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Effects and potential mechanisms of transcranial direct current stimulation (tDCS) on auditory hallucinations: A meta-analysis

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ABSTRACT

Auditory hallucinations are the most common psychiatric symptoms of schizophrenia with high recurrence and refractoriness. Transcranial direct current stimulation (tDCS), a novel, non-invasion and affordable brain stimulation technique, has been recently applying on the schizophrenia patients to treat the auditory hallucinations. To analyze the efficacy of tDCS treatment on such symptoms and to reveal its potential working mechanisms, we carried out a structured literature search in PubMed, Embase and Cochrane Library database up to May 12, 2018. Five studies that met inclusion criteria with a total of 137 patients were included in this meta-analysis. After pooling all the data, we found that there was no significant effect between active group and sham group of tDCS ($p = 0.18$). When we removed one study that did not collaboratively stimulate the frontal-temporal sites, the active tDCS group marks a significant improvement of therapeutic effect compared with sham group ($p = 0.007$). Our findings suggested that tDCS could be a promising tool to alleviate auditory hallucinations, provided that the simulation sites and protocols are targeting at the sensorimotor frontal-parietal network.

1. Introduction

Schizophrenia is a mental illness of unknown etiology and mainly characterized by positive and negative symptoms as well as cognitive impairment (Insel, 2010; Sims, 1988). Positive symptoms are divided into delusions, disordered thoughts and speech, and auditory hallucinations (AH) (Liddle, 1987). Auditory verbal hallucinations (AVH) are the most pronounced symptom in schizophrenia patients with auditory hallucinations (Sommer et al., 2012).

AVH refer to the symptoms of hearing voices in the absence of the external stimulus (Stephane et al., 2001). It is reported that 50%−70% of patients with AVH during the treatment phrase (Meltzer, 1992; Waters, 2012). Accumulating studies have demonstrated that hallucinations are resistant to antipsychotic treatment in 25%−30% adult schizophrenia patients, which resulted in functional disability and persistent cognitive deficits (Falloon and Talbot, 1981; Upthegrove et al., 2016). Recent advance in neuroimaging research have showed that AVH in schizophrenia is associated with abnormal activity in frontal and temporo-parietal areas (Allen et al., 2012; Hoffman et al., 2000; Jardri et al., 2011). Increased activation in such regions may be correlated with the deficits of self-monitoring functions (Allen et al., 2007; Frith and Corcoran, 2009; McGuire, 1995; Tian and Poeppel, 2012; Waters, 2012), corollary discharge and motor-to-sensory transformation functions (Ford and Mathalon, 2005; Tian and Poeppel, 2012) and sensory gating functions (Bak et al., 2014). The abnormal of these functions may be the causes of AVH.

Among numerous studies that apply neuromodulation on these frontal and temporo-parietal target regions for interventions of AVH (David, 2004), non-invasive neurostimulation techniques are thought to be practically useful to alleviate treatment-resistant of auditory

Abbreviations: AH, auditory hallucination; AVH, auditory verbal hallucination; tDCS, transcranial direct current stimulation; RCT, Randomized controlled trial; AHRS, Auditory Hallucination Rating Scale; TPJ, temporo-parietal junction

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hallucinations in patients with schizophrenia (Brunelin, 2013; Hoffman et al., 2000). Transcranial Direct Current Stimulation (tDCS) is one of such non-invasive techniques that are recently introduced to treat AVH. In the clinical setting, tDCS could have some advantages over rTMS such as ease of use, lower cost, and well-tolerated (Brunoni et al., 2011; Priori et al., 2009). tDCS applies weak and constant electric current on the scalp (Nitsche and Paulus, 2000), which results in weak electric field that alters neural activity and modulate cortical connectivity (Keeser et al., 2011; Lee et al., 2017). The anodal stimulation is positive stimulation that increases the neuronal excitability of the area being stimulated. Cathodal stimulation decreases the neuronal excitability of the area being stimulated (Nitsche et al., 2003). One of the major function advantages of tDCS is that the polarity of current flow can selectively manipulate the neural activity of excitatory or inhibitory status (Keeser et al., 2011). The long-term effects of tDCS seem to change the efficacy of GABAergic activity, NMDA receptors, and modulation the long-term potentiation and depression (Agarwal et al., 2013; Koops et al., 2015; Nitsche et al., 2008).

Such tDCS induced modulation can be effective on alleviate AVH. For instance, a recent clinical observation showed a significant reduction of auditory hallucinations in schizophrenia after fronto-temporal tDCS with the anode placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode placed over the left temporo-parietal junction (TPJ) cortex (Brunelin et al., 2012). This phenomenon might be attributed to the fact that placing the cathodic electrode over the Wernicke region can reduce cerebral blood flow and decrease functional connectivity between left TPJ and inner speech production brain areas (Mondino et al., 2016). A recent study showed that tDCS applying on frontal and temporal-parietal regions modulates the neural signal transformation from motor to sensory regions (corollary discharge function) in patients with AVH (Nawani et al., 2014).

Increasing number of studies were conducted to explore the effects of tDCS for auditory hallucinations (Fitzgerald et al., 2014; Frohlich et al., 2016; Mondino et al., 2016; Smith et al., 2015). However, inconsistent treatment results were obtained. It is urgent to examine the validity, as well as to provide insights on the potential neural mechanisms of this new type of treatment. In such a case, meta-analysis is a superior option as it allows easily reaching a broad set of subjects. Meanwhile, by collaboratively controlling experimental variables, such as sample size, symptom measurement, and stimulation protocols, meta-analysis can enhance statistical power, summarize the common and effective practice and provide guidance for future research of tDCS on AVH. Therefore, this meta-analysis pooled published literature to validate the efficacy of tDCS for auditory hallucinations.

2. Methods

2.1. Search strategy

We carried out an electronically literature search from PubMed, EMBASE, and the Cochrane Library published before May 12, 2018. The search terms were ("Auditory Hallucination" or "Auditory Hallucinations" or "Verbal Auditory Hallucinations" or "Phonism" or "Voice") and ("Transcranial Direct Current Stimulation" or "tDCS" or "Transcranial Electrical Stimulation"). All results were limited to human studies published in English. Reference lists of the included articles were manually scanned to identify further relevant studies. All identified publications were imported into the reference manager EndNote X6 and duplicated records were removed. Then articles were then manually scanned to select for the meta-analysis. Two authors further independently assess the relevance of the articles to the topic based on their titles and abstracts and full texts (see Inclusion and Exclusion Criteria for details). Any disagreements were resolved by discussion and consensus with a third person.

2.2. Inclusion and exclusion criteria

The inclusion criteria for studies were: (a) studies using tDCS in the intervention group, (b) assessment of the severity of auditory hallucinations in schizophrenia or other type of schizophrenia spectrum disorders, (c) diagnosis was established using Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases and Related Health Problems (ICD), (d) methodological design based on randomized controlled trials (RCTs), (e) data were presented as mean and standard deviation for auditory hallucinations levels.

The exclusion criteria were: (a) studies without a control group, (b) patients with auditory hallucinations presenting neuropsychiatric comorbidities, (c) studies that use cortical stimulation techniques other than tDCS.

2.3. Data extraction and quality assessment

The following data was extracted from identified studies using standard and comprehensive forms: the name of the first author, year of publication, demographic information of participants, including gender and average age, sample size and mean and SD, diagnostic criteria of schizophrenia spectrum disorders, type of intervention, outcome measures.

Study quality was evaluated for risk of bias using the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011). The tool distinguished studies based on six-item scale: sequence generation, random allocation to groups, blinding, missing data, selective reporting and other biases. We identified the level of biases into high, medium and low based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria in each of studies (Guyatt et al., 2008). Two authors independently assessed the study quality.

2.4. Statistical analysis

The random-effects model was chosen due to more conservative than the fixed-effects model, as well as lower type I error and wider confidence interval (CI) (Ades et al., 2005; Fang et al., 2018). To pool different scales, we used the standardized mean difference (SMD) as the summary statistic in this meta-analysis (Vesterinen et al., 2014), as it reveals the effect size of the treatment relative to the variability observed in the same study. Heterogeneity of studies was assessed. If $p < 0.1$ and $I^2 > 50\%$, the heterogeneity of studies was significant, otherwise it was not significant. Finally, to assess the stability of the result, a sensitivity analysis was performed. All the analyses were done with Review Manager 5.3 software.

3. Result

3.1. Result of the search

From the electronic search, a total of 85 publications were identified, from which we excluded 28 due to repetition. The titles and abstracts of 57 articles were read, 33 were excluded because they were not consistent with the topic of this meta-analysis. After reading the full text of the remaining 24 articles, another 18 studies were further excluded because they did not meet the inclusion criteria. As a result, only 6 studies fulfilled the eligibility criteria and were selected. One study was excluded in that the demographic data for each group was not provided (Fitzgerald et al., 2014). Ultimately, 5 articles were included in this meta-analysis. The selection process was summarized in Fig. 1.

3.2. Study characteristics

All included studies conducted a randomized, double-blind, sham-

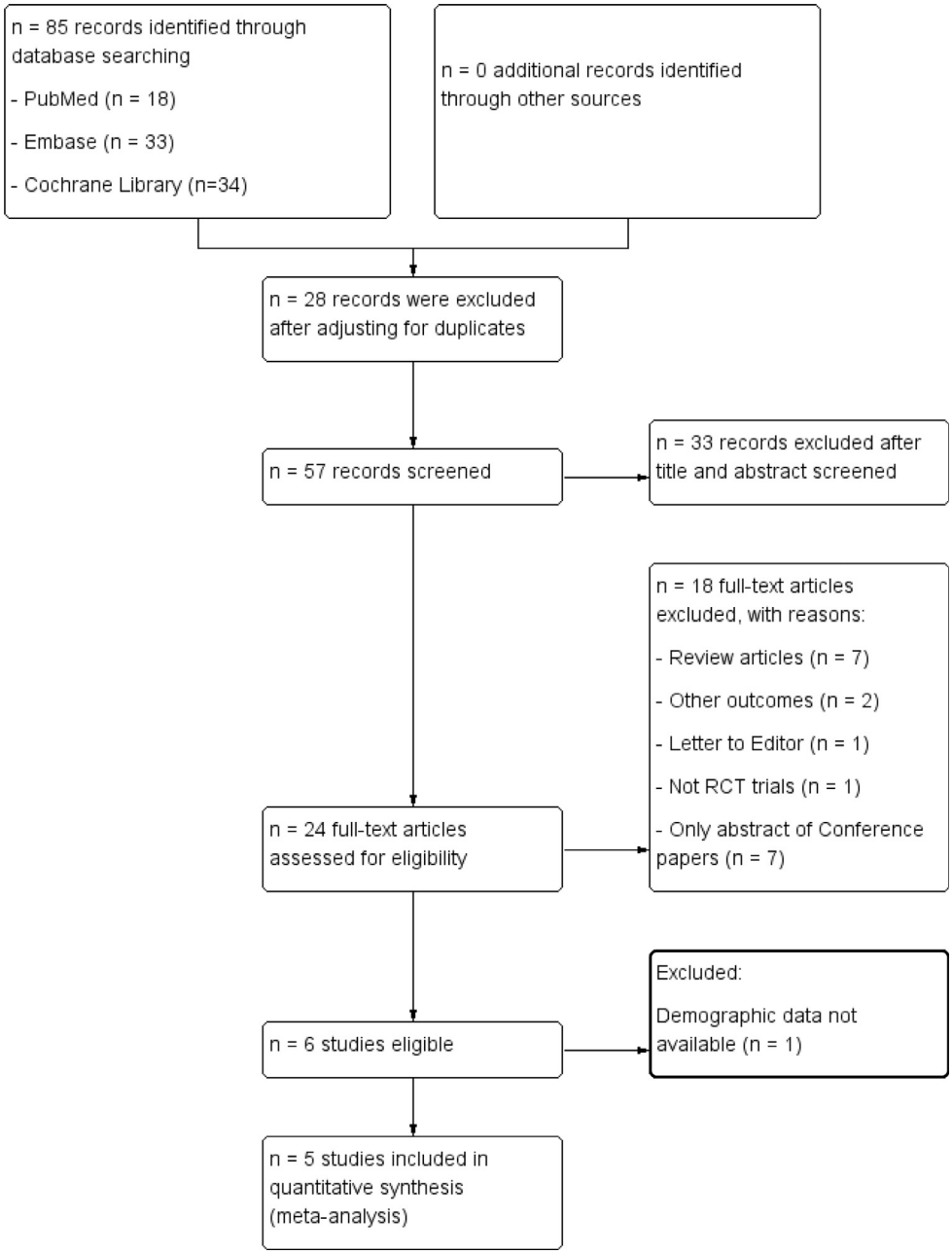

Fig. 1. Flow diagram of included/excluded studies.

Table 1
Clinical parameters of each study included on the meta-analysis.

Study	Groups	Sample size	Age (mean)	Diagnosis	Diagnostic criteria	Outcome measures
Bose (2018)	tDCS group	12	31.25 ± 8.32	Schizophrenia	DSM-IV	AHRS
	Control group	13	31.38 ± 7.56			
Brunelin (2012)	tDCS group	15	40.4 ± 9.9	Schizophrenia	DSM-IV	AHRS
	Control group	15	35.1 ± 7.0			
Frohlich (2016)	tDCS group	13	43.4 ± 12.6	Schizophrenia and schizoaffective disorder	DSM-IV	AHRS
	Control group	13	40.0 ± 10.7			
Mondino (2016)	tDCS group	11	36.7 ± 9.7	Schizophrenia	DSM-IV	AHRS
	Control group	12	37.3 ± 9.7			
Smith (2015)	tDCS group	17	46.8 ± 11.1	Schizophrenia and schizoaffective disorder	DSM-IV	PANSS
	Control group	16	44.9 ± 9.2			

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition;
PANSS = Position and Negative Syndrome Scale; AHRS = Auditory Hallucination Rating Scale.

Table 2
tDCS parameters of each study included on the meta-analysis.

Study	tDCS device	Electrodes location	Sessions (n/day)	Current (mA)	Time (min)
Bose (2018)	Neuroconn eldith DC Stimulator Plus	A: F3 FP1 C: T3 P3	10(2*/day)	2	20
Brunelin (2012)	Neuroconn eldith DC Stimulator Plus	A: F3 FP1 C: T3 P3	10(2*/day)	2	20
Frohlich (2016)	Neuroconn eldith DC Stimulator Plus	A: F3 FP1 C: T3 P3 Return electrode: Cz	5(1*/day)	2	20
Mondino (2016)	Neuroconn eldith DC Stimulator Plus	A: F3 FP1 C: T3 P3	10(2*/day)	2	20
Smith (2015)	Chattanooga Ionto System stimulator	A: F3; C: FP2	5(1*/day)	2	20

F3 FP1 = left dorsolateral prefrontal cortex (DLPFC).
T3 P3 = left temporoparietal junction (TPJ).
Cz = posterior midline.

controlled tDCS trials. Five studies in total involved 137 DSM-IV schizophrenia patients with auditory hallucinations from two groups: 68 in the active (tDCS treatment) group, 69 in the sham (control) group, respectively. In the active group, one study placed the anode over the LDLPFC (F3) and the cathode over the contralateral supraorbital ridge (Fp2) (Smith et al., 2015). Another four studies (Bose et al., 2018; Brunelin et al., 2012; Frohlich et al., 2016; Mondino et al., 2016) both placed the anode over the F3/FP1 (left dorsolateral prefrontal cortex) and the cathode over the T3/P3 (left temporo-parietal junction), but one study (Frohlich et al., 2016) added a third electrode: a return electrode over Cz (posterior midline). The treatments sites were all focused on the left hemisphere. In all five studies, active tDCS (2 mA for 20 min) was performed once or twice daily, for 5 to 10 sessions. In the sham group, the stimulation was set at 2 mA lasting only 40 s, though the electrodes remained in place for 20 min. The clinical and stimulation parameters performed in each study are shown in Tables 1 and 2, respectively.

In Smith et al. (2015), Frohlich et al. (2016), Mondino et al. (2016) and Brunelin et al. (2012), the AVH symptom severity (AHRS score, or PANSS score) was not statistically significant different at baseline between active tDCS and sham groups. In Bose et al. (2018), no significant difference in AVH (AHRS score) was observed at baseline. However, differences were found between two groups in other positive and negative symptoms. Patients in sham tDCS group had statistically significant greater SAPS and SANS scores at baseline. These baseline differences were controlled for their potential confounding effects in further analyses.

In Brunelin et al. (2012), symptom assessments were conducted immediately before the first tDCS session, and 5 days, 1 and 3 months after tDCS. In Mondino et al. (2016) and Bose et al. (2018), the severity of symptom was assessed at baseline (before application of the first stimulation) and re-assessed immediately after 5 days of twice-daily (10 sessions) tDCS administration. In Frohlich et al. (2016), AVH were assessed before the first tDCS session and immediately after the final tDCS session, as well as a follow-up test 30–45 days after completion of stimulation sessions. In Smith et al. (2015), psychiatric symptoms were assessed with PANSS scale at baseline and after the 5th tDCS session.

3.3. Primary outcomes

The primary outcome was change in the severity of the AVH measured by the Auditory Hallucination Rating Scale (AHRS) (Brunelin et al., 2012; Frohlich et al., 2016; Mondino et al., 2016) and P3 of PANSS (Smith et al., 2015).

Three studies demonstrated a therapeutic benefit of tDCS as reducing the severity of AVH (Brunelin et al., 2012; Mondino et al., 2016; Bose et al., 2018). Out of these three studies, one study (Brunelin et al., 2012) provided a longitudinal dataset. Immediately after treatment, the mean AHRS scores reduced from 28.3 (4.1) to 19.9 (5.8) in the tDCS group, significantly larger than that in the sham group [from 27.2 (6.9) to 25.1 (7.7)] [($d = 1.58$, $p < 0.001$)]. Interestingly, the tDCS effect could last beyond the immediate treatment – AHRS score was reduced 36% and 38% for the active tDCS group at 1 month and 3 months post-tests, respectively. Whereas in the sham group, the score was reduced 3% at 1 month and 5% at 3 months. These results suggest that tDCS treatment effect could be long-lasting.

3.4. Meta-Analyses

In the present paper, four studies reported the AHRS score and one study (Smith et al., 2015) reported the P3 score in PANSS as the outcome measure of AVH. We pooled the whole data and found no significant difference between active tDCS group and sham group ($Z = 1.33$, $p = 0.18$, Fig. 2A). While there was an obvious heterogeneity in effect size estimates ($p < 0.01$, $I^2 = 70\%$, Fig. 2A). After performing a sensitivity analysis by removing one study (Smith et al., 2015) that did not perform the stimulation on frontal-parietal network, we find a more homogeneous result ($p = 0.19$, $I^2 = 37\%$, Fig. 2B), yielding a significant statistical difference ($p = 0.007$).

3.5. Risk of biases

The risks of biases are reported in Table 3. Random allocation to an active tDCS group and blinded assessment of outcome were described in all the five studies. Brunelin et al. (2012) and Frohlich et al. (2016) did not describe randomization clearly, and Brunelin et al. (2012) did not report the concealment of allocation clearly, therefore the risk for these items was unclear. Based on the GRADE criteria, the results of the studies were inconsistent. And only 5 studies included in the meta-analysis, therefore the publication bias is also unclear.

4. Discussion

The present meta-analysis including five randomized clinical trials aimed to assess the treatment effects of tDCS on auditory hallucinations in schizophrenia. Our results with all five studies did not show significant difference between active group and sham group of tDCS. However, when only including four studies that all induced stimulation currents in frontal-parietal network with stimulation pairing between F3/FP1 and T3/P3 sites, a significant effect was seen on the active tDCS group compared to the sham group. Therefore, considering the limited available data, tDCS seems to be a promising tool to alleviate auditory hallucinations. However, more high-quality RCT studies are required to further validate the efficacy and working mechanisms of tDCS for auditory hallucinations in schizophrenia.

The major finding of this meta-analysis is that the simulation sites

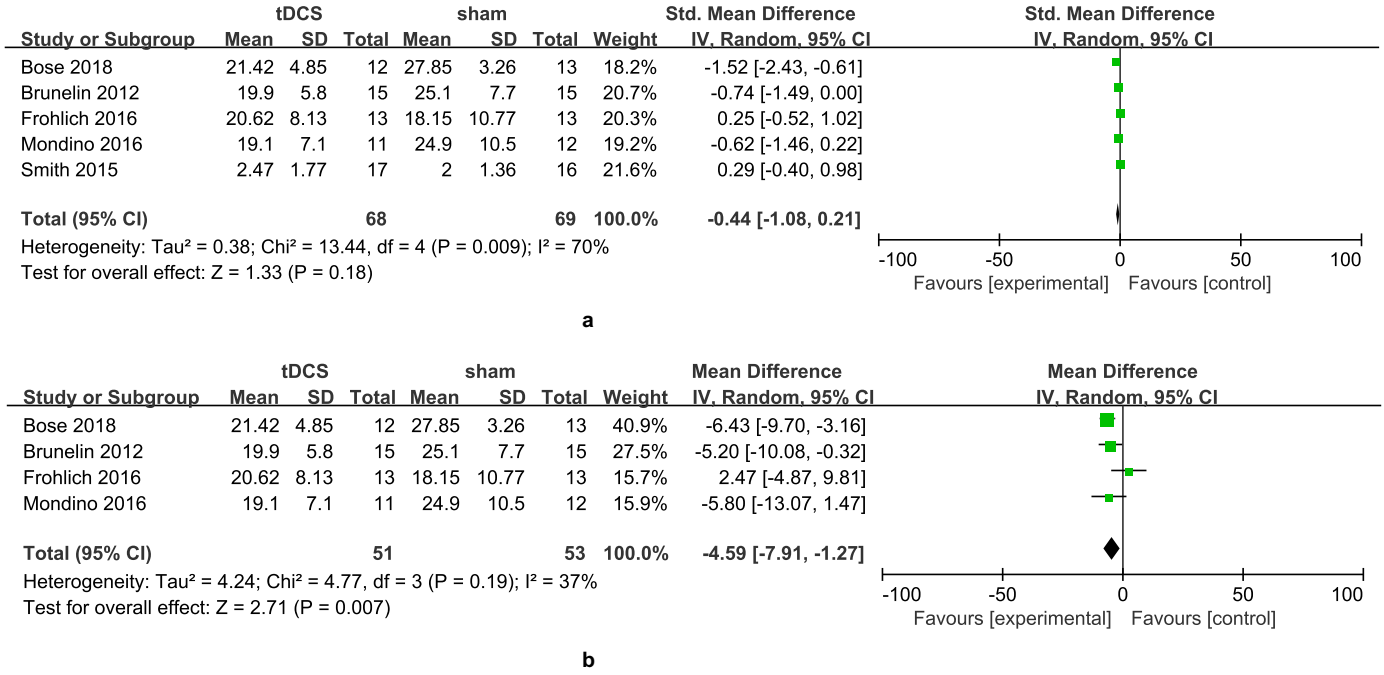

Fig. 2. (A) Result of Meta-analysis of tDCS for Auditory Hallucinations. **(B)** Result of sensitivity analysis of tDCS for Auditory Hallucinations.

are crucial for obtaining positive treatment effects of tDCS on alleviating AVH in schizophrenia. The consistent and effective simulation sites are pairing between F3/FP1 and T3/P3 sites. Neurophysiological studies have shown the importance of the left hemisphere for hallucinations in Schizophrenia, for example the hyperactivity of left TPJ areas play a crucial role in the presence of positive symptoms (Shergill et al., 2000; Silbersweig et al., 1995). This is consistent with the significant AVH symptom reduction when applied the tDCS stimulation over the left hemisphere in the included studies. This stimulation protocol enables a potential current flow in the sensorimotor network via the connection between frontal and parietal/temporal regions (Psomiades et al., 2017). Such current stimulation may affect and improve monitoring functions that have been hypothesized as a possible neural mechanism for auditory hallucination (Tian and Poeppel, 2012).

Interestingly, previous studies using neuroimaging and scalp electrophysiology methods have demonstrated that malfunction in frontal-parietal network may mediate the deficits in source-monitoring, dysfunction of corollary discharge, and inefficient gating of sensory information in patients with AVH (Bak et al., 2014; Ford and Mathalon, 2005; Wang et al., 2011). These findings are consistent with our results, supporting the linking between motor and sensory systems may be the neurobiological basis for the ameliorative effects of tDCS on AVH. Further research in combination of clinical and neuroimaging methods is needed to explore the differential contribution from the stimulation of brain regions in the frontal-parietal network. With the development of artificial neural network (ANN), the optimized MRI guided stimulation combine with neural computational modeling are practicable toward implementing “personalized neuromodulation” (Datta et al., 2012; Diederen et al., 2013).

This meta-analysis provides a valuable way to estimate and infer the potentials of tDCS treatment method. In the included literatures, only three studies proved a significant therapeutic effect of tDCS on the AVH in schizophrenia patients. In Frohlich et al. (2016) and Smith et al. (2015) studies, they did not find a significant difference between active tDCS and sham tDCS. The inconsistent outcomes are not enough to draw any conclusions about the treatment effects. However, when we pooled data from these studies and considered various constraints based on neuroscientific theories, the meta-analysis results are consistent and reliable.

The meta-analysis also provides an opportunity to compare and summarize several factors that could potential influence the tDCS treatment effects. For example, the treatment effect may limit to particular homogeneous patient groups. Trials that presented the positive effects of tDCS included only schizophrenic patient individuals, whereas other studies that show the negative effects of tDCS also included schizoaffective disorder patients in their samples. The inconsistent outcomes, therefore could be because of specific deficits in distinct patient groups. This hints that types of patients should be a factor to consider before applying tDCS treatment.

The amount of treatment could be another important factor. The total number of daily tDCS sessions presented in the studies of Frohlich et al. (2016) and Smith et al. (2015) was less than that in other studies (Bose et al., 2018; Brunelin et al., 2012; Mondino et al., 2016). In the study of Frohlich et al. (2016) that also applied stimulation over

Table 3
Evaluation of risk of bias in the 5 included studies based on the seven items in the Cochrane Risk of Bias tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants and providers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other biases
Bose (2018)	Low	Low	Low	Low	Low	Low	Low
Brunelin (2012)	unclear	unclear	Low	Low	Low	Low	Low
Frohlich (2016)	Low	Low	Low	Low	Low	Low	Low
Mondino (2016)	unclear	unclear	Low	Low	Low	Low	Low
Smith (2015)	Low	Low	Low	Low	Low	Low	Low

frontal-parietal network, the effect of active tDCS on AVH did not reach significance. The less amount of treatment could be an important factor that contributed to the null effect. Compared with other studies that showed significant symptom reduction, this study had only 5 sessions of stimulation, significantly less than 20 sessions in other studies. Therefore, stimulation sessions that were conducted only once a day for 5 days could be insufficient to obtain an ideal therapeutic effect. Our results suggest that the effectiveness of current protocols is constrained by 'dose'. The effect of tDCS could be improved by increasing the amount of treatment. Studies with rTMS have shown that the effect of stimulation on the motor cortex needs to be maintained for a period of time, which are capable of exceeding the cycle of the motor cortex (Carpenter et al., 2012). Therefore, the more ideal tDCS protocol about the amount of stimulation needs to be established for conducting further studies in this area.

Symptom assessment tools could also influence on the evaluation of tDCS treatment. The finally included four studies in this meta-analysis measured the change of auditory hallucinations using AHRS, while the removed study (Smith et al., 2015) used P3 in the PANSS scale. The previous study pointed out that the item of hallucinations in the PANSS scale is unreliable to measure the severity of auditory hallucinations in a detailed manner (Santor et al., 2007). As the AHRS scale presents an excellent capacity for evaluating the hallucinatory symptoms, it is more suitable scale to evaluate the hallucinations refractory to treatment in population samples containing schizophrenia (Haddock et al., 1999). Therefore, consistent and reliable symptom assessment tools should be implemented.

Compared with meta-analysis studies that aim for a summary of findings in a relatively established research topic, some reviews focus on exploring potential questions and mechanisms in a new direction of research with a limited set of available studies (Hirsch et al., 2018; Vacas et al., 2018; Lan et al., 2017; Bala et al., 2013). The goal of this study is consistent with the latter group and aims to explore the relative new direction of tDCS in treatment for AVH and its potential underlying mechanisms. Therefore, we included four studies that were available at the time. Moreover, because of the goal of this study – exploring a potential treatment effect of a method and its underlying mechanism, rather than summarizing common findings among studies (e.g. shared cortical regions among fMRI studies), we pooled data from multiple studies based on their common features and manipulations. The pooling yielded a sample size of more than 40 in our study, which is comparable to most of empirical studies. Our preliminary results suggest that tDCS may be a good treatment for AVH and the potential underlying mechanism could be the motor-to-sensory transformation in self-monitoring and control. More high-quality RCT studies are required to further validate the efficacy and the proposed working mechanism of tDCS for auditory hallucinations in schizophrenia."

4.1. Limitations

Several limitations of our meta-analysis should be mentioned here. First, the sample size of this studies included in this meta-analysis was small and statistical power could therefore be limited to identifying changes with large effect sizes. Moreover, patients were on continuous therapy during the trials still in combination with other psychotropic drugs, the potential confounding effects of different medications may confuse the effect of tDCS. Furthermore, the state of illness and localization of the electrodes might affect the result. Therefore, a better way to determine the parameters of the stimulus and to evaluate the clinical outcomes is needed to determine tDCS as a therapeutic possibility and its potential working mechanisms for auditory hallucinations in schizophrenia. Last, the amount of tDCS sessions could be another important factor. Previous studies shown that reduction in AVH may rely on "dose-dependent" hyperpolarization in auditory or speech-related regions (Krishnan et al., 2011; Lesh et al., 2010). However, it would be hard, if not impossible to examine this assumption because of the inter-study variability in the tDCS montages. Computational modeling about the spatial distribution of electric fields induced by tDCS would be a fruitful way forward in linking treatment amount and efficacy. Future clinical trials should specify the stimulation parameters (e.g., the electrode/coil configuration, current amplitude, pulse width, frequency, number of pulse) and should combine neuroimaging data to implement MRI guided stimulation along with computational modeling for optimize tDCS protocols. If effective, tDCS might be compliment to or even replace the antipsychotic medication and would be feasible toward 'personalized neuromodulation'.

5. Conclusion

This meta-analysis revealed significant therapeutic effects of tDCS on reducing severity and frequency of AVH in schizophrenia. These significant effects were obtained by limiting the simulation sites on frontal-parietal regions. These results suggest that tDCS is a promising tool to alleviate AVH, and the possible neural mechanisms of monitoring functions in sensorimotor frontal-parietal network may constrain the stimulation protocols as one of the crucial factors to obtain the treatment effects.

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Role of contributors

F.Y X.T and C.Z designed the study. F.Y and X.F conducted the literature searches and analysis. F.Y and C.Y undertook the statistical analysis. W.T and L.H managed the assessment of risk of Bias and GRADE. F.Y wrote the draft manuscript. F.Y, X.F, C.Y, L.H, C. Z, and X.T contributed to the final manuscript.

Conflict of interest

All authors report that they have no conflicts of interest.

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