A meta-analysis of transcranial direct current stimulation for schizophrenia: "Is more better?"

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ABSTRACT

Transcranial direct current stimulation (tDCS) has generated interest in recent years as a potential adjunctive treatment for patients with schizophrenia. The primary objective of this meta-analysis was to evaluate the efficacy of tDCS on positive symptoms, particularly auditory hallucinations, and negative symptoms. A literature search of randomized sham-controlled trials was conducted using the OVID database on October 9, 2018. The standardized mean differences (SMDs) were calculated to examine changes in symptom severity between active and sham groups for the following symptom domains: auditory hallucinations, positive symptoms (including auditory hallucinations), and negative symptoms. Moderator analyses were performed to examine the effects of study design and participant demographics. We identified 10 eligible studies. Main-analyses showed no effects of tDCS on auditory hallucinations (7 studies, n = 242), positive symptoms (9 studies, n = 313), or negative symptoms (9 studies, n = 313). Subgroup analyses of studies that applied twice-daily stimulation showed a significant reduction in the severity of auditory hallucinations (4 studies, n = 138, SMD = 1.04, $p = 0.02$). Studies that applied ≥ 10 stimulation sessions showed a reduction in both auditory hallucination (5 studies, n = 186, SMD = 0.86, $p = 0.009$) and negative symptom severity (7 studies, n = 257, SMD = 0.41, $p = 0.04$). Meta-regression analyses revealed a negative association between mean age and the SMDs for auditory hallucinations and negative symptoms, and a positive association between baseline negative symptom severity and the SMDs for negative symptoms. Our findings highlight the need to optimize tDCS parameters and suggest twice-daily or 10 or more stimulation sessions may be needed to improve clinical outcomes in patients with schizophrenia.

1. Introduction

Schizophrenia is a chronic disorder that affects approximately 1% of the world's population (McGrath et al., 2008; Simeone et al., 2015). The primary treatment for patients with schizophrenia is antipsychotic medications. However, studies have reported that 25–30% of patients show partial or no response despite the optimization of currently available treatment strategies (Lindenmayer, 2000; Suzuki et al., 2011). Furthermore, antipsychotic medications have limited efficacy in treating negative or cognitive symptoms (George et al., 2013), indicating the need for alternative treatment approaches.

Non-invasive neurostimulation techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are increasingly being investigated as a potential treatment tool for various neuropsychiatric conditions (Dayan et al., 2013; Kuo et al., 2014). Several meta-analyses have shown the efficacy of rTMS in reducing the severity of auditory hallucinations and negative symptoms in patients with schizophrenia (Dlabac-de Lange et al., 2010; Shi et al., 2017; Slotema et al., 2012). However, current guidelines suggest that there is insufficient evidence to recommend rTMS as a treatment for patients with schizophrenia (Hasan et al., 2015; Lefaucheur et al., 2017).

tDCS has generated interest as a substantially cheaper, portable, and easier to use neurostimulation method than rTMS (Gandiga et al., 2006; Tortella et al., 2015). Along with employing a more convincing sham stimulation, these qualities make tDCS optimal for randomized controlled trials (RCT) and clinical use, if proven efficacious (Gandiga et al., 2006). tDCS induces a weak electric current (typically 1–2 mA) that flows from the anodal to cathodal electrodes placed on the scalp (Miranda et al., 2006). While the precise mechanism remains to be elucidated, it is thought that anodal stimulation increases cortical excitability whereas cathodal stimulation decreases cortical excitability, causing the respective depolarization and hyperpolarization of neurons (Cambiaghi et al., 2010; Nitsche and Paulus, 2000).

The use of tDCS to enhance cognition in patients with schizophrenia is especially promising (Hoy et al., 2014; Nienow et al., 2016; Orlov et al., 2017). A recent meta-analysis of 6 RCTs in schizophrenia reported a positive effect of tDCS on working memory and attention (Mervis et al., 2017). With respect to positive and negative symptoms, initial case studies and open-labelled studies investigating the effects of tDCS have shown positive results (Mondino et al., 2015). In the first RCT of tDCS in schziophrenia, Brunelin et al. reported a significant reduction in the severity of auditory hallucinations, with tDCS' effects lasting 3 months after stimulation in refractory schizophrenia. The same study showed moderate effects on positive and negative symptoms (Brunelin et al., 2012). However, the results of subsequent open-labelled and sham-controlled trials have been inconsistent, in part due to the use of different tDCS protocols employed across studies.

The present study builds upon previous meta-analyses that investigated the effects of tDCS in patients with schizophrenia. Aleman et al. included 5 RCTs and reported a trend toward a significant effect of tDCS over the frontal cortex on negative symptoms (Cohen's d = 0.50, p = 0.08) (Aleman et al., 2018). Similarly, Kennedy et al. and Osoegawa et al. reported a positive effect of tDCS on negative symptoms (7 RCTs, Hedge's g = −0.63, p = 0.02 and 6 RCTs, Hedge's g = 0.5, 95% CI 0.02–0.97, respectively) (Kennedy et al., 2018; Osoegawa et al., 2018). The present study will include 10 RCTs to evaluate the effects of tDCS on positive (including a separate analysis for auditory hallucinations) and negative symptoms. Importantly, moderator analyses will also be performed to examine the influence of study protocol and participant demographics on clinical outcomes. Given the heterogeneity of tDCS methodology among studies, moderator analyses will help establish optimal tDCS protocol parameters for patients with schizophrenia (Kennedy et al., 2018).

2. Methods

2.1. Literature search

This meta-analysis was conducted in accordance with the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) group (Moher et al., 2009). English language publications from 1950 to October 2018 were searched for using the OVID database (Embase, Medline®, and PsycINFO). The following terms were used to conduct the search: (transcranial direct current stimulation or tDCS) and (schizophreni* or psychosis). The reference sections of review articles were gleaned for relevant publications overlooked by the search strategy. Two individuals (JK and PG) performed the search (last search: October 9, 2018), assessed eligibility, and extracted the data.

2.2. Eligibility criteria

Studies were included if: (1) they consisted of at least 5 participants with schizophrenia or schizoaffective disorder, (2) they included a sham group, and (3) data were sufficient to obtain the standardized mean difference (SMD) for the change in severity of the primary outcomes. If a study tested 2 electrode montages, the effects of both were

combined for the main-analyses, but analyzed separately for subgroup analyses. Studies that only reported on the frequency of symptoms were excluded. Studies that combined tDCS with intervention strategies other than antipsychotic medication (e.g., psychoeducation or cognitive training) were also excluded.

2.3. Possible duplication of data

If ≥ 2 studies reported on completely overlapping samples, data from the study with the largest sample size was included to reduce multiple weighting of the same data. If there was a possibility of an overlap, and this was not specified in the publication, the authors were contacted for clarification. If two studies reported on partially overlapping samples, both studies were included in the main-analyses and subgroup analyses. If significant effects were observed, subsequent analyses were performed to exclude the study with a smaller sample size.

2.4. Recorded variables

2.4.1. Demographic and clinical characteristics

Where available, demographic and clinical characteristics, including age, sex, age at illness onset, duration of illness, baseline symptom severity, and antipsychotic drug and daily dose were obtained.

2.4.2. Outcome measures

The main outcomes included in this meta-analysis were auditory hallucinations, positive symptoms (including auditory hallucinations), and negative symptoms. For each study, symptom severity at baseline and post-tDCS were obtained for both the active and sham groups.

2.4.3. Auditory hallucinations

The severity of auditory hallucinations was measured using one of the following scales: Auditory Hallucinations Rating Scale (AHRS) (Hoffman et al., 2003), Psychotic Symptom Rating Scales (PSYRATS) auditory hallucinations subscale (Haddock et al., 1999), or the Positive and Negative Syndrome Scale (PANSS) P3 hallucinatory behavior item (Kay et al., 1987). Higher scores on these scales represent greater severity of auditory hallucination.

2.4.4. Positive symptoms

Symptom severity was derived from both the original version of the PANSS that includes 3 subscales, i.e., positive, negative, and general psychopathology subscales (Kay et al., 1987), or the 5-factor-model (Higuchi et al., 2014; Lindenmayer et al., 1995). If available, the Scale for the Assessment of Positive Symptoms (SAPS) or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) was also measured.

Positive symptom severity was measured using the PANSS positive subscale, including the PANSS P3 hallucinatory behavior item (Kay et al., 1987), or the PANSS positive factor (Higuchi et al., 2014; Lindenmayer et al., 1995). Higher scores on these scales represent greater positive symptom severity. The SAPS was used in 1 study to assess symptom severity at baseline (Bose et al., 2017). However, no post-tDCS treatment SAPS scores were reported.

2.4.5. Negative symptoms

Negative symptom severity was measured using the PANSS negative subscale (Kay et al., 1987), the PANSS negative factor (Higuchi et al., 2014; Lindenmayer et al., 1995), or the SANS (Andreasen, 1983). In studies where both PANSS and SANS were reported, SANS was included in the analyses according to the NIMH consensus statement on negative symptoms (Kirkpatrick et al., 2006). Higher scores on both of the PANSS and the SANS represent greater negative symptom severity. In studies where both PANSS negative subscale and PANSS negative factor

scores were reported, the PANSS negative subscale scores were preferred to maximize the sample for comparison between studies. Studies that reported PANSS negative factor scores were separately analyzed in a subgroup analysis.

As depressive symptoms are frequently reported in conjunction with negative symptoms, a separate exploratory analysis was performed for depressive symptoms. Depressive symptoms in schizophrenia were measured using the Calgary Depression Rating Scale (CDRS) or the PANSS depressive factor scores (Lindenmayer et al., 1995).

2.5. Data analysis

2.5.1. Meta-analysis

The meta-analysis was performed using Review Manager Version 5.3 (http://tech.cochrane.org/revman). Main-analyses were performed to investigate the effects of tDCS on each of the main outcomes.

The mean change in symptom severity (i.e., post-tDCS minus baseline score), or if available, the adjusted mean change (i.e., estimated mean difference including the baseline score as a covariate) and standard deviation (SD) of the mean change were extracted separately for the active and sham groups. If SD values for the mean change were not available, and the correlation coefficients were not reported, the post-tDCS scores and SDs were used in accordance with the guidelines from the Cochrane Handbook for Systematic Review of Intervention (9.4.5.2 Meta-analysis of change scores) (http://www.cochrane-handbook.org).

SMD for each study were calculated by dividing the mean difference between groups (i.e., active minus sham) by the pooled SDs. A total SMD was calculated for each symptom domain. Positive SMDs were interpreted as favoring active stimulation and negative SMDs were interpreted as favoring sham stimulation. The inverse variance statistical method and random effects model were used to account for study heterogeneity. Two-sided 95% confidence intervals (CIs) were used to assess significance.

2.5.2. Moderator analyses

Subgroup analyses were performed to separately examine: (1) the effects of tDCS parameters (i.e., sessions per day and total number of stimulation sessions) (Woods et al., 2016), (2) the effects of electrode placement (i.e., left fronto-temporoparietal placement for auditory hallucinations, bi-frontal placement for negative symptoms, and both left fronto-temporoparietal and bi-frontal placement for positive symptoms), (3) studies that reported PANSS positive and negative factors scores, and (4) non-overlapping samples. Subgroups of studies that applied once- or twice-daily, 5 or ≥10 stimulation sessions were analyzed separately. The fronto-temporoparietal placement was defined as anode placed over the left prefrontal cortex (i.e., F3 or between F3 and FP1 using the 10/20 international EEG electrode placement system) and the cathode over the left temporoparietal junction (i.e., between T3 and P3). The bi-frontal placement was defined as anode over the left prefrontal cortex (i.e., F3 or between F3 and FP1), and cathode over the right supraorbital region (i.e., F4 or FP2) (Mondino et al., 2015).

Meta-regression analyses were conducted using Comprehensive Meta-Analysis (CMA) (www.meta-analysis.com). The relationships between SMDs for each study and age, percent (%) male, sample size, and baseline symptom severity were examined. This was not possible for age of illness onset, duration of illness, and medication dose as an insufficient number of studies reported these values.

2.5.3. Sensitivity analysis

Study heterogeneity was assessed using I^2 statistic, with $I^2 \geq 50\%$ indicating significant heterogeneity (DerSimonian and Laird, 1986). If heterogeneity was present, leave-one-out sensitivity analyses were conducted to assess for the possible potential influence of a single study on total SMDs and *p*-values.

2.5.4. Publication bias

Publication bias was assessed using Egger's regression test (Egger et al., 1997). If publication bias was observed a trim-and-fill procedure was applied (Duval and Tweedie, 2000).

2.5.5. Risk of bias

Risk of bias of studies was evaluated using the 'risk of bias' assessment tool (Higgins JPT and Sterne, 2011). The following domains were assessed: selection bias (i.e., random sequence generation, allocation concealment), performance bias (i.e., blinding of participant and personnel), attrition bias (incomplete outcome data), detection bias (i.e., blinding of outcome assessment), and reporting bias (i.e., selective reporting).

3. Results

3.1. Included studies

The literature search identified 10 eligible studies (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Gomes et al., 2018; Jeon et al., 2018; Mondino et al., 2016; Palm et al., 2016; Smith et al., 2015). Of these, 1 study reported on partially overlapping samples (Mondino et al., 2016). Of note, Gomes et al. (2015), which was included in previous meta-analyses, was excluded from the current study due to complete sample overlap with a more recent study by the same investigators (Gomes et al., 2018). Fig. 1 displays the PRISMA flow diagram of the inclusion and exclusion process. The participant characteristics and the tDCS parameters for each of the studies included are listed in Table 1. A total of 338 participants were included. Of the included studies, 7 reported on auditory hallucinations (n = 242), and 9 reported on both positive and negative symptoms (n = 313). With respect to the tDCS parameters, 6 studies used a left fronto-temporoparietal electrode placement (n = 190) (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016), and 4 studies used a bi-frontal placement (n = 126) (Gomes et al., 2018; Jeon et al., 2018; Palm et al., 2016; Smith et al., 2015). Nine studies used a current of 2 mA, and 1 study used 2 tDCS machines to simultaneously apply +2 mA under the anode, and –2 mA under the cathode (n = 24) (Frohlich et al., 2016). Nine studies applied tDCS for 20-min per session and 1 study (Jeon et al., 2018) applied tDCS for 30-min per session. Two studies applied tDCS once-daily for 5-days (Frohlich et al., 2016; Smith et al., 2015). Eight studies applied tDCS for ≥10 stimulation sessions, of which 4 applied twice-daily stimulation across 5-days (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Mondino et al., 2016), and the other 3 studies applied once-daily stimulation for 10 days (Gomes et al., 2018; Jeon et al., 2018; Palm et al., 2016) or 15-days (Fitzgerald et al., 2014) (Fig. 2).

3.2. Auditory hallucinations

Seven studies were included in the analysis of auditory hallucinations (n = 242) (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016; Smith et al., 2015). There was no main effect of tDCS on the severity of auditory hallucinations (SMD = 0.50, 95% CI -0.09–1.09, *p* = 0.10) (Fig. 3A).

A subgroup analysis of studies that applied twice-daily stimulation (4 studies, n = 138) (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Mondino et al., 2016) or 10 or more sessions (5 studies, n = 186) (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Mondino et al., 2016) (Fig. 4A) showed a significant reduction in the severity of auditory hallucinations with active compared to sham stimulation (SMD = 1.04, 95% CI 0.20–1.89, *p* = 0.02 and SMD = 0.86, 95% CI 0.22–1.51, *p* = 0.009, respectively). . The findings remained significant after excluding Mondino et al.,
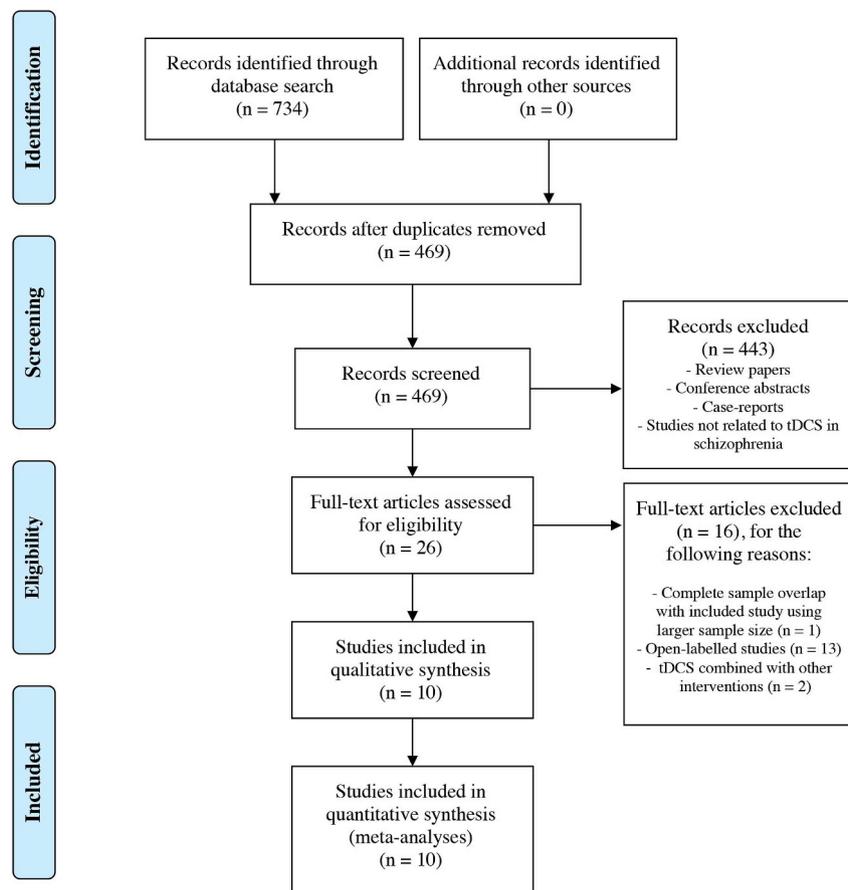
Fig. 1. PRISMA flow diagram illustrating the literature search, and the inclusion and exclusion process.

(2016) that reported on a partially overlapping sample. A subgroup analysis of studies that applied once-daily stimulation showed no effect. A subgroup analysis of studies using a left fronto-temporoparietal placement (6 studies, n = 190) did not reach significance (SMD = 0.68, 95% CI -0.02–1.38, $p = 0.06$) (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016).

Meta-regression analyses showed a negative association between SMD for each study and mean age (7 studies, slope = −0.15, 95% CI -0.22 to −0.09, $p < 0.001$) (Figure S1A). There were no association between SMD and % male, sample size, or baseline AHRS scores.

3.3. Positive symptoms

Nine studies were included in the analysis of positive symptoms (n = 313) (Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Gomes et al., 2018; Jeon et al., 2018; Mondino et al., 2016; Palm et al., 2016; Smith et al., 2015). Five studies only reported PANSS positive subscale scores (Fitzgerald et al., 2014; Frohlich et al., 2016; Jeon et al., 2018; Mondino et al., 2016; Smith et al., 2015), 2 studies only reported PANSS positive factor scores (Brunelin et al., 2012; Chang et al., 2018), and 2 studies reported both (Gomes et al., 2018; Palm et al., 2016).

There was no main effect of tDCS on positive symptom severity (SMD = 0.03, 95% CI -0.24–0.31, $p = 0.81$) (Fig. 3B). Subgroup analyses showed no effect of tDCS parameters (once-daily or twice-daily, or 10 or more sessions) or electrode placement (i.e., fronto-temporoparietal or bi-frontal design) on positive symptom severity. There was also no effect observed in studies that measured positive symptom severity using PANSS positive factor scores. Meta-regression analyses revealed no associations between SMD and mean age, % male, sample size, or baseline PANSS positive subscale scores.

3.4. Negative symptoms

Nine studies were included in the analysis of negative symptoms (n = 313) (Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Gomes et al., 2018; Mondino et al., 2016; Palm et al., 2016; Smith et al., 2015). Five studies only reported PANSS negative subscale scores (Fitzgerald et al., 2014; Frohlich et al., 2016; Jeon et al., 2018; Mondino et al., 2016; Smith et al., 2015), 2 studies only reported PANSS negative factor scores (Gomes et al., 2018; Palm et al., 2016). Fitzgerald et al. and Palm et al. also reported SANS scores (Fitzgerald et al., 2014; Palm et al., 2016).

There was no main effect of tDCS on negative symptom severity (SMD = 0.27, 95% CI -0.09–0.62, $p = 0.14$) (Fig. 3C). A subgroup analysis of studies with ≥10 stimulation sessions (7 studies, n = 257) revealed a significant reduction in negative symptoms (SMD = 0.41, 95% CI 0.01–0.81, $p = 0.04$) (Fig. 4B) (Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Gomes et al., 2018; Jeon et al., 2018; Mondino et al., 2016; Palm et al., 2016). Subgroup analyses of studies that applied once-daily (3 studies, n = 113) or twice-daily stimulation (6 studies, n = 200), bi-frontal electrode placement (4 studies, n = 126), or measured negative symptom severity using PANSS negative factor scores (4 studies, n = 134) showed no effect of tDCS on negative symptom severity.

Meta-regression analyses revealed a negative association between SMD and age (9 studies, slope = −0.08, 95% CI -0.16 to −0.02, $p = 0.02$) (Figure S1B). There was also a positive association between SMD and baseline PANSS negative subscale score (7 studies, slope = −0.16, 95% CI 0.04–0.28, $p = 0.009$) (Figure S1C). There was no association between SMD and % male.

Table 1
Participant characteristics and tDCS parameters for each included study.

Authors (Year)	n	Diagnosis	Mean Age (SD, if available)	Sex (% Male)	Medication Status (Equivalent Dose [mg/dl])	Electrode Placement	Electric Current (mA)	Single Session Duration (min)	Session /Day	Total Sessions	Extracted Outcome Measures
Chang et al. (2018)	60 (30 Active 30 Sham)	SCZ and SA with persistent auditory hallucination without remission despite adequate treatments for more than 3 months	44.3	45%	CPZ Eq: 493.6	Fronto-temporoparietal	+2	20	2	10	AHRS PANSS
Jeon et al. (2018)*	25 (25 Active 27 Sham)	SCZ	39.9	48%	CPZ Eq: 581.7	Bi-frontal	+2	30	1	10	PANSS CDRS
Jeon et al. (2018)	24 (12 Active 12 Sham)	SCZ	36.5	29%	N/A	Bi-frontal	+2	20	1	10	PANSS CDRS
Bose et al. (2017)	25 (12 Active 13 Sham)	SCZ with persistent auditory verbal hallucination without remission despite treatment with at least 1 antipsychotic medication at an adequate dosage for at least 3 months	31.3	56%	CPZ Eq: 705.4	Fronto-temporoparietal	+2	20	2	10	PSYRAT
Fröhlich et al. (2016)	26 (13 Active 13 Sham)	19 SCZ and 7 SA with at least 3 auditory hallucinations per week with at least 2 antipsychotic agents of adequate dose and duration	41.7	77%	N/A	Fronto-temporoparietal	A: +2 C: -2	20	1	5	AHRS PANSS
Mondino al. (2016)	23 (11 Active 12 Sham)	SCZ with persistent daily hallucinations without remission despite antipsychotic medication at an adequate dosage for at least 3 months	37.2	65%	OLN Eq: 30.4	Fronto-temporoparietal	+2	20	2	10	AHRS PANSS
Palm et al. (2016)	20 (10 Active 10 Sham)	SCZ with predominant negative symptoms	36.2 (11.4)	75%	CPZ Eq: 520.1	Bi-frontal	+2	20	1	10	PANSS SANS CDRS
Smith et al. (2015)	30 (15 Active 15 Sham)	19 SCZ and 14 SA Note. data from 3 participants were not included	45.8	72%	N/A	Bi-frontal	+2	20	1	5	PANSS
Fitzgerald et al. (2014)	24 (24 Active 24 Sham)	17 SCZ and 7 SA with persistent hallucinations and negative symptoms with a failure to respond to at least two adequate trials of antipsychotic medication	39.3 (11.7)	62%	N/A	Fronto-temporoparietal	+2	20	1	15	PANSS SANS
Brunelin et al. (2012)	30 (15 Active 15 Sham)	SCZ with persistent daily hallucinations without remission despite antipsychotic medication at an adequate dosage for at least 3 months	37.7	73%	CPZ Eq: 1101.5	Fronto-temporoparietal	+2	20	2	10	AHRS PANSS

SCZ: Schizophrenia, SA: Schizoaffective, OLN: Olanzapine, CPZ Eq: Chlorpromazine antipsychotic dose equivalents in mg/day, PANSS: Positive and Negative Syndrome Scale, Fronto-temporoparietal: anode/left prefrontal cortex (i.e., F3 or between F3 and FP1) and cathode/left temporoparietal junction (i.e., between T3 and P3), Bi-frontal: anode/left prefrontal cortex (i.e., F3 or between F3 and FP1) and cathode/right supraorbital region (i.e., F4 and FP2) using the 10/20 international EEG electrode placement system, AHRS: Auditory Hallucinations Rating Scale, PSYRATS: Psychotic Symptom Rating Scales, SANS: Scale for the Assessment of Negative Symptoms, CDRS: Calgary Depression Rating Scale. *Mean age, % male, and CPZ Eq of participants included at baseline (26 active and 28 sham).
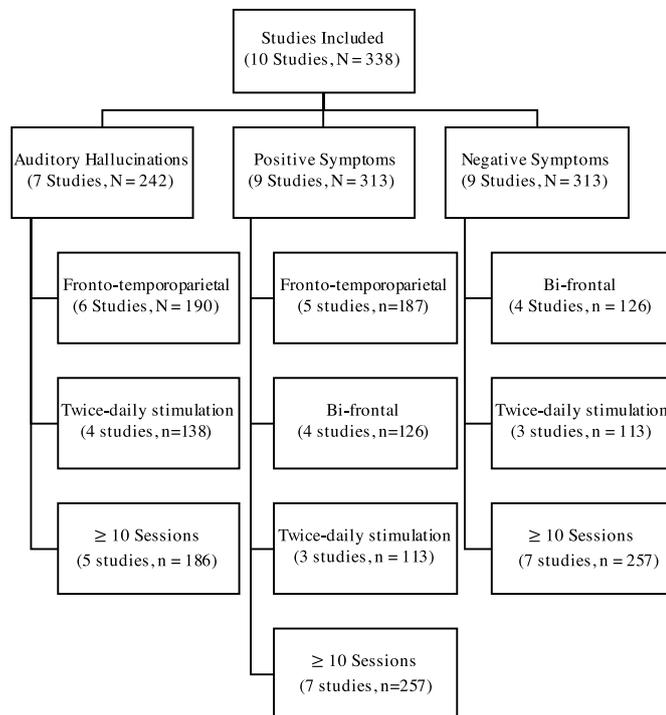
Fig. 2. Flow diagram with breakdown of all included studies. Fronto-temporoparietal: anode/left prefrontal cortex (i.e., F3 or between F3 and FP1) and cathode/left temporoparietal junction (i.e., between T3 and P3), Bi-frontal: anode/left prefrontal cortex (i.e., F3 or between F3 and FP1) and cathode/left supraorbital region (i.e., F4 and FP2) using the 10/20 international EEG electrode placement system.

3.5. Exploratory measures

Five studies were included in the analysis of depressive symptoms (n = 186) (Brunelin et al., 2012; Chang et al., 2018; Gomes et al., 2018; Jeon et al., 2018; Palm et al., 2016). Three studies reported CDRS scores (Gomes et al., 2018; Jeon et al., 2018; Smith et al., 2015) and 2 studies reported PANSS depressive factor scores (Brunelin et al., 2012; Chang et al., 2018). There was no main effect of tDCS on depressive symptoms (SMD = 0.20, 95% CI -0.23–0.62, p = 0.36).

3.6. Sensitivity analysis

There was high heterogeneity in the SMDs of studies examining the effect of tDCS on auditory hallucinations ($I^2 = 79\%$) and negative symptoms ($I^2 = 57\%$), but not positive symptoms ($I^2 = 32\%$). No single study examining the effects of tDCS on auditory hallucinations or negative symptoms contributed to the heterogeneity.

3.7. Publication bias

Egger's regression tests showed no publication bias for the main-analyses.

3.8. Risk of bias

The risk of "selection bias (i.e., biased allocation to intervention)" was "unclear" for 3 studies as they did not describe the sequence generation process. The risk of "performance bias" was "unclear" for 6 studies as they did not describe how the blinding of outcome assessment was ensured until the end of the study. The risk of "detection bias" was "low" for all studies. The risk of "attribution bias" and "reporting bias" was "low" for all studies. In total, 3 of 8 studies (37.5%) showed a

"low risk" on all items. The risk of bias assessment for each study is displayed in Figure S2.

4. Discussion

4.1. Main findings

Our main analyses did not show an effect of tDCS on positive or negative symptoms. However, subgroup analyses indicate that the frequency and total number of tDCS sessions may be important to improve clinical outcomes. Specifically, studies that applied twice-daily stimulation reduced the severity of auditory hallucinations, and studies that applied 10 or more stimulation sessions reduced both auditory hallucinations and negative symptom severity.
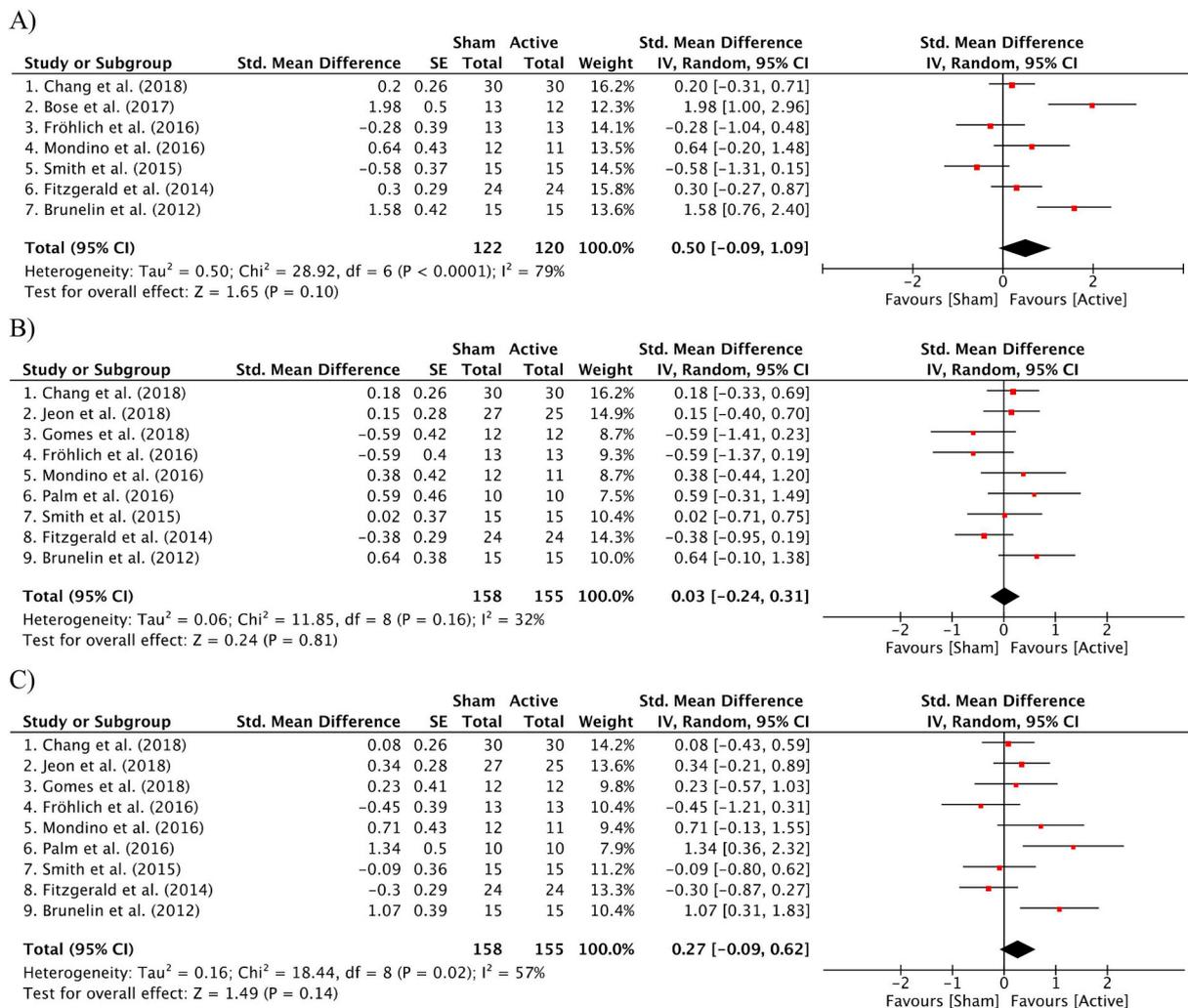
Since only a small number of studies were included in the subgroup analyses of electrode placement, at the current stage, it is unclear which electrode placement (i.e. bi-frontal, fronto-temporoparietal, or another proposed arrangement) is the most efficacious for auditory hallucinations and negative symptoms. However, the improvement of auditory hallucinations, independent of positive symptoms, suggests tDCS may have specificity for this symptom category. Further RCTs are needed to account for potential confounders and to directly compare the different electrode placements.

Meta-regression analyses showed that a lower mean age was associated with a greater reduction in auditory hallucinations and negative symptoms with tDCS. Furthermore, higher baseline negative symptom severity was associated with a greater reduction in negative symptoms, indicating studies with higher mean baseline symptom severity showed greater response to tDCS.
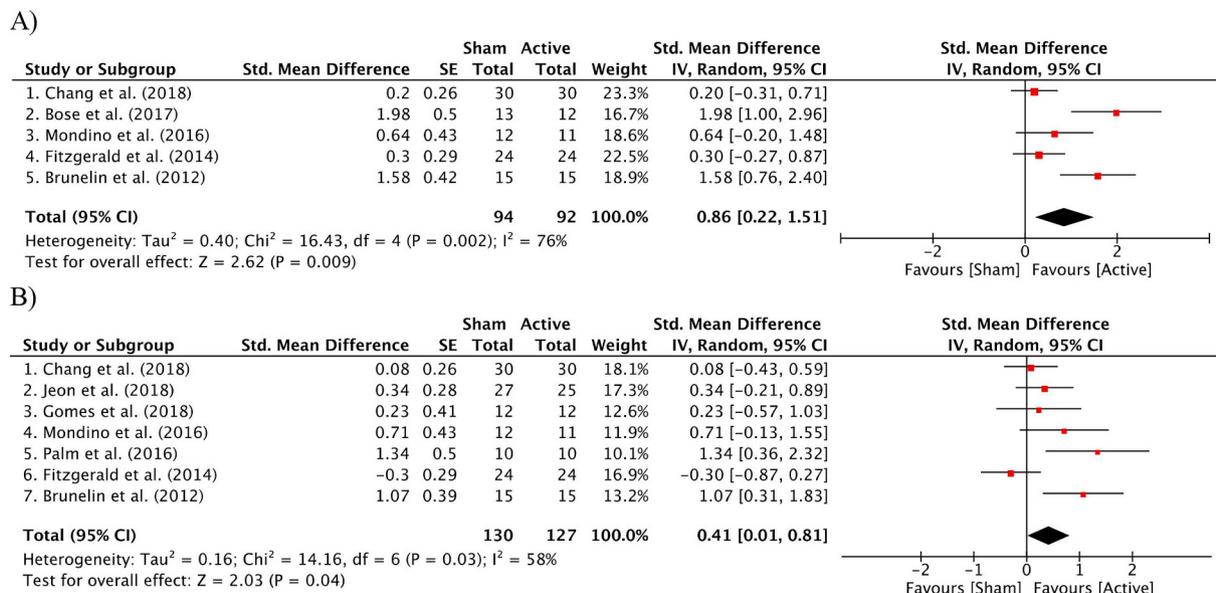
4.2. Analysis of included studies

4.2.1. Studies included for auditory hallucinations

Of the 7 studies included in the analysis of auditory hallucinations (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016; Smith et al., 2015), 1 study used a bi-frontal design (Smith et al., 2015), and 6 studies used a fronto-temporoparietal design (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016). All 6 studies reported on the effect of tDCS on auditory hallucinations as the primary outcome in treatment refractory patients, defined as having persistent auditory hallucinations or negative symptoms without remission despite treatment with at least one or two antipsychotic medications. Brunelin et al. using fronto-temporoparietal tDCS reported a robust effect of tDCS on auditory hallucinations, which was sustained up to 3 months (Brunelin et al., 2012). Mondino et al. (2016), which reported on partially overlapping samples, and Bose et al. (2017) reported similar results. All 3 studies (Bose et al., 2017; Brunelin et al., 2012; Mondino et al., 2016) applied twice-daily tDCS across 5-days for a total of 10 stimulation sessions. However, the most recent study by Chang et al., (2018), using the same parameters, failed to replicate the findings. The other 2 of the 5 studies using a left fronto-temporoparietal design did not find an effect of tDCS on auditory hallucinations (Fitzgerald et al., 2014; Frohlich et al., 2016). Fitzgerald et al. (2014) applied once-daily tDCS across 15-days and showed no changes in the severity of auditory hallucinations. However, it should be noted that this study included 24 participants that received unilateral (i.e., fronto-temporoparietal tDCS applied to the left-hemisphere) or bilateral stimulation (i.e., fronto-temporoparietal tDCS applied to both hemispheres) using 2 tDCS devices. All 24 participants received at least 1 active stimulation condition; specifically, 13 received active unilateral and 11 received active bilateral stimulation. In this meta-analysis, the effects of both montages were pooled for the main-analysis, but analyzed separately for subgroup analyses. Frohlich et al. (2016) applied once-daily left fronto-temporoparietal stimulation across 5-days and showed no improvement in

A)

Study or Subgroup	Std. Mean Difference	SE	Sham Total	Active Total	Weight	Std. Mean Difference IV, Random, 95% CI
1. Chang et al. (2018)	0.2	0.26	30	30	16.2%	0.20 [−0.31, 0.71]
2. Bose et al. (2017)	1.98	0.5	13	12	12.3%	1.98 [1.00, 2.96]
3. Fröhlich et al. (2016)	−0.28	0.39	13	13	14.1%	−0.28 [−1.04, 0.48]
4. Mondino et al. (2016)	0.64	0.43	12	11	13.5%	0.64 [−0.20, 1.48]
5. Smith et al. (2015)	−0.58	0.37	15	15	14.5%	−0.58 [−1.31, 0.15]
6. Fitzgerald et al. (2014)	0.3	0.29	24	24	15.8%	0.30 [−0.27, 0.87]
7. Brunelin et al. (2012)	1.58	0.42	15	15	13.6%	1.58 [0.76, 2.40]
Total (95% CI)			**122**	**120**	**100.0%**	**0.50 [−0.09, 1.09]**

Heterogeneity: Tau^2 = 0.50; Chi^2 = 28.92, df = 6 (P < 0.0001); I^2 = 79%
Test for overall effect: Z = 1.65 (P = 0.10)

B)

Study or Subgroup	Std. Mean Difference	SE	Sham Total	Active Total	Weight	Std. Mean Difference IV, Random, 95% CI
1. Chang et al. (2018)	0.18	0.26	30	30	16.2%	0.18 [−0.33, 0.69]
2. Jeon et al. (2018)	0.15	0.28	27	25	14.9%	0.15 [−0.40, 0.70]
3. Gomes et al. (2018)	−0.59	0.42	12	12	8.7%	−0.59 [−1.41, 0.23]
4. Fröhlich et al. (2016)	−0.59	0.4	13	13	9.3%	−0.59 [−1.37, 0.19]
5. Mondino et al. (2016)	0.38	0.42	12	11	8.7%	0.38 [−0.44, 1.20]
6. Palm et al. (2016)	0.59	0.46	10	10	7.5%	0.59 [−0.31, 1.49]
7. Smith et al. (2015)	0.02	0.37	15	15	10.4%	0.02 [−0.71, 0.75]
8. Fitzgerald et al. (2014)	−0.38	0.29	24	24	14.3%	−0.38 [−0.95, 0.19]
9. Brunelin et al. (2012)	0.64	0.38	15	15	10.0%	0.64 [−0.10, 1.38]
Total (95% CI)			**158**	**155**	**100.0%**	**0.03 [−0.24, 0.31]**

Heterogeneity: Tau^2 = 0.06; Chi^2 = 11.85, df = 8 (P = 0.16); I^2 = 32%
Test for overall effect: Z = 0.24 (P = 0.81)

C)

Study or Subgroup	Std. Mean Difference	SE	Sham Total	Active Total	Weight	Std. Mean Difference IV, Random, 95% CI
1. Chang et al. (2018)	0.08	0.26	30	30	14.2%	0.08 [−0.43, 0.59]
2. Jeon et al. (2018)	0.34	0.28	27	25	13.6%	0.34 [−0.21, 0.89]
3. Gomes et al. (2018)	0.23	0.41	12	12	9.8%	0.23 [−0.57, 1.03]
4. Fröhlich et al. (2016)	−0.45	0.39	13	13	10.4%	−0.45 [−1.21, 0.31]
5. Mondino et al. (2016)	0.71	0.43	12	11	9.4%	0.71 [−0.13, 1.55]
6. Palm et al. (2016)	1.34	0.5	10	10	7.9%	1.34 [0.36, 2.32]
7. Smith et al. (2015)	−0.09	0.36	15	15	11.2%	−0.09 [−0.80, 0.62]
8. Fitzgerald et al. (2014)	−0.3	0.29	24	24	13.3%	−0.30 [−0.87, 0.27]
9. Brunelin et al. (2012)	1.07	0.39	15	15	10.4%	1.07 [0.31, 1.83]
Total (95% CI)			**158**	**155**	**100.0%**	**0.27 [−0.09, 0.62]**

Heterogeneity: Tau^2 = 0.16; Chi^2 = 18.44, df = 8 (P = 0.02); I^2 = 57%
Test for overall effect: Z = 1.49 (P = 0.14)

Fig. 3. Forest plots displaying the standardized mean differences (SMDs) between active and sham groups for the studies included in the main-analyses. SMDs were derived for each of the following symptom domains: (A) auditory hallucinations, (B) positive symptoms (including auditory hallucinations), and (C) negative symptoms.

A)

Study or Subgroup	Std. Mean Difference	SE	Sham Total	Active Total	Weight	Std. Mean Difference IV, Random, 95% CI
1. Chang et al. (2018)	0.2	0.26	30	30	23.3%	0.20 [−0.31, 0.71]
2. Bose et al. (2017)	1.98	0.5	13	12	16.7%	1.98 [1.00, 2.96]
3. Mondino et al. (2016)	0.64	0.43	12	11	18.6%	0.64 [−0.20, 1.48]
4. Fitzgerald et al. (2014)	0.3	0.29	24	24	22.5%	0.30 [−0.27, 0.87]
5. Brunelin et al. (2012)	1.58	0.42	15	15	18.9%	1.58 [0.76, 2.40]
Total (95% CI)			**94**	**92**	**100.0%**	**0.86 [0.22, 1.51]**

Heterogeneity: Tau^2 = 0.40; Chi^2 = 16.43, df = 4 (P = 0.002); I^2 = 76%
Test for overall effect: Z = 2.62 (P = 0.009)

B)

Study or Subgroup	Std. Mean Difference	SE	Sham Total	Active Total	Weight	Std. Mean Difference IV, Random, 95% CI
1. Chang et al. (2018)	0.08	0.26	30	30	18.1%	0.08 [−0.43, 0.59]
2. Jeon et al. (2018)	0.34	0.28	27	25	17.3%	0.34 [−0.21, 0.89]
3. Gomes et al. (2018)	0.23	0.41	12	12	12.6%	0.23 [−0.57, 1.03]
4. Mondino et al. (2016)	0.71	0.43	12	11	11.9%	0.71 [−0.13, 1.55]
5. Palm et al. (2016)	1.34	0.5	10	10	10.1%	1.34 [0.36, 2.32]
6. Fitzgerald et al. (2014)	−0.3	0.29	24	24	16.9%	−0.30 [−0.87, 0.27]
7. Brunelin et al. (2012)	1.07	0.39	15	15	13.2%	1.07 [0.31, 1.83]
Total (95% CI)			**130**	**127**	**100.0%**	**0.41 [0.01, 0.81]**

Heterogeneity: Tau^2 = 0.16; Chi^2 = 14.16, df = 6 (P = 0.03); I^2 = 58%
Test for overall effect: Z = 2.03 (P = 0.04)

Fig. 4. Forest plots displaying the standardized mean differences (SMDs) between active and sham groups for the subgroup of studies with 10 or more stimulation sessions. The SMDs are displayed for the following symptom domains: (A) auditory hallucinations, and (B) negative symptoms.

auditory hallucinations. Of the 7 studies included in the main-analysis of auditory hallucinations, 1 study by Smith et al. (2015) applied once-daily bi-frontal stimulation for 5-days and showed no effect of tDCS on auditory hallucinations.

4.2.2. Studies included for positive and negative symptoms

Of the 9 studies (Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Gomes et al., 2018; Jeon et al., 2018; Mondino et al., 2016; Palm et al., 2016; Smith et al., 2015) included in the main-analyses of positive and negative symptoms, 4 studies used a bi-frontal design (Gomes et al., 2018; Jeon et al., 2018; Palm et al., 2016; Smith et al., 2015). The main outcome was negative symptoms in only 1 of these 4 studies (Palm et al., 2016) and cognition in the other 3 (Gomes et al., 2018; Jeon et al., 2018; Smith et al., 2015). The study by Palm et al. which included 20 schizophrenia participants with pre-dominant negative symptoms showed an effect of once-daily bi-frontal tDCS on reducing negative symptom severity (Palm et al., 2016). Jeon et al. found once-daily bi-frontal tDCS across 10 days improved cognition, but not negative symptoms (Jeon et al., 2018). Smith et al. using once-daily bi-frontal tDCS across 5-days also showed a significant effect of tDCS on cognitive performance, but not negative symptoms (Smith et al., 2015). Gomes et al. showed that once-daily bi-frontal tDCS across 10-days did not improve cognition, but significantly reduced negative symptom severity (Gomes et al., 2018). As the main outcome for the latter studies was not negative symptoms, the inclusion criteria for these studies were not specific to patients with predominant negative symptoms. This may explain the relatively low effect size observed in these studies.

The other 5 of 9 studies used a left fronto-temporoparietal design (Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016). Of the 4 studies that used a left fronto-temporoparietal design, Brunelin et al. (2012) also found a significant effect of twice-daily left fronto-temporoparietal tDCS on negative symptoms, which is theoretically plausible as anodal stimulation is being applied to the presumably hypoactive prefrontal cortex associated with negative symptoms (Caravaggio et al., 2017). Mondino et al. (2016) which reported on a partially overlapping study sample, found a moderate effect of tDCS on negative symptoms, while Chang et al., Fitzgerald et al., and Frohlich et al. (Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016) did not find an effect.

All 5 studies that were included in the exploratory analysis of depressive symptoms applied 10 stimulation sessions (Brunelin et al., 2012; Chang et al., 2018; Gomes et al., 2018; Jeon et al., 2018; Palm et al., 2016), suggesting the efficacy of tDCS for negative symptoms may be independent of its effect on depressive symptoms. However, it is important to note that all of the studies included in this meta-analysis reported changes in depressive symptoms as a secondary outcome. Further, the interpretation of our findings is limited by the use of different tDCS protocols and measures of depressive symptoms across the studies.

4.3. Moderator analyses

Our subgroup analyses of studies that applied 10 or more sessions showed a significant reduction in both auditory hallucinations and negative symptoms with active compared to sham stimulation. The cumulative clinical effect of a greater number of sessions is also reported in the rTMS literature (Schulze et al., 2018). However, our interpretation warrants caution as Fitzgerald et al. applied once-daily tDCS for 15 days, showed no significant change in auditory hallucinations (Fitzgerald et al., 2014). Alternatively, it is possible that the frequency of stimulation (i.e., twice-daily compared to once-daily) may be more critical given that most of the studies that reported a significant reduction in auditory hallucinations applied twice-daily tDCS. That being said, the optimal stimulation frequency remains debated with some studies reporting neurophysiological and clinical advantages of

twice-daily stimulation with brief inter-stimulation intervals (e.g., within 20-min of the first-session) (Goldsworthy et al., 2015; Monte-Silva et al., 2013), while other studies have reported no benefit of twice-daily compared to once-daily stimulation (Alonzo et al., 2012; Blumberger et al., 2012).

Meta-regression analyses suggest a negative association between age and the SMDs for both auditory hallucinations and negative symptoms. Our results are consistent with the findings from a recently published meta-analysis of open-labelled and sham-controlled studies investigating the effect of tDCS on auditory hallucinations in patients with schizophrenia (Lee et al., 2018). Relatedly, studies using a TMS paired-associated stimulation (PAS) technique in healthy adults showed that the magnitude of PAS-induced plasticity in the motor cortex was greater in younger participants (Muller-Dahlhaus et al., 2008). Furthermore, findings from rTMS studies suggest that younger patients with depression have better clinical outcomes and respond with fewer treatment sessions (Pallanti et al., 2012). No association was observed between % male and SMD for the included studies.

We were unable to account for other confounders, such as brain volume, age of illness onset, illness duration, and duration of antipsychotic use, as these data were not consistently reported across studies. Further RCTs are needed to account for these potential confounders.

4.4. Limitations

The present study must be considered in light of several limitations. First, the studies included in this meta-analysis did not have consistent inclusion criteria. Of the 10 studies included, 6 studies included patients with refractory auditory hallucinations, defined as having persistent auditory hallucinations despite antipsychotic medication (Bose et al., 2017; Brunelin et al., 2012; Chang et al., 2018; Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016). Gomes et al., Jeon et al., and Smith et al. did not specifically include treatment-refractory patients (Gomes et al., 2018; Jeon et al., 2018; Smith et al., 2015), and Palm et al. included patients with predominant negative symptoms a determined by clinician judgement (Palm et al., 2016). Given the evidence supporting pathophysiological differences in individuals with treatment-refractory schizophrenia, further studies are needed to differentiate the effects of tDCS in these groups (Nakajima et al., 2015; Iwata et al., 2018). Second, we combined studies with different primary outcomes (i.e., auditory hallucinations, negative symptoms, or cognition), scales, and electrode placement. Although subgroup analyses were performed to separate these effects, a relatively small number of studies included in our subgroup analyses limits the interpretation of the results. Third, the long-term effects of tDCS were not explored, as the duration between the last stimulation visit and follow-up visits were variable across studies, or not reported. Inclusion of more sham-controlled trials with follow-up data will allow for more robust analyses to investigate the long-term effects of tDCS in patients with schizophrenia. Fourth, only the effects of age and sex were considered. We were unable to account for other confounding factors, such as tobacco use, the amount of dopamine D_2 receptor (D_2R) blockade by antipsychotics, which are reported to affect tDCS outcomes. Brunelin et al. observed that although tDCS caused a significant reduction in symptom severity in non-smokers, it had no effect in smokers (Brunelin et al., 2015). A recent open-labelled study by Agarwal et al. showed that patients taking antipsychotic drugs with lower affinity for D_2R responded better to tDCS compared to patients on higher-affinity antipsychotics (Agarwal et al., 2016). Future studies are required to better understand and control for the influence of tobacco use and antipsychotics on tDCS efficacy.

5. Conclusions

In summary, the results of this meta-analysis suggest that twice-daily or 10 or more stimulation sessions may be needed to improve

clinical outcomes in patients with schizophrenia. Going forward, tDCS studies in patients with schizophrenia should consider incorporating neurophysiology or neuroimaging techniques to develop a better mechanistic understanding of how tDCS exerts its effects, which may help optimize protocol parameters.

Conflicts of interests

Acknowledgements

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.12.009.

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