The effects of transcranial direct current stimulation (tDCS) on clinical symptoms in schizophrenia: a systematic review and meta-analysis

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Abstract

Objective: This systematic review and meta-analysis aims to examine the effects of transcranial direct current stimulation (tDCS) on clinical symptoms in schizophrenia.

Methods: A literature search was performed for articles published in English using the following databases: MEDLINE, EMBASE, PsycINFO, INSPEC, the Cumulative Index to Nursing & Allied Health Literature Plus (CINAHL Plus), AMED, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, EU Clinical Trials Register, and WHO International Clinical Trials Registry Platform, from their inception to October 2019. The primary outcome variables were the clinical symptoms of schizophrenia including positive symptoms, negative symptoms, and auditory hallucinations.

Results: 16 randomized controlled trials (RCTs) were included in the meta-analysis, with a sample of 326 patients with active and with 310 sham tDCS. Active tDCS was found to be more effective in improving positive symptoms [standardized mean difference (SMD) = 0.17; 95% confidence interval (CI) 0.001 to 0.33], negative symptoms [SMD = 0.43, 95% CI 0.11, 0.75] and auditory hallucinations [SMD = 0.36 95% CI 0.02, 0.70]. Subgroup analyses showed better results in cases of pure diagnosis of schizophrenia, higher frequency and more sessions of stimulation.

Conclusion: tDCS was effective in improving positive symptoms, negative symptoms and auditory hallucination in schizophrenia. It therefore has potential as a safe and well-tolerated adjunctive intervention for schizophrenia.

Keywords: transcranial direct current stimulation (tDCS); schizophrenia; systematic review; meta-analysis.

Abbreviations:

AHRS, Auditory Hallucination Rating Scale; CI, Confidence Interval; DLPFC, dorsolateral prefrontal cortex; PANSS, Positive and Negative Syndrome Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SANS, Scale for the Assessment of Negative Symptoms; SMD, standardized mean difference; tDCS, transcranial direct current stimulation; TPJ, temporoparietal junction.

1. Introduction

Schizophrenia is a major mental health disorder, with a massive effect on individual health sate, quality of life, and a relevant socio-economic impact, and a high prevalence. Antipsychotics are the first-line treatment for schizophrenia. However, it is estimated that around 10–30% of patients with schizophrenia show little or no response to antipsychotics, and another 30% experience residual symptoms despite antipsychotic treatment (Hasan et al., 2012). The adverse effects of antipsychotics are also a major concern (Stroup and Gray, 2018).

Such limitations of current therapy motivate the search for new treatment options, which are effective and well-tolerated. Transcranial direct current stimulation (tDCS) is one of the options explored in recent research. It is a non-invasive method of neurostimulation in which a weak direct electric current (amplitude at about 1-3 mA) is applied through electrodes placed on the scalp. It is portable, relatively inexpensive and easy to use. It is a very safe intervention tool, whereby common adverse effects are largely limited to the stimulation site, including itchiness, redness, tingling and a burning sensation.

Recently, a number of meta-analyses of tDCS for schizophrenia has been conducted. Two have focused on negative symptoms (Aleman et al., 2018; Osoegawa et al., 2018); one has focused on auditory hallucinations (Yang et al., 2019); and two have covered broader symptom dimensions, including positive, negative, and hallucination symptoms (Kennedy et al., 2018; Kim et al., 2019). The results of tDCS for positive and hallucination symptoms were negative in the whole group analyses of the respective studies, but Kim et al. (2019) found a significant improvement after performing a subgroup analysis by only including studies with 10 or more sessions. The results of tDCS meta-analyses for negative symptoms were more heterogeneous. Aleman et al. (Aleman et al., 2018) showed an non-significant effect of tDCS for negative symptoms, while Osoegawa et al. (Osoegawa et al., 2018) and Kennedy et al. (Kennedy et al., 2018) showed a significant improvement with a moderate effect size. After including 2 more studies in Kim et al. (2019), tDCS improved negative symptoms significantly only in a subgroup analysis, where only studies with more than 10 sessions were included.

In summary, evidence for evaluating tDCS as a treatment option for schizophrenia is still inconclusive based on previous meta-analyses. However, some more studies (Chang et al., 2020; Kantrowitz et al., 2019; Koops et al., 2018; Lindenmayer et al., 2019; Valiengo et al., 2019) have become available after the publication of the latest meta-analysis (Kim et al., 2019), and one of them (Valiengo et al., 2019) has the largest sample size (n=100) to date. Furthermore, factors that may affect the efficacy of tDCS are yet to be determined, such as diagnosis and dosage of stimulation. Therefore, we conducted a systematic review and meta-analysis, with the intention of providing a comprehensive and up-to-date review, as well as a quantitative meta-analysis of existing studies on the treatment efficacy of tDCS on positive, negative, and auditory hallucination symptoms in schizophrenia.

2. Method

2.1 Eligibility criteria

2.1.1 Types of studies

Only randomized controlled trials (RCTs) with a prefoper sham-tDCS as control were included. Non-English language studies were excluded.

2.1.2 Types of participants

Patients were aged 18 years or older with a diagnosis of schizophrenia, or other psychotic disorders such as schizoaffective disorder and delusional disorder.

2.1.3 Types of outcome measures

For positive symptoms, outcome measures included the Positive subscale or the positive factor of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or Scale for the Assessment of Positive Symptoms (SAPS). For negative symptoms, outcome measures included the Negative subscale or the negative factor of the PANSS or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989). For auditory hallucinations, outcome measures included the Auditory Hallucination Rating Scale (AHRS) (Hoffman et al., 2003), and the auditory hallucination score in PANSS (PANSS P3).

2.2 Search strategy

A literature search was performed for articles published in English from 1950 to October 2019 using the following databases: MEDLINE, EMBASE, PsycINFO, INSPEC, the Cumulative Index to Nursing & Allied Health Literature Plus (CINAHL Plus), AMED, and Cochrane Central Register of Controlled Trials (CENTRAL). Ongoing trial and research register searches were carried out on ClinicalTrials.gov, EU Clinical Trials Register, and WHO International Clinical Trials Registry Platform. The following keywords were used to identify articles related to tDCS-related clinical trials in schizophrenia: “transcranial direct (current or DC or electric) stimulation”, “tDCS”, “C-tDCS”, “A-DCS”, “S-tDCS”, “anode or anodes or anodal or cathode or cathodes or cathodal or bifocal or sham or electrode”, “brain (stimulation or treatment or intervention)”, “electric stimulation (stimulation or treatment or intervention)”; and schizophrenia: “schizophrenia”, “psychotic disorder”, “delusional disorder”, “paranoid”, “hallucination”, “schizoaffective disorder”, “schizophreniform disorder”, and “(chronic or severe or serious or persistent) mental disorder”.

Three authors (C. P. W., L. L. L. C. and L.W.Y.) evaluated the titles and abstracts independently to determine whether the studies fulfilled the inclusion criteria. Reference lists of all included articles were reviewed for any unidentified studies. All RCTs, with both parallel and crossover designs, were included regardless of blinding or publication status (i.e. full papers or abstracts). Case studies, case series, open trials, ongoing studies, review articles, and animal studies were excluded. If more than one paper had been published based on the same study population, only the most recent and informative one was included. Any disagreements were resolved by discussion or by an independent party (C. W. C.). The study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.3 Data extraction

Three authors (C. P. W., L. L. L. C. and L.W.Y.) independently extracted the data using a semi-structured form for each trial and cross-checked the results for accuracy. Disagreements regarding data extraction were resolved by consensus between the authors or by an independent party (C. W. C.). If the data were reported from multiple time points, those obtained immediately after intervention were used. The corresponding authors of the studies were contacted for clarification or missing information.

2.4 Quality assessment

The methodological quality of the trials included in the meta-analysis were examined by the three reviewers according to the six domains of the Cochrane Collaboration's tool for assessing the risk of bias (Higgins et al., 2019): (i) sequence generation; (ii) allocation concealment; (iii) blinding of the participants; (iv) blinding of the assessors; (v) method of addressing incomplete outcome data; and (vi) selective reporting. The methodological quality was classified as a low, high or uncertain risk of bias in each domain.

2.5 Data synthesis and analysis

2.5.1 Meta-analysis

To examine the treatment effect, we carried out a meta-analysis by pooling the available data from the RCTs. For the outcome variables, a pooled effect size was calculated using a random effects model and presented as the standardized mean difference (SMD) with 95% confidence intervals (CIs). We used the random effects model because the estimates of the treatment effect were assumed to vary between trials because of real differences and sampling variability (Riley et al., 2011). Forest plots were generated with Comprehensive Meta-Analysis (CMA) v3 software (Borenstein, 2013). Heterogeneity between trials was assessed with the I^2, and a value of >50% was considered substantial heterogeneity (Higgins et al., 2003).

2.5.2 Subgroup analyses

Some studies only recruited patients with schizophrenia, but some studies also included schizoaffective disorder and other psychotic disorders. It would be important to know whether the diagnosis of patients recruited in the studies would have an impact on the effect of tDCS. Besides, according to a previous meta-analysis conducted by Kim et al. (2019), the frequency and the total number of sessions may have impact on the tDCS effect. Therefore, the subgroup analyses were performed to explore the effect of these possible moderators including diagnosis, frequency of sessions and the total number of sessions.

2.5.3 Meta-regression analyses

Meta-regression analyses were conducted using Comprehensive Meta-Analysis version 3 (Borenstein, 2013). The relationships between SMDs for each study and age, gender, sample size, duration of illness, medication dose and baseline symptom severity were examined.

3. Results

3.1 Identification and selection of studies

The initial search yielded a total number of 20,770 records. A detailed PRISMA flow diagram of the inclusion and exclusion process is presented in **Figure 1.** One in-press article (Chang et al., 2020) was included in the ongoing trials and research registers search. Fitzgerald et al. (Fitzgerald et al., 2014) reported two pilot RCTs (Trial 5: bilateral tDCS; Trial 6: unilateral tDCS) in their paper and this resulted in the inclusion of 16 trials. Finally, 15 RCTs studies (Bose et al., 2018; Brunelin et al., 2012; Chang et al., 2019; Chang et al., 2020; Fitzgerald et

al., 2014; Fröhlich et al., 2016; Gomes et al., 2018; Jeon et al., 2018; Kantrowitz et al., 2019; Koops et al., 2018; Lindenmayer et al., 2019; Mondino et al., 2016; Palm et al., 2016; Smith et al., 2015; Valiengo et al., 2019) reporting 16 trials fulfilling the inclusion criteria were identified.

3.2 Description of studies

3.2.1 Participants

The meta-analysis includes a total number of 636 patients (326 in the active treatment group and 310 in the sham-controlled group). The demographic data of the trials is shown in **Table 1**. About two-thirds of the participants were male and their mean age was 39.76 years. All patients were diagnosed with either schizophrenia or schizoaffective disorder. A significant number of participants were reported to have refractory symptoms. The mean years of illness was 13.68 years. The sample size of studies was generally small, except for Valiengo et al. (Valiengo et al., 2019), which had 100 participants.

3.2.2 Description of tDCS intervention parameters and sessions

The design of tDCS intervention is summarized in **Table 2**. Each of the selected 16 trials had a sham-controlled parallel group design. The stimulation of the active treatment condition was delivered at 2mA for 20 minutes per session in all trials, either once a day in seven trials or twice a day in nine trials, with the number of trial days ranging from 5 to 20. Electrodes were placed at similar positions, with the anode at the dorsolateral prefrontal cortex (DLPFC) (either unilateral or bilateral) in all trials and the cathode most often at the left temporoparietal junction (TPJ~~)~~

3.2.3 Adverse events

The common side effects and their frequency are listed in **Table 3**. Burning sensation was the most common adverse events in active tDCS (21.08%) but less frequently reported in sham tDCS (13.48%). There were no serious adverse events reported. One study (Mondino et al., 2016) did not provide relevant information on adverse effects.

3.3 Effect of tDCS intervention

Positive symptoms were measured by the positive symptoms subscale of the PANSS. There were 14 trials with a positive PANSS score. Among these studies, there was only one trial (Brunelin et al., 2012) that showed significant improvement in positive symptoms compared with the sham condition, while others did not show any effect.

The negative symptoms were measured by the negative symptoms subscale of the PANSS. There were 14 trials with a negative PANSS score. Among these studies, there were 6 trials that showed improvement in negative symptoms, while others did not show any effect.

The hallucination symptoms were measured by AHRS or PANSS P3. There were 12 trials with AHRS or PANSS P3. Among these studies, there were 4 trials that showed improvement in hallucination symptoms, while others did not show any effect.

3.4 Quality assessments

Table 4. shows the methodological qualities of the trials with Cochrane criteria. Except for the allocation concealment, other risks of bias-were described as low risk in most of the studies. Allocation concealment was insufficiently reported in most studies, and was therefore described as an uncertain risk. There was only one trial (Mondino et al., 2016) with higher risks of bias (3 or more items in risks of bias rated as uncertain risk or high risk). Overall, the quality of the included trials was good.

3.5 Meta-analysis

3.5.1 Positive symptoms

The meta-analysis of 14 trials and 566 participants (286 in the active treatment group and 280 in the sham-controlled group) showed a marginally significant reduction on positive symptoms in active tDCS compared with sham tDCS [SMD = 0.17, 95% CI 0.001, 0.33], with an insignificant heterogeneity between trials (I^2 = 0.9%) **(Figure 2A).**

Meta-regression analyses revealed no associations between SMD and the mean age, gender, sample size, duration of illness, medication dose and baseline symptom severity.

3.5.2 Negative symptoms

The meta-analysis of 14 trials and 566 participants (286 in the active treatment group and 280 in the sham-controlled group) showed a significant reduction on negative symptoms in active tDCS compared with sham tDCS [SMD = 0.43, 95% CI 0.11, 0.75], with a significant heterogeneity between trials (I^2 = 68.2%) **(Figure 2B).**

Since there was significant heterogeneity (I^2 ≥50%) in the negative symptoms in the main analysis, sensitivity analyses were performed. After performing a sensitivity analysis in the negative symptoms by excluding one study at a time, the result remained significant.

Meta-regression analyses revealed no associations between SMD and the mean age, gender, sample size, duration of illness, medication dose and baseline symptom severity.

3.5.3 Auditory hallucination

The meta-analysis of 12 trials and 462 participants (238 in the active treatment group and 224 in the sham-controlled group) showed a significant reduction on auditory hallucination symptoms in active tDCS compared with sham tDCS [SMD = 0.36 95% CI 0.02, 0.70], with a significant heterogeneity between trials (I^2 = 64.6%) **(Figure 2C).**

Since there was significant heterogeneity (I^2 ≥50%) in the auditory hallucination in the main analysis, sensitivity analyses were performed. A sensitivity analysis was performed by excluding one study at a time. The exclusion of two studies (Bose et al., 2018; Brunelin et al., 2012) with higher effect sizes, resulted in the loss of the significance of the superiority of active tDCS over sham tDCS.

Meta-regression analyses showed a negative association between SMD and mean age (12 studies, slope = -0.09, 95% CI -0.16 to -0.01 % male, $p = 0.0184$).

3.6 Subgroup analysis

3.6.1 Diagnosis

We separated the analysis of studies with a pure diagnosis of schizophrenia from the studies with mixed diagnosis (including schizophrenia and other psychotic disorders). Only the schizophrenia group showed a moderate effect of tDCS on negative symptoms in active tDCS compared with sham tDCS [SMD 0.57, 95% CI 0.14, 1.00, $I^2 = 58.5\%$] **(Figure 3A)**, while the mixed diagnosis group did not show any significant effect. No significant effect of tDCS on positive symptoms and auditory hallucination was evident in either group.

3.6.2 Dosage of stimulation

We carried out a separation analysis according to the frequency of sessions (the number of tDCS trials per day i.e. 1 trial per day vs 2 trials per day) and the total number of tDCS sessions (<10 sessions or ≥10 sessions). Only the group with 2 trials per day showed significant improvement ~~i~~n negative symptoms [2 trials per day group: SMD 0.49, 95% CI 0.07, 0.91, $I^2 = 74.5\%$] and auditory hallucinations [2 trials per day group: SMD 0.54, 95% CI 0.12, 0.97, $I^2 = 73\%$]. **(Figure 3B, 3C)** However, those with only 1 trial per day did not show any significant effect in all symptoms Similarly, the group with fewer than 10 sessions did not show any significant effect in all symptoms. Only those with more than 10 sessions showed significant effects on auditory hallucination [≥10 sessions group: SMD 0.66, 95% CI 0.21, 1.12, $I^2 = 66.6\%$] **(Figure 3D).**

3.7 Publication bias

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

4. Discussion

4.1 Main analysis

To date, this meta-analysis is the most comprehensive, with the largest sample size investigating the effect of tDCS on the symptoms of schizophrenia. The main result of this meta-analysis shows that active tDCS has a significant improvement in all symptoms of schizophrenia including positive symptoms, negative symptoms and auditory hallucinations compared with sham tDCS, with a mild to moderate effect size. This is the first meta-analysis showing that active tDCS significantly reduces positive symptoms and auditory hallucinations in schizophrenia, although the effect on positive symptoms was only marginal and the effect on auditory hallucination became insignificant in sensitivity analyses. All previous metanalyses (Aleman et al., 2018; Osoegawa et al., 2018; Yang et al., 2019; Kennedy et al., 2018) showed insignificant effects of tDCS on these two aspects of schizophrenia symptoms, except for Kim et al. (2019), who found a significant improvement of auditory hallucinations in a subgroup analysis including studies with 10 or more sessions. This different result is most likely explained by the higher number of RCTs which were included in the current study, as

compared with previous meta-analyses. Moreover, the present study supports the conclusion of other meta-analyses that active tDCS significantly reduced negative symptoms with a moderate effect size (0.42). This effect persisted after performance of a sensitivity analysis.

Besides, our subgroup analysis result suggests that tDCS effect are better in patients who suffer from schizophrenia, as compared with those suffering from other psychotic disorders such as schizoaffective disorder. Only the schizophrenia group showed a moderate effect of tDCS on negative symptoms in active tDCS, as compared with sham tDCS. A similar finding was reported in another meta-analysis focusing on auditory hallucinations (Yang et al., 2019), which showed effects only in schizophrenia patients, but not in patients with schizoaffective disorder. This could probably be explained by the distinct mechanisms of pathophysiology in different psychotic disorders. It thus would be advantageous to recruit a more homogenous diagnostic group of patients in future tDCS studies, to avoid mixed effects based on patient groups with different diagnoses.

As suggested also by the previous meta-analysis (Kim et al., 2019), the frequency and the total number of sessions affected the therapeutic impact of tDCS. Only the group with 2 trials per day showed a significant effect on negative symptoms and auditory hallucinations, and only the group which received more than 10 sessions showed a significant effect on auditory hallucinations. In contrast, groups with 1 trial per day or less than 10 sessions showed no significant effect on any symptom. These results suggest that higher frequency and larger total number of sessions increases the effect of tDCS in schizophrenia.

Baseline symptom severity may affect the impact of treatment, as suggested in previous repetitive transcranial magnetic stimulation (rTMS) studies in schizophrenia (Shi et al., 2014). However, such an effect was not seen in the current study. The meta-regression did not show any significant correlations between tDCS effects and the baseline symptoms severity. With respect to demographic variables, only age had a negative association with the tDCS effect on auditory hallucinations. Also this result was consistent with that of a previous tDCS meta-analysis (Kim et al., 2019).

4.2 Limitations

There were few limitations of the current study. First, we only included studies which applied some major outcome measurements for positive, negative symptoms and auditory hallucinations. This may lead to fewer studies included in the meta-analysis. However, all studies included in the largest meta-analysis previously conducted (Kim et al., 2019), which used a broader outcome measurement criterion, were included in the current study. The main advantage of the use of homogenous measurement tools in our study is reduced data heterogeneity. Besides, some included studies used more than one measurement for the same symptom. We have tried to rerun the analysis by using another measurement result in these studies. The significant difference in the positive symptoms, negative symptoms and auditory hallucination was maintained. Second, we have not included outcome measures of cognitive symptoms in schizophrenia, which contribute significantly to the clinical symptoms of schizophrenia. Third, we have not considered some other factors, which may have an impact on the physiological effects of tDCS, such as smoking (Brunelin et al., 2015), type of medication (Agarwal et al., 2016), and functional impairment level. However, we conducted a meta-regression analysis to gauge the effect of age, gender, sample size, duration of illness, medication dose, and baseline symptom severity on tDCS efficacy.

4.3 Conclusion and implications

This current study delivers supporting evidence for a positive effect of tDCS on positive symptoms, negative symptoms and auditory hallucination in schizophrenia. However, the use of tDCS for schizophrenia in clinical settings still needs further evaluation from more clinical trials. Future studies are needed to determine the optimal stimulation parameters. Based on the results of the present meta-analysis, we suggest to use a higher frequencies (such as 2 trials per day), and total number of sessions (at least 10 sessions) in order to induce an adequate clinical effect of tDCS on schizophrenia symptoms. Moreover, in difference to schizophrenia patients, tDCS did not have an effect on patients with schizoaffective disorder. Therefore, the inclusion criteria in future trials should be specific and avoid involving heterogenous groups in order to draw meaningful conclusions.

Appendix A. Table 1 – 4

Appendix B. Figure captions

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Appendix A.

Table 1. Demographic characteristics of the included studies

Trial No.	Authors (year)	*n*	Gender (M/F)	Mean age	Mean years of illness	Diagnosis and characteristics	Baseline (Mean +SD)						Mean antipsychotic dosage (mg/day)
							PANSS +ve 3 scales (5 scales)		PANSS -ve 3 scales (5 scales)		AHRS/ (PANSS P3)		
							Active	Sham	Active	Sham	Active	Sham	
1.	Bose *et al*. (2018)	25	14/11	31.3	8.6	Sz with persistent AVH without remission despite treatment with at least 1 antipsychotic medication at an adequate dosage for at least 3 months	N/A	N/A	N/A	N/A	31.00 ± 4.65	29.85 ± 2.85	CPZ eq: 705.4
2.	Brunelin *et al*. (2012)	30	22/8	37.8	N/A	Sz with persistent daily hallucinations without remission despite antipsychotic medication at an adequate dosage for at least 3 months	(21.20 ± 6.90)	(20.00 ± 3.50)	(16.20 ± 5.00)	(20.50 ± 6.50)	28.30 ± 3.50	27.10 ± 6.90	CPZ eq: 1101.5
3.	Chang *et al*. (2020)	60	30/30	44.9	15.3	Sz/schizoaffective disorder (non-acute phase of illness)	(12.37 ± 4.51)	(13.40 ± 2.77)	(20.43 ± 4.33)	(22.57 ± 4.41)	N/A	N/A	CPZ eq: 527.4
4.	Chang *et al*. (2019)	60	27/33	44.3	16.8	Sz/schizoaffective disorder exhibiting persistent AVH in spite of ≧3-month treatment with antipsychotic drugs	15.83 ± 5.06	14.93 ± 3.96	19.70 ± 4.74	18.40 ± 4.37	29.13 ± 5.31	29.07 ± 4.83	CPZ eq: 493.6*
5.	Fitzgerald *et al*. (2014)	11	15/9	39.3	23.2	Sz/schizoaffective disorder, persistent hallucinations and negative symptoms with a failure to respond to at least two adequate trials of antipsychotic medication	12.80 ± 2.70	11.20 ± 5.00	12.00 ± 3.30	12.00 ± 6.80	(3.80 ± 1.60)	(3.50 ± 1.80)	N/A
6.	Fitzgerald *et al*. (2014)	13					13.50 ± 4.20	11.00 ± 4.40	20.20 ± 3.90	21.80 ± 5.80	(3.60 ± 2.30)	(3.20 ± 1.80)	
7.	Fröhlich *et al*. (2016)	26	22/4	41.7	16	Sz/schizoaffective disorder with at least 3 AH per week with at least 2 antipsychotic agents of adequate dose and duration	20.54 ± 4.77	20.08 ± 6.03	19.00 ± 7.56	16.00 ± 6.65	27.00 ± 6.90	26.69 ± 6.30	N/A
8.	Gomes *et al*. (2018)	24	17/7	36.5	13.0	Sz	16.25 ± 3.12	13.25 ± 3.19	23.75 ± 5.56	21.67 ± 8.40	N/A	N/A	N/A
9.	Jeon *et al*. (2018)	54	26/28	39.9	13.6	Sz	20.31 ± 6.57	18.07 ± 5.79	23.19 ± 6.96	21.54 ± 6.05	N/A	N/A	CPZ eq: 581.6
10.	Kantrowitz *et al*. (2019)	89	67/22	39.1	N/A	Sz/schizoaffective disorder with resistant AVH despite a stable dose of antipsychotic medication for at least 1 month	20.30 ± 4.10	19.10 ± 5.20	17.30 ± 5.00	17.30 ± 5.00	24.80 ± 5.70	25.20 ± 5.70	CPZ eq: 722
11.	Koops *et al*. (2018)	34	19/15	44.2	N/A	Sz with resistant AH at least 5 times/ week with insufficient treatment response to at least two different types of antipsychotic medication in adequate dosages	N/A	N/A	N/A	N/A	28.10 ± 5.82	28.8 ± 4.69	N/A
12.	Lindenmayer *et al*. (2019)	28	24/4	40.2	0.2	Sz/schizoaffective disorder with persistent AVH with at least two failed antipsychotic trials at adequate dosages	21.87 ± 2.36	21.08 ± 3.64	19.10 ± 1.11	19.01 ± 1.36	25.00 ± 3.55	24.38 ± 4.43	CPZ eq: 891.81
13.	Mondino *et al*. (2016)	23	15/8	37.0	12.0	Sz with with persistent daily hallucinations without remission despite antipsychotic medication at an adequate dosage for at least 3 months	18.50 ± 4.4	19.80 ± 4.20	18.10 ± 5.50	19.40 ± 4.60	27.20 ± 4.10	27.8 ± 8.0	Ozp eq: 24.3
14.	Palm *et al*. (2016)	20	15/5	36.1	10.5	Sz with predominant negative symptoms	10.00 ± 3.9	10.70 ± 4.10	24.00 ± 5.40	25.10 ± 4.10	N/A	N/A	CPZ eq: 520.1
15.	Smith *et al*. (2015)	33	24/9	45.8	N/A	Sz/schizoaffective disorder	14.67 ± 6.25	17.47 ± 6.60	17.73 ± 7.85	19.80 ± 6.61	(2.60 ± 1.84)	(2.67 ± 1.59)	N/A

16.	Valiengo *et al.* (2019)	100	80/20	35.3	14.2	Sz with prominent negative symptoms	14.26 ± 4.27	14.24 ± 4.09	25.00 ± 3.93	25.10 ± 3.44	9.44 ± 11.91	7.66 ± 12.74	CPZ eq: 497.75

M = male, F = female; N/A = not available; Sz = schizophrenia; AH = auditory hallucination; AVH = auditory visual hallucination; CPZ = chlorpromazine; Ozp = Olanzapine, eq = equivalents. * Mean obtained from Chang et al., 2018

Table 2. Description of tDCS intervention in the included trials

Study No.	Authors (year)	Current x duration (mA x min)	Trial frequency	Trial Days	Total sessions	Polarity	Anode	Cathode	Electrode area (cm^2)	Primary Outcome (Assessment Tool)	Follow-up	Effects on symptoms (Effect Size)		
												AVH	Positive	Negative
1.	Bose *et al*. (2018)	2 x 20	2/day	5	10	A/C/S	Left DLPFC (between F3 & FP1)	Left TPJ (between T3 & P3)	35	Change in AVH severity (AHRS)	None	Improved (d=1.98)	No effect	No effect
2.	Brunelin *et al.* (2012)	2 x 20	2/day	5	10	A/C/S	Left DLPFC (between F3 & FP1)	Left TPJ (between T3 & P3)	35	Change in AVH severity (AHRS)	1 and 3 months	Improved (d=1.58)	Improved (d=0.64)	Improved (d=1.07)
3.	Chang *et al.* (2020)	2 x 20	2/day	5	10	A/C/S	Bilateral DLPFC (between F3 & FP1; between F4 & FP2)	Ipsilaterally placed on the forearms	35	Change in negative symptoms (PANSS -ve subscale)	1 and 3 months	N/A	No effect	Improved (d=0.2)
4.	Chang *et al*. (2019)	2 x 20	2/day	5	10	A/C/S	Left DLPFC (between F3 & FP1)	Left TPJ (between T3 & P3)	35	Change in AVH severity (AHRS*)	3 months	No effect	No effect	No effect
5.	Fitzgerald *et al*. (2014)	2 x 20	1/day	15	15	A/C/S	Bilateral DLPFC (F3/4)	Bilateral TP (TP3/4)	35	Overall clinical outcomes	None	No effect	No effect	No effect
6.	Fitzgerald *et al*. (2014)	2 x 20	1/day	15	15	A/C/S	Left DLPFC (F3)	Left TP (TP3)	35	Overall clinical outcomes	None	No effect	No effect	No effect
7.	Fröhlich *et al.* (2016)	2 x 20	1/day	5	5	A/C/S (return electrode over Cz)	Left DLPFC (between F3 & FP1)	Left TPJ (between T3 & P3)	35	Change in AVH severity (AHRS)	1 month	No effect	No effect	No effect
8.	Gomes *et al*. (2018)	2 x 20	1/day	10	10	A/C/S	Left DLPFC	Right DLPFC	25	Change in cognition	3 months	N/A	No effect	Improved (d=0.23)
9.	Jeon *et al.* (2018)	2 x 20	1/day	10	10	A/C/S	Left DLPFC (F3)	Right DLPFC (F4)	25	Change in cognition	3 months	N/A	No effect	No effect
10.	Kantrowitz *et al*. (2019)	2 x 20	2/day	5	5	A/C/S	Left DLPFC (between F3 & FP1)	Left TPJ (between T3 & P3)	38.8	Change in AVH severity (AHRS)	1 and 3 months	No effect	No effect	No effect
11.	Koops *et al*. (2018)	2 x 20	2/day	5	5	A/C/S	Left DLPFC	Left TPJ	35	Change in AVH severity (AHRS)	1 and 3 months	No effect	No effect	No effect
12.	Lindenmayer *et al*. (2019)	2 x 20	2/day	20	40	A/C/S	Left DLPFC (between F3 & FP1)	Left TPJ between T3 a& P3)	35	Change in AVH severity (AHRS)	None	Improved (d=0.47)	No effect	No effect
13.	Mondino *et al*. (2016)	2 x 20	2/day	5	10	A/C/S	Left DLPFC (between F3 & FP1)	Left TPJ (between T3 & P3)	35	Change in AVH severity (AHRS)	None	Improved (d=0.69)	No effect	Improved (d=0.56)
14.	Palm *et al*. (2016)	2 x 20	1/day	10	10	A/C/S	Left DLPFC (F3)	Right Orbitofrontal region (FP2)	35	Change in negative symptoms (SANS)	2 weeks	N/A	No effect	Improved (d=1.78)
15.	Smith *et al*. (2015)	2 x 20	1/day	5	5	A/C/S	Left DLPFC (F3)	Right Supraorbital ridge (FP2)	5.08	Change in cognition	None	No effect	No effect	No effect

16.	Valiengo *et al*. (2019)	2 x 20	2/day	5	10	A/C/S	Left DLPFC (F3)	Left TPJ (between T3 & P3)	35	Change in negative symptoms (PANSS -ve subscale)	2, 4, 6 and 12 weeks	No effect	No effect	Improved (d=0.18)

A = anodal; C = cathodal; S = sham; Cz = posterior midline), DLPFC = dorsolateral prefrontal cortex; TP = temporoparietal area; TPJ = temporoparietal junction; AVH = auditory visual hallucination; AHRS = Auditory Hallucination Rating Scale; PANSS = Positive and Negative Syndrome Scale;; SANS = Scale for the Assessment of Negative Symptoms; CDSS = Calgary Depression Scale for Schizophrenia; N/A = not available

Table 3 Percentage of adverse events in included studies with available quantitative data

Adverse event	tDCS	Sham
Skin flush/ redness under the electrodes	15.68	6.74
Burning sensation under the electrodes	21.08	13.48
Daytime sedation/ sleepiness	15.68	19.66
Itchiness under the electrodes	15.68	11.8
Pricking/ tingling under the electrodes	11.89	7.87
Headache	11.35	10.67
Neck pain	5.95	4.49
Scalp pain/ head pressure	3.78	5.06
Trouble concentrating	12.97	11.24
Acute mood change	2.16	6.74
Tinnitus	2.70	0.56

Table 4. The risks of bias of the included trials using Cochrane's criteria

Trial No.	Authors (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of assessors (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)
1.	Bose *et al*. (2018)	+	+	+	+	+	+
2.	Brunelin *et al.* (2012)	?	?	+	+	+	+
3.	Chang *et al*. (2020)	+	+	+	+	+	+
4.	Chang *et al.* (2019)	?	?	+	+	+	+
5.	Fitzgerald *et al*. (2014)	+	+	+	+	?	+
6.	Fitzgerald *et al*. (2014)	+	+	+	+	?	+
7.	Fröhlich *et al.* (2016)	+	?	+	+	+	+
8.	Gomes *et al*. (2018)	+	?	+	+	+	+
9.	Jeon *et al.* (2018)	+	?	+	+	?	+
10.	Kantrowitz *et al*. (2019)	+	?	+	+	?	+
11.	Koops *et al*. (2018)	+	?	+	+	+	+
12.	Lindenmayer *et al*. (2019)	?	?	+	+	+	+
13.	Mondino *et al*. (2016)	?	?	+	+	?	+
14.	Palm *et al*. (2016)	+	?	+	+	+	+
15.	Smith *et al*. (2015)	+	?	+	+	+	+
16.	Valiengo *et al.* (2019)	+	+	+	+	?	+

'+' = low risk of bias, '-' = high risk of bias, '?' = uncertain risk.

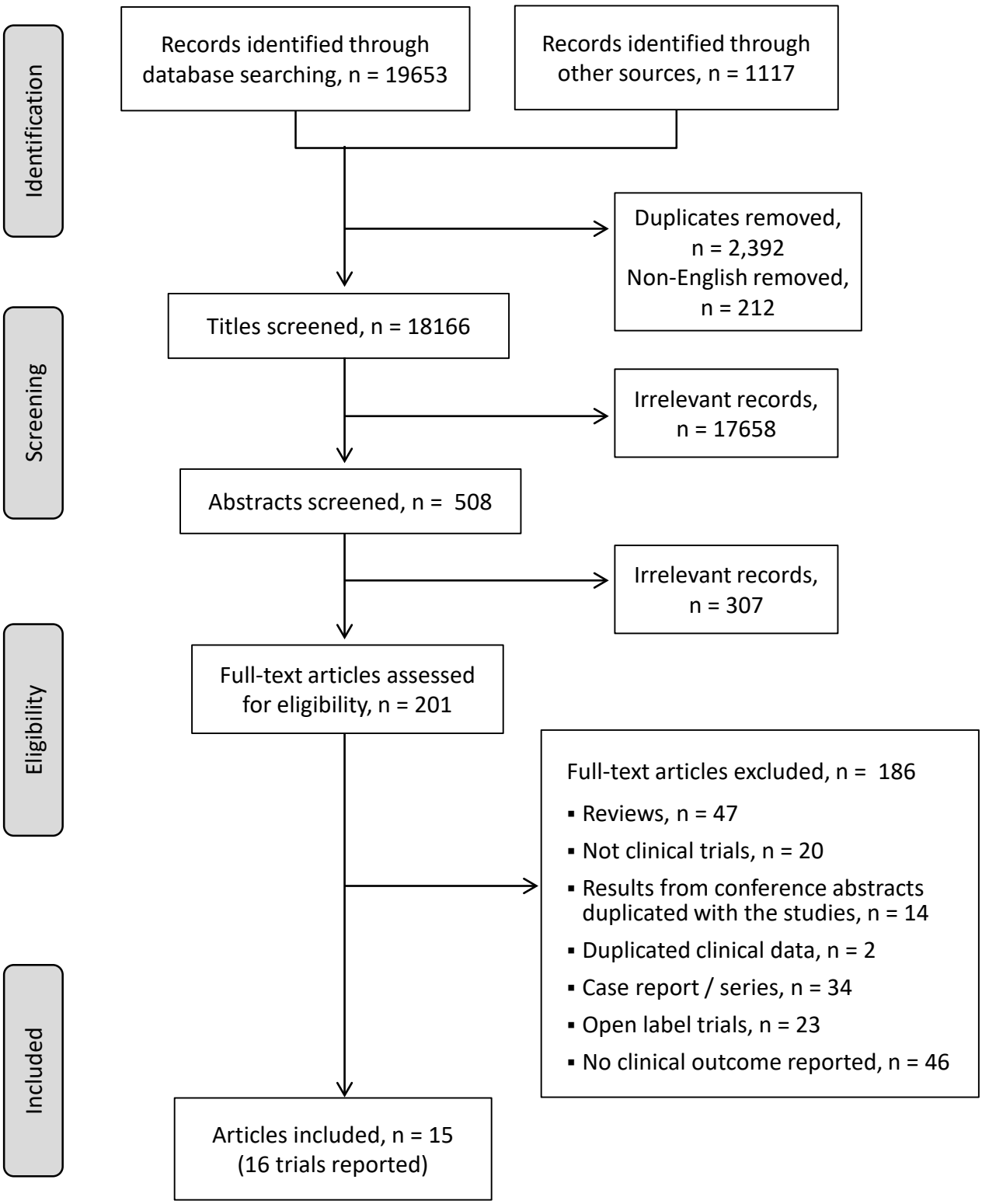
Appendix B. Figures Caption

Figure 1. PRISMA flow diagram illustrating the literature search, inclusion and exclusion process.

Figure 2. Forrest plots displaying the standardized mean differences (SMDs) between active and sham groups for the studies included in the main analysis. SMDs were derived for each of the following domains: (A) positive symptoms, (B) negative symptoms, and (C) hallucinations.

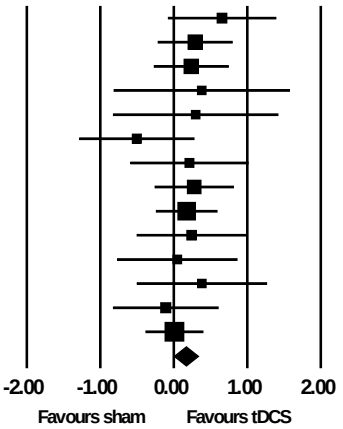
Figure 3. Forrest plots displaying the standardized mean differences (SMDs) between active and sham groups for the subgroup analyze. The SMDs are displayed for the following domains and subgroup categories: (A) Negative symptoms - pure diagnosis of schizophrenia, (B) Negative symptoms – 2 trials per day, C) Hallucinations – 2 trials per day, and D) Hallucinations – 10 or more sessions.

Figure 1. Flowchart of systematic review



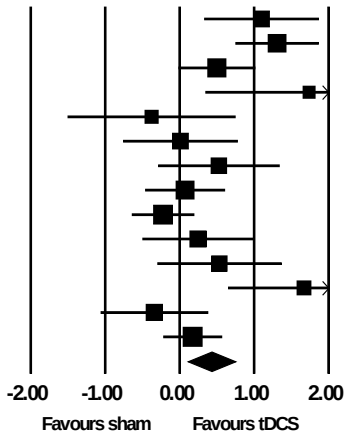
A) Positive symptoms

Study name	Outcome	Std diff in means	Standard error
Brunelin et al. (2012)	PANSS Positive	0.657	0.375
Chang et al. (2020)	PANSS Positive	0.293	0.260
Chang et al. (2019)	PANSS Positive	0.238	0.259
Fitzgerald et al. (2014a)	PANSS Positive	0.381	0.611
Fitzgerald et al. (2014b)	PANSS Positive	0.298	0.573
Frohlich et al. (2015)	PANSS Positive	-0.502	0.398
Gomes et al. (2018)	PANSS Positive	0.213	0.409
Jeon et al. (2018)	PANSS Positive	0.278	0.274
Kantrowitz et al. (2019)	PANSS Positive	0.175	0.213
Lindenmayer et al. (2019)	PANSS Positive	0.242	0.380
Mondino et al. (2016)	PANSS Positive	0.048	0.417
Palm et al. (2015)	PANSS Positive	0.383	0.451
Smith et al. (2015)	PANSS Positive	-0.109	0.365
Valiengo et al. (2019)	PANSS Positive	0.009	0.200
		0.167	0.084



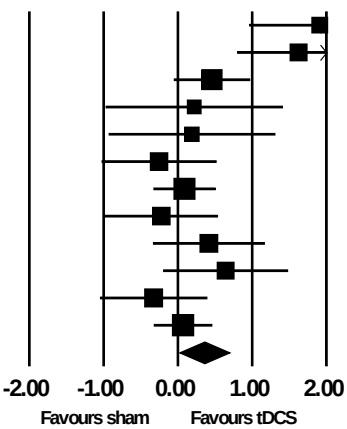
B) Negative symptoms

Study name	Outcome	Std diff in means	Standard error
Brunelin et al. (2012)	PANSS negative	1.100	0.392
Chang et al. (2020)	PANSS negative	1.309	0.285
Chang et al. (2019)	PANSS negative	0.500	0.262
Fitzgerald et al. (2014a)	PANSS negative	1.739	0.710
Fitzgerald et al. (2014b)	PANSS negative	-0.376	0.575
Frohlich et al. (2015)	PANSS negative	0.012	0.392
Gomes et al. (2018)	PANSS negative	0.527	0.415
Jeon et al. (2018)	PANSS negative	0.073	0.272
Kantrowitz et al. (2019)	PANSS negative	-0.223	0.213
Lindenmayer et al. (2019)	PANSS negative	0.247	0.380
Mondino et al. (2016)	PANSS negative	0.534	0.425
Palm et al. (2015)	PANSS negative	1.671	0.519
Smith et al. (2015)	PANSS negative	-0.339	0.368
Valiengo et al. (2019)	PANSS negative	0.175	0.200
		0.429	0.163



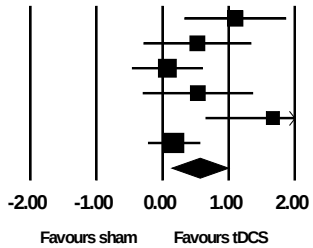
C) Hallucinations

Study name	Outcome	Std diff in means	Standard error
Bose et al. (2018)	AHRS	1.911	0.483
Brunelin et al. (2012)	AHRS	1.626	0.421
Chang et al. (2019)	AHRS	0.459	0.262
Fitzgerald et al. (2014a)	PANSS AH	0.220	0.607
Fitzgerald et al. (2014b)	PANSS AH	0.190	0.571
Frohlich et al. (2015)	AHRS	-0.253	0.394
Kantrowitz et al. (2019)	AHRS	0.089	0.212
Koops et al. (2018)	AHRS	-0.223	0.388
Lindenmayer et al. (2019)	AHRS	0.417	0.383
Mondino et al. (2016)	AHRS	0.643	0.428
Smith et al. (2015)	PANSS AH	-0.326	0.368
Valiengo et al. (2019)	AHRS	0.070	0.200
		0.358	0.172



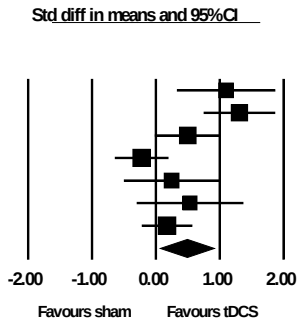
A) Negative symptoms - pure diagnosis of schizophrenia

Study name	Outcome	Std diff in means	Standard error
Brunelin et al. (2012)	PANSS negative	1.100	0.392
Gomes et al. (2018)	PANSS negative	0.527	0.415
Jeon et al. (2018)	PANSS negative	0.073	0.272
Mondino et al. (2016)	PANSS negative	0.534	0.425
Palm et al. (2015)	PANSS negative	1.671	0.519
Valiengo et al. (2019)	PANSS negative	0.175	0.200
		0.566	0.219



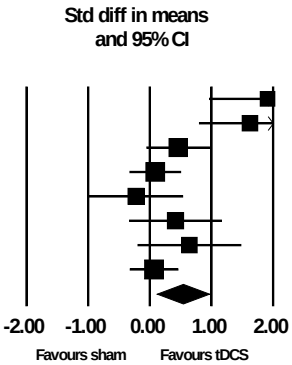
B) Negative symptoms – 2 trials per day

Study name	Outcome	Std diff in means	Standard error
Brunelin et al. (2012)	PANSS negative	1.100	0.392
Chang et al. (2020)	PANSS negative	1.309	0.285
Chang et al. (2019)	PANSS negative	0.500	0.262
Kantrowitz et al. (2019)	PANSS negative	-0.223	0.213
Lindenmayer et al. (2019)	PANSS negative	0.247	0.380
Mondino et al. (2016)	PANSS negative	0.534	0.425
Valiengo et al. (2019)	PANSS negative	0.175	0.200
		0.488	0.216



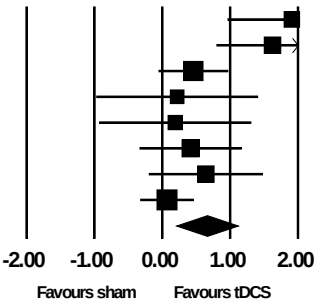
C) Hallucinations – 2 trials per day

Study name	Outcome	Std diff in means	Standard error
Bose et al. (2018)	AHRS	1.911	0.483
Brunelin et al. (2012)	AHRS	1.626	0.421
Chang et al. (2019)	AHRS	0.459	0.262
Kantrowitz et al. (2019)	AHRS	0.089	0.212
Koops et al. (2018)	AHRS	-0.223	0.388
Lindenmayer et al. (2019)	AHRS	0.417	0.383
Mondino et al. (2016)	AHRS	0.643	0.428
Valiengo et al. (2019)	AHRS	0.070	0.200
		0.541	0.216



D) Hallucinations – 10 or more sessions

Study name	Outcome	Std diff in means	Standard error
Bose et al. (2018)	AHRS	1.911	0.483
Brunelin et al. (2012)	AHRS	1.626	0.421
Chang et al. (2019)	AHRS	0.459	0.262
Fitzgerald et al. (2014a)	PANSS AH	0.220	0.607
Fitzgerald et al. (2014b)	PANSS AH	0.190	0.571
Lindenmayer et al. (2019)	AHRS	0.417	0.383
Mondino et al. (2016)	AHRS	0.643	0.428
Valiengo et al. (2019)	AHRS	0.070	0.200
		0.662	0.232



Vitae

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