2017.12.025.

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