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Title

Efficacy of Transcranial Direct Current Stimulation to Improve Insight in Patients with Schizophrenia: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Running title

Effects of tDCS on Insight in Schizophrenia

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Abstract

Background and Hypothesis: Impaired insight into the illness and its consequences is associated with poor outcomes in schizophrenia. While transcranial direct current stimulation (tDCS) may represent a potentially effective treatment strategy to relieve various symptoms of schizophrenia, its impact on insight remains unclear. To investigate whether tDCS would modulate insight in patients with schizophrenia, we undertook a meta-analysis based on results from previous RCTs that investigated the clinical efficacy of tDCS. We hypothesize that repeated sessions of tDCS will be associated with insight improvement among patients.

Study Design: PubMed and ScienceDirect databases were systematically searched to identify RCTs that delivered at least 10 tDCS sessions in patients with schizophrenia. Primary outcome was the change in insight score, assessed by the PANSS item G12 following active tDCS sessions as opposed to sham stimulation. Effect sizes were calculated for all studies and pooled using a random-effects model. Meta-regression and subgroup analyses were conducted.

Study Results: Thirteen studies (587 patients with schizophrenia) were included. A significant pooled effect size (g) of -0.46 (95% CI [-0.78; -0.14]) in favor of active tDCS was observed. Age and G12 score at baseline were identified as significant moderators, while change in total PANSS score was not significant.

Conclusions: Ten sessions of active tDCS with either frontotemporoparietal or bifrontal montage may improve insight into the illness in patients with schizophrenia. The effect of this treatment could contribute to the beneficial outcomes observed in patients following stimulation.

Key words: tDCS, psychosis, neuromodulation

Introduction

Lack of patient insight into the illness is a key characteristic of many psychiatric disorders, including bipolar disorder,[1] obsessive-compulsive disorder,[2] and dementias.[3] Among patients with schizophrenia, the estimated prevalence of poor insight, corresponding to a general unawareness of illness, can be up to 50%.[4,5] Insight deficit includes lack of awareness of the symptoms of the illness, the need for and willingness to undergo treatment, and the consequences of the illness on the patient's life.[6] Poor insight has been regularly associated with negative attitudes toward medication[7] and nonadherence to antipsychotic treatment.[8–11] Treatment nonadherence in schizophrenia represents a heavy economic cost, estimated between $13.92 and $18.36 million a year in the United States,[12] since it increases the risk of relapse, rehospitalization rates, and suicide attempts.[12,13] Poor insight is directly associated with a higher risk of relapse,[14] which further emphasizes the importance of fostering better insight into the illness. Unfortunately, available treatments such as antipsychotic medication and psychotherapy provide either little or no improvement in patients' insight into their illness.[15]

Transcranial direct current stimulation (tDCS) is a safe, low-cost tool for modulating the activity and connectivity of targeted brain regions and related neural networks.[16,17] tDCS consists of applying weak electric currents through two electrodes placed over the scalp, with polarity-dependent effects on cortical excitability: currents entering the brain at the anode site are thought to increase cortical excitability while currents exiting the brain at the cathode site are thought to decrease cortical excitability.[18] For clinical purposes, repeated sessions of tDCS show promising results in alleviating some of the symptoms of schizophrenia and may also improve cognition in these patients.[19] The means by which tDCS alleviates symptoms remains unclear, and one can hypothesize that a beneficial effect on metacognitive processes, and especially on insight capacities, could be considered to explain tDCS's clinical effect since insight impairments have been associated with alteration in the activity of brain regions regularly targeted by tDCS (frontal and temporoparietal regions for example).[20] Nevertheless, to date, only 5 articles from 3 different randomized controlled trials (RCTs) have studied the effect of tDCS on insight in patients with schizophrenia using different scales;[21–25] thus, drawing firm conclusions remains difficult.[26] An underutilized source of informative data on the impact of

tDCS on insight is a widely used psychiatric assessment scale:[27] the Positive and Negative Syndrome Scale (PANSS) and its item G12.[28] This item assesses the lack of judgment and insight into the illness using a 7-level scale (ranging from 1, no impairment, to 7, extreme lack of insight). Gathering these often-unexamined data would provide a new source of evidence in establishing the potential benefits of treatment with tDCS on insight.

Since insight deficits are a major problem in the management of patients with schizophrenia, we conducted a systematic review and meta-analysis of randomized, sham-controlled clinical trials to evaluate the association between tDCS treatment and improvement in PANSS G12 scores in patients with schizophrenia. We hypothesized that, compared to sham tDCS, active tDCS will be associated with a decrease in G12 scores, which corresponds to an improvement in patient insight.

Methods

The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[29] The protocol was registered on the PROSPERO database (CRD42021243147).

Literature search and selection criteria

Two authors (OA and MM) searched independently for articles in the PubMed and ScienceDirect databases with no restriction of date for eligible studies using the following keywords: ("tDCS" OR "transcranial direct current stimulation") AND ("PANSS" OR "positive and negative syndrome scale") AND "schizophrenia"). The search was conducted between November 2020 and March 2021. In ScienceDirect, research was refined using *research articles*, *book chapters* and *other* limits. Selected studies met the following inclusion criteria: (1) inclusion of patients with schizophrenia or schizoaffective disorder; (2) comparison between active and sham stimulation; and (3) assessment of symptoms before and after tDCS sessions using the PANSS. The selection procedure was repeated on the full text of eligible studies. We excluded studies that were not RCTs, that combined tDCS with a therapy other than antipsychotic treatments, and that did not offer at least 10 sessions of tDCS. This

choice was based on three recent meta-analyses that found a significantly greater clinical effect of tDCS in studies that delivered at least 10 sessions compared to those that delivered fewer than 10 sessions.[30–32]

Data extraction and main outcome

Age, sex, diagnosis, illness duration, antipsychotic dose, PANSS total scores and G12 score at baseline, stimulation parameters (including the electrode placements), sham and blinding procedures were extracted from included studies. Authors who reported using the PANSS were contacted to provide the mean change in G12 score, defined as the score assessed immediately after completion of tDCS treatment minus the score assessed before the treatment, that was our main outcome. Additionally, they were asked to check extracted data from articles for accuracy.

Quality and risk of bias assessments

The quality of the included studies was measured independently by one author (OA) and by the contacted authors of each study using the Jadad scale.[33] These two scores were averaged to assess overall quality.

Risk of bias was evaluated independently by two authors (OA and MB) using a Traffic Light plot and a Summary plot,[34] constructed in accordance with the guidelines from the Agency for Healthcare Research and Quality.[35]

Statistical analysis

All statistical analyses were performed with R software, version 4.1.2 (R Core Team, 2021), using the *metafor*, *meta* and *dmetar* packages. The significant α level was set at 0.05. Hedges' g effect size (ESg) along with the 95% confidence interval was computed based on mean (SD) scores of G12. The overall ESg was pooled from each study using a random-effects model and was interpreted according to Cohen's guidelines (0.2=small; 0.5=medium; 0.8=large effect).[36] Global heterogeneity significance was calculated from Cochran's Q-test and quantified using the I^2 and τ^2 statistics.[37]

150 To explore the causes of the heterogeneity, meta-regression analyses were conducted individually for
151 each moderator, such as electrode montage (studies were grouped into bifrontal montage when both
152 electrodes were placed over prefrontal areas at F3, F4 or FP2, and frontotemporoparietal montage
153 when the anode was placed over prefrontal areas at F3-FP1, F3 or F4 and the cathode over
154 temporoparietal areas at T3-P3), current density (intensity divided by electrode size), total charge per
155 session (intensity by session duration) and per tDCS regimen (intensity by session duration by number
156 of session), G12 score at baseline, changes in PANSS total score, PANSS total score at baseline, age
157 of patient, illness duration, and antipsychotic dose. Age and illness duration can impact insight in
158 patients[20,38,39] and antipsychotic dose may influence the response to tDCS.[40] In addition, we proceeded
159 to exploratory separate subgroup analyses in cases of significance after FDR correction for multiple
160 tests. Since no clear hypothesis on the relationship between a specific age and response to tDCS or
161 insight could be generated from the literature, we divided studies into one group with a below-average
162 age (<40 years) and one group with an above-average age (≥40 years), based on the mean age of
163 participants included in the studies combined (mean split of age). Concerning G12 scores, we divided
164 studies into a group with, on average, an absence of or minimal lack of insight (<3); and a group with,
165 on average, at least a mild lack of insight (≥3). This division was based on the hypothesis that there
166 would have to be an already marked impairment of insight for tDCS to influence it.

167 Finally, publication bias was assessed by visual examination of the funnel plot and using Egger's
168 regression test. Potential outlier studies were controlled by visual examination of QQ plots and Baujat
169 plots. Meta-outlier detection and leave-one-out meta-analyses were conducted to investigate the effect
170 of potential outliers on the pooled effect size.

171

172 **Results**

173 *Search results*

174 The initial search strategy identified 116 records. After the removal of duplicate studies and the
175 exclusion of ineligible studies, 21 full texts were assessed, of which 17 met our inclusion criteria

176 (Figure 1). Among them, three studies presented the same sample[21,24,25] and two studies had partially
177 overlapping samples;[41,42] in these cases, we chose the record with the largest sample size. One eligible
178 study was excluded because the data could not be provided upon request.[43] A total of 13 RCTs from
179 12 independent groups were included in our meta-analysis.[21,23,41,44–53]

180 *Characteristics of studies*

181 These studies included 587 participants, 297 of whom received active tDCS and 290 of whom
182 received sham tDCS. Details of these studies are provided in Table 1 & 2 and in *Supplementary*
183 *Materials Appendix 1*. All included RCTs showed a high range of quality scores (scores≥3) on the
184 Jadad scale, except for 1 study which had a low-quality score (score=2).[52] Visual inspection of the
185 traffic light plot revealed that most studies showed a low overall risk of bias and that only 2 studies[46,47]
186 showed a potential moderate risk of bias (Supplementary Figure 1). The main risk of bias was the bias
187 arising from the randomization process (Supplementary Figure 2).

188 *Insight and tDCS treatment*

189 A forest plot of the distribution of effect sizes is presented in Figure 2. The overall ESg was -0.46
190 (medium effect, 95% CI [-0.78; -0.14]) and reached statistical significance (P=0.005), indicating a
191 greater decrease in G12 scores among patients who received active tDCS than among those who
192 received sham tDCS. The individual ES ranged from -1.94 to 0.19. We found significant heterogeneity
193 (Q=41.9, P<0.001), which was moderate-to-high (I^2=71.4%, τ^2=0.23).

194 *Moderator and subgroup analyses*

195 Post hoc analyses were conducted to explore potential sources of global heterogeneity (individual
196 results of meta-regression shown in Supplementary Table 1). Only the age of participants and baseline
197 G12 score model reached significance, therefore influencing ESg.

198 Next, we conducted exploratory subgroup analyses to further investigate the influence of age of
199 participants and baseline G12 score on the association between tDCS and insight improvement
200 (Supplementary Table 2). Regarding age, studies including patients with an average age over 40 years

201 showed a significantly larger ESg compared to those including patients with an average age below 40
202 years (Q=4.11, P=0.04). No significant difference was found between studies with on average at least
203 a mild lack of insight (average≥3) and those with on average an absence of or minimal lack of insight
204 (average<3, Q=0.62, P=0.43).

205 *Sensitivity analyses*

206 No outlier study could be identified by the QQ plot (Supplementary Figure 3**)** but the study of Chang
207 and colleagues[23] substantially influenced the overall ESg, as indicated by the Baujat plot
208 (Supplementary Figure 4). In that respect, meta-outlier detection led to exclusion of the Chang and
209 colleagues' study. Leave-one-out meta-analysis showed that the estimated ES as well as the between-
210 study heterogeneity were stable by excluding a single study with the exception of Chang et al., 2020:
211 range of SMDs -0.40 to -0.53 compared to -0.31 (Supplementary Table 3). When excluding the Chang
212 et al.' study, the ESg remained significant at -0.31 (small effect, 95% CI [-0.54; -0.09], P=0.006) and
213 no significant heterogeneity was observed (Q=16.92, P=0.11). Additional sensitivity exploratory
214 analyses without the study of Chang and colleagues were conducted (Supplementary Table 4). Only
215 meta-regression for baseline G12 score changed dramatically when excluding Chang et al. 2020
216 (P=0.02 *vs.* P=0.84).

217 Publication bias was unlikely since the funnel plot and Egger's regression test did not indicate any
218 significant asymmetry (P=0.38, Supplementary Figure 5).

219 **Discussion**

220 Our meta-analysis indicated that tDCS treatment was significantly associated with improvement in
221 insight among patients with schizophrenia. Indeed, we observed a significant, moderate effect size
222 (ESg=-0.46) in favor of a decrease in G12 scores after repeated sessions of tDCS (at least ten),
223 associated with moderate-to-high heterogeneity (I^2=71.4%). Our results are consistent with those
224 reported by 5 articles investigating the effect of tDCS using other insight measures that showed
225 significant improvement in insight after active tDCS compared to sham tDCS.[21–25] Although our
226 findings highlighted a statistically significant effect on insight, it remains to be determined whether

227 this effect is clinically meaningful and translates into a functional improvement. To do so, several
228 recent studies have recommended to test the clinical meaning of treatment-induced changes against
229 clinicians' subjective perception of clinical improvement, as measured with the scores at the Clinical
230 Global Impression Scales.[54–56] We recommend future tDCS studies to systematically evaluate and
231 report such measures.

232 Improvements in insight should be considered a mechanism underlying the clinical efficacy of tDCS
233 by leading to better medication adherence[38] and compliance with treatment.[57] Improvements in insight
234 could also benefit patients' quality of life, as insight improvements correlate with reductions in
235 symptoms[57] and with enhancement of social functioning.[4] Finally, awareness of illness and symptoms
236 could enhance prognosis by improving the involvement of patients in their own recovery.[58] Impaired
237 insight is a transdiagnostic construct, since it is found in many psychiatric disorders[1–3], and it is
238 underpinned by several commonalities among them.[59] It is therefore important to focus on insight
239 because it represents a therapeutic target that can affect many patients.

240 In view of the tDCS parameters, we note that all the electrode setups used targeted the dorsolateral
241 prefrontal cortex (DLPFC). Several neuroimaging studies support the role of the DLPFC as a key
242 region for insight into the illness. For instance, insight has been inversely correlated with gray matter
243 volume deficits in the right DLPFC, bilateral cerebellum, and posterior part of the right temporal
244 inferior gyrus in schizophrenia.[60] Lack of insight has also been associated with white matter deficits in
245 the frontal, temporal and parietal regions,[61] and structural hemispheric asymmetry in the DLPFC.[20]
246 Additionally, a functional magnetic resonance imaging study in patients with schizophrenia
247 highlighted the implication of the DLPFC in both unawareness of symptoms and misattribution of
248 symptoms.[62] The combination of structural and functional abnormalities of frontal, parietal and
249 temporal areas of the brain and dysfunction in their connectivity may lead to the impairment of
250 insight.[59] Stimulating the DLPFC using either a bifrontal tDCS montage with the anode placed over
251 the left DLPFC or a frontotemporoparietal montage with the anode over the left or right DLPFC may
252 promote its excitability[18] and re-establish the proper functioning of such networks, since tDCS can
253 modulate the activity of networks associated with the targeted regions.[17] Given that targeting the

254 DLPFC with transcranial alternating current stimulation has led to improvements in retrospective self-
255 evaluations and metacognition among healthy subjects,[63] one could hypothesize that in patients with
256 schizophrenia, stimulating the DLPFC with the anode will also enhance these cognitive functions,
257 thereby improving insight into their illness. Our moderator analyses did not reveal the superiority of
258 any particular electrode arrangement between bifrontal and frontotemporoparietal montages. However,
259 Chang and colleagues' study (2020) which was identified as a significant outlier because of its large
260 ESg was the only one using a bi-anodal montage, *i.e.*, with two anodes targeting the left and right
261 DLPFC and two extracephalic cathodes. These findings nevertheless suggest a potential influence of
262 the electrode arrangement on the observed effect.

263 In addition to the DLPFC stimulation, it seems also likely that the improvement of insight into illness
264 result from cathodal tDCS-induced inhibition[18] of left temporoparietal/posterior parietal areas. Indeed,
265 almost half of the included studies used a frontotemporoparietal montage with the cathode placed at
266 T3-P3, which can partially cover the temporoparietal areas and adjacent posterior parietal areas. These
267 regions, namely the left angular gyrus and posterior parietal areas, have been reported to be
268 hyperactive in patients with schizophrenia who present impairment in insight.[64,65] Furthermore, an
269 alteration in interhemispheric balance, characterized particularly by a left hemispheric dominance of
270 the temporoparietal areas and prefrontal regions, has been associated with poor insight[65] and could be
271 related to alterations in the white matter tracts of the posterior part of the corpus callosum.[66] The
272 association between the stimulation of the left temporoparietal/posterior parietal areas and improved
273 insight is also supported by two studies that delivered cathodal stimulation to these regions. A single
274 biparietal tDCS session with the cathode over the left posterior parietal area has been reported to
275 reduce the interhemispheric imbalance in patients with impaired insight and this mechanism has been
276 proposed to contribute to improved insight.[22] In addition, a study investigating the impact of high-
277 definition tDCS targeting the left temporoparietal area with the cathode described a significant
278 improvement in insight in patients with schizophrenia.[67]

279 Exploratory moderator analyses showed a significant influence of participant's age and G12 score at
280 baseline on the improvement of insight after tDCS treatment. First, it appears that the higher the G12

281 score at baseline, the greater the improvement in insight following tDCS. However, these findings are
282 mainly driven by Chang et al., 2020's study, in which patients had the highest mean G12 score at
283 baseline. Indeed, sensitivity analysis revealed that the influence of G12 score at baseline did not
284 remain significant after the exclusion of this study. Since a significant overall ESg is still observed
285 even after excluding Chang et al., 2020's study, G12 score at baseline does not appear to be a
286 determinant factor of the improvement in insight induced by tDCS. Second, the older the patient the
287 greater the improvement. These results are surprising since recent meta-analyses showed a negative
288 association between age and the tDCS-induced reduction of hallucinations and negative symptoms in
289 patients with schizophrenia.[30,68] In addition, age has been associated with an alteration of the
290 efficiency of tDCS to induce brain plasticity.[69] The opposite association found here between age and
291 tDCS-induced improvement in insight could be related to the complex interaction between age and
292 insight: the course of insight impairment follows a U-shaped trajectory where insight impairment
293 increases with the first episode of psychosis, decreases over midlife, and increases again in late life,
294 with fluctuations depending on the other episodes occurring throughout the patient's life.[70] The
295 complex interaction between age, insight and tDCS-induced neural plasticity deserves further
296 investigations.

297 We identified a moderate risk of bias associated with the randomization process in about half of the
298 studies. This risk seems to be mainly due to a lack of reporting sufficient random sequence generation
299 description in the published articles. It is noteworthy that the lack of reporting sufficient details does
300 not necessarily reflect a bias in the randomization process itself but may be related to a lack of
301 awareness of the importance of reporting such information, or a lack of space related to the inherent
302 space limitation of scientific articles. The second questionnaire on the study quality[33] we used helps to
303 mitigate this bias since the authors were given the opportunity to rate their studies themselves, so as
304 not to penalize the study for aspects that were merely not mentioned in the published article.
305 Nevertheless, it is critical to report details about the randomization process since this process prevents
306 the influence of potentially confounding factors, whether known or not.[71] The potential risk found in

307 some of the included studies is therefore difficult to interpret but could be responsible for the existence
308 of unidentified biases that were not subsequently controlled for.

309 Finally, one could question the specificity of tDCS effects on insight compared to other symptoms.
310 However, adding the change in PANSS total score as a moderator in our main analysis revealed no
311 significant influence of this parameter on tDCS-induced insight changes. These findings suggest that,
312 although tDCS was associated with improvements in insight (current study) and other symptoms of
313 schizophrenia (e.g.,[30–32]), these effects may occur independently and result from nonrelated
314 mechanisms. A large prospective RCT or a meta-analysis based on individual participant data is
315 needed to properly address this question of specificity of the effect of tDCS on insight vs. other
316 symptoms, and to investigate the causal relationship and temporality between these improvements.

317 *Limitations*

318 Some methodological limitations must be emphasized. First, most of the included studies had small
319 sample sizes, which could be responsible for inflated individual ES estimation. Second, using a single
320 item to assess modifications in insight into the illness could limit the interpretations of current results
321 and their clinical significance. Nevertheless, a high correlation of G12 scores with detailed scales of
322 insight has repeatedly been observed,[61,72] suggesting that G12 scores can be considered a good
323 indicator of changes in insight. It should be noted that despite its correlation with the total scores of
324 detailed scales of insight, G12 score does not systematically correlate with the subscales of those
325 insight scales and therefore does not present the same subtlety in the assessment of insight. However, a
326 recent article highlighted a high variability in insight dimensions between those detailed scales,
327 questioning their respective interpretation.[73] Third, exploratory post hoc analyses identified some
328 variables that significantly influenced our primary outcome. These results enable us to establish new
329 working hypotheses that should be investigated in further studies, but they do not allow us to draw
330 firm conclusions about the effect of moderators on the association between improvement in insight
331 and tDCS. Fourth, PANSS interrater reliability measures were not systematically reported
332 (Supplementary Table 5), thus this potential bias could be not controlled. Fifth, we were interested in
333 the short-term effect of tDCS. Just as the improvement of positive or negative symptoms is maintained

334 over time after repeated tDCS sessions, it is reasonable to assume that improvement in insight, as
335 measured by a decrease in G12 scores, will be observed over a few months. Further studies should
336 nevertheless investigate this question. Finally, controversies exist regarding the effects of tDCS,
337 mostly arising from meta-analyses that find no reliable effects of tDCS on behaviour (e.g.,[74 75] for a
338 review of the key points of controversy). The most notable criticisms raised are the lack of
339 reproducibility of the effects of tDCS and the large inter-individual variability, restricting the
340 generalizability of the results. Several factors have been pointed out as plausible reasons for the
341 variability of the findings including differences in stimulation settings and parameters such as
342 stimulation intensity and duration, size of electrodes, location and orientation of electrodes (Table 2),
343 as well as differences in experimental design including sample sizes, choices of control conditions and
344 blinding procedures (i.e., procedures implemented to ensure that participants/tDCS operators/outcome
345 assessors are not aware of the type of stimulation they are receiving/delivering). Namely, control
346 conditions and blinding procedures are of paramount importance in clinical tDCS studies since they
347 could bias the adequate estimation of tDCS effects through the occurrence of a "placebo effect". In the
348 reviewed studies, control conditions all consisted of sham stimulations supposed to only mimic
349 transient effects of active tDCS on the scalp but not to induce physiological effects (Supplementary
350 Table 6). Not only are these sham conditions questionable when successful blinding is not achieved,
351 but they could also mask a differential effect of active stimulation by causing cerebral changes and
352 therefore be a hidden source of variability[76]. In addition, the effectiveness of the chosen blinding
353 strategy was not systematically assessed or reported by the authors (Supplementary Table 7). When
354 done, a post-stimulation questionnaire was generally used in which participants and providers had to
355 guess whether they had received active or sham stimulation, and the validity of such method for
356 measuring blinding effectiveness has recently been questioned[77]. Efforts should be made to improve
357 blinding and sham procedures and their evaluation through the development of new methods.

358

Conclusion

The results of the current systematic review and meta-analysis revealed a significant association, with a moderate effect size, between tDCS treatment and improvement in the PANSS G12 score for insight into the illness among patients with schizophrenia. Participants who received at least ten sessions of active tDCS displayed greater improvements in insight than patients who received sham tDCS. It is important to note that although the effect is statistically significant, it is unclear whether this effect would transfer into clinical meaningful improvement in real life. Further randomized controlled studies are needed to investigate the role of different variables of tDCS-induced changes in insight.

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603 **Figure legends**

604

605 **Figure 1. PRISMA flow diagram of included studies.**

606 Abbreviations: RCTs, randomized controlled trials; tDCS, transcranial direct current stimulation.

607

608 **Figure 2. Forest plot showing comparison of insight, as measured by the G12 score, among**

609 **patients with schizophrenia who received either active or sham tDCS.**

610 Abbreviations: ES, effect size; CI, confidence interval; RE, random effect.

Table 1. Sociodemographic and Clinical Characteristics of Included Studies.

Authors, year	Jadad score[a]	Diagnosis	Treatment condition	n	Age (y)	Female n (%)	Illness duration (y)	Antipsychotic dose (CPZE, mg/day)	PANSS total score at baseline	G12 score at baseline	Mean changes in total PANSS score after tDCS treatment	Mean changes in G12 score after tDCS treatment
Brunelin et al., 2012	3	SZ	Active	15	40.4 (9.9)	3 (20)	NR	994 (714)	76.9 (16.4)	2.3 (1.4)	-9.2 (8.1)	-0.53 (1.33)
			Sham	15	35.1 (7.0)	5 (33)	NR	1209 (998)	82.8 (15.4)	2.2 (1.2)	-2.3 (10.1)	-0.13 (0.83)
Palm et al., 2016	5	SZ	Active	10	38.4 (12.9)	5 (50)	7.1 (6.1)	559 (304)	79.5 (20.0)	2.7 (1.2)	-14.2 (21.1)	-0.333 (1.00)
			Sham	10	34.1 (10.7)	0 (0)	13.8 (12.1)	481 (226)	85.6 (6.8)	2.4 (1.4)	0.8 (7.1)	-0.125 (0.354)
Chang et al., 2018	4	SZ - SZAff	Active	30	46.4 (10.3)	16 (53)	19.7 (10.4)	494 (307)	72.3 (13.2)	4.2 (1.2)	-2.6 (3.8)	-0.87 (1.14)
			Sham	30	42.2 (10.3)	17 (57)	13.9 (7.5)	493 (284)	66.7 (12.5)	3.7 (0.8)	-0.3 (1.2)	-0.03 (0.18)
Gomes et al., 2018	5	SZ	Active	12	39.2 (9.3)	2 (17)	16.0 (11.6)	NR	81.6 (16.0)	3.1 (1.2)	-10.7 (6.1)	-0.42 (0.90)
			Sham	12	33.7 (12.1)	5 (42)	10.0 (7.3)	NR	71.0 (19.9)	3.3 (1.4)	-0.8 (6.1)	-0.42 (1.08)
Jeon et al., 2018	5	SZ	Active	26	40.0 (9.4)	13 (50)	12.8 (9.8)	546 (403)	85.8 (21.1)	3.6 (1.3)	-13.8 (27.1)	0.07 (0.48)
			Sham	28	39.9 (12.4)	15 (54)	14.3 (10.5)	614 (430)	79.1 (16.6)	3.4 (1.3)	-7.0 (19.6)	0.25 (0.80)
Koops et al., 2018	4	Mixed sample[b]	Active	28	44.0 (11)	14 (50)	NR	NR	68.0 (16.0)	2.7 (1.3)	-5.4 (8.1)	-0.32 (0.94)
			Sham	26	44.0 (12)	15 (58)	NR	NR	64.0 (17.0)	3.5 (1.3)	-2.2 (7.5)	0.08 (0.81)
Mellin et al., 2018	4	SZ - SZAff	Active	7	29.6 (11.0)	3 (43)	6.4	NR	58.9 (14.7)	2.9 (2.3)	-4.1 (3.7)	0.14 (0.38)
			Sham	7	38.9 (10.0)	3 (43)	14.3	NR	57.0 (11.6)	2.6 (1.5)	-1.7 (4.4)	0.71 (1.11)
Kantrowitz et al., 2019	5	SZ - SZAff	Active	47	38.2 (9.9)	15 (32)	NR	806 (768)	75.3 (12.9)	3.3 (1.4)	-3.3 (9.4)	-0.149 (1.23)
			Sham	42	40.1 (8.6)	7 (17)	NR	628 (466)	73.2 (14.4)	3.0 (1.3)	-2.1 (9.0)	0.075 (1.28)
Lindenmayer et al., 2019	4	SZ - SZAff	Active	12	41.4 (11.3)	2 (17)	NR	958 (364)	81.5 (7.5)	3.6 (1.1)	-8.2 (7.3)	0.083 (0.515)
			Sham	13	39.9 (10.5)	2 (15)	NR	896 (275)	82.8 (9.4)	3.6 (1.2)	-2.3 (6.6)	0.077 (0.760)
Weickert et al., 2019	4	SZ - SZAff	Active	6	45.5 (1.9)	4 (67)	22 (0.9)	555 (249)	59.5 (NR)	2.5 (1.6)	-5.0 (5.7)	-1.6 (1.5)
			Sham	6	31.3 (3.6)	2 (33)	8.3 (3.4)	1009 (261)	65.3 (NR)	3.0 (1.3)	-0.5 (15.9)	-0.6 (0.9)
Chang et al., 2020	5	SZ - SZAff	Active	30	44.7 (10.7)	11 (37)	14.7 (9.5)	532 (348)	67.4 (13.0)	4.5 (1.0)	-10.8 (7.1)	-2.00 (1.17)
			Sham	30	45.0 (10.9)	19 (63)	15.8 (10.6)	523 (332)	73.3 (10.3)	4.7 (0.9)	-1.4 (4.4)	-0.23 (0.50)
Smith et al., 2020	2	SZ	Active	24	43.7 (14.1)	15 (62)	17.9 (11.7)	NR	62.0 (15.6)	3.6 (1.2)	-3.3 (13.8)	-0.381 (0.921)
			Sham	21	47.1 (11.9)	12 (57)	19.7 (11.1)	NR	58.7 (9.9)	3.7 (1.2)	-4.4 (9.9)	0.0833 (1.06)
Valiengo et al., 2020	5	SZ	Active	50	34.6 (8.4)	9 (18)	14.2 (8.1)	475 (225)	73.6 (15.8)	2.8 (1.4)	-5.3 (10.2)	0 (1.30)
			Sham	50	35.9 (10.1)	11 (22)	14.1 (8.7)	500 (400)	73.9 (13.4)	3.0 (1.4)	-3.1 (7.9)	-0.24 (1.25)

Otherwise specified, results are given as mean (SD).

[a]Jadad scores correspond to the average of the scores given by the author OA and by the main author of the associated article.

[b]Koops et al. (2018) included 21 patients with SZ, 4 patients with psychosis NOS, 1 patient with schizoaffective disorder, 1 patient with affective disorder, and 1 patient with borderline personality disorder.

[c]Chang et al. (2020) used a bi-anodal montage over the left and right dorsolateral prefrontal cortices, with extracephalic cathodes as reference electrodes.

Abbreviations: CPZE, chlorpromazine equivalent; NR, not reported; PANSS, positive and negative symptom scale; SZ, schizophrenia; SZAff, schizoaffective disorder.

Table 2. Characteristics of Included Studies.

Authors, year	Electrode montage (anode/cathode)	Electrode size (cm^2)	Intensity (mA)	Session duration (min)	Number of tDCS session	Current density (mA/cm^2)	Total charge per session[b] (C/cm^2)	Total charge per regimen[c] (C/cm^2)
Brunelin et al., 2012	F3-FP1/T3-P3	35	2	20	10	0.06	0.068	0.68
Palm et al., 2016	F3/FP2	35	2	20	10	0.06	0.068	0.68
Chang et al., 2018	F3-FP1/T3-P3	35	2	20	10	0.06	0.068	0.68
Gomes et al., 2018	F3/F4	25	2	20	10	0.08	0.096	0.96
Jeon et al., 2018	F3/F4	25	2	30	10	0.08	0.144	1.44
Koops et al., 2018	F3-FP1/T3-P3	35	2	20	10	0.06	0.068	0.68
Mellin et al., 2018	F3-FP1/T3-P3	25	2	20	10	0.08	0.096	0.96
Kantrowitz et al., 2019	F3-FP1/T3-P3	38.81	2	20	10	0.05	0.062	0.62
Lindenmayer et al., 2019	F3-FP1/T3-P3	35	2	20	40	0.06	0.068	2.74
Weickert et al., 2019	F4/T3-P3	35	2	20	20	0.06	0.068	1.37
Chang et al., 2020	F3-FP1 + F4-FP2 /forearms[a]	35	2	20	10	0.06	0.068	0.68
Smith et al., 2020	F3/FP2	5.08	2	20	10	0.39	0.472	4.72
Valiengo et al., 2020	F3/T3-P3	35	2	20	10	0.06	0.068	0.68

[a]Chang et al. (2020) used a bi-anodal montage targeting the left and right dorsolateral prefrontal cortex with extracephalic cathodes. [b]Total charge per session(C/cm2) = stimulation intensity (A)/electrode size (cm2) x duration (s). [c]Total charge per tDCS regimen (C/cm2) = stimulation intensity (A)/electrode size (cm2) x duration (s) x number of sessions.