

1 **Title**

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

4 **Running title**

5 Effects of tDCS on Insight in Schizophrenia

6

7 **Authors**

8 Ondine ADAM^{1,2}, MSc; Martin BLAY¹, BSc; Andre R. BRUNONI^{3,4}, MD, PhD; Hsin-An CHANG⁵,
9 MD; July S. GOMES⁶, PhD; Daniel C. JAVITT^{7,8,9}, MD, PhD; Do-Un JUNG¹⁰, MD, PhD; Joshua T.
10 KANTROWITZ^{7,8,9}, MD; Sanne KOOPS¹¹, PhD; Jean-Pierre LINDENMAYER^{9,12,13}, MD; Ulrich
11 PALM^{14,15}, MD, PhD; Robert C. SMITH^{9,12}, MD, PhD; Iris E. SOMMER¹¹, MD, PhD; Leandro do
12 Costa Lane VALIENGO^{3,4}, MD, PhD; Thomas W. WEICKERT^{16,17,18}, PhD; Jérôme BRUNELIN^{1,2,†},
13 PhD; Marine MONDINO^{1,2,†,*}, PhD

14

15 **Affiliations**

16 ¹ Centre Hospitalier Le Vinatier, Bron, France

17 ² INSERM U1028; CNRS UMR5292; PSYR2 Team; Lyon Neuroscience Research Center; Université
18 Claude Bernard Lyon 1, Université Jean Monnet, Lyon, France

19 ³ Laboratório de Neurociências (LIM-27), Departamento e Instituto de Psiquiatria, Hospital das
20 Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil

21 ⁴ Serviço Interdisciplinar de Neuromodulação (SIN), Departamento e Instituto de Psiquiatria, Hospital
22 das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brazil

23 ⁵ Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei,
24 Taiwan

25 ⁶ Interdisciplinary Laboratory of Clinical Neurosciences, Federal University of Sao Paulo, Sao Paulo,
26 Brazil

27 ⁷ Columbia University, New York, NY, USA

28 ⁸ New York State Psychiatric Institute, New York, NY, USA

29 ⁹ Nathan Kline Institute, Orangeburg, NY, USA

30 ¹⁰ Department of Psychiatry, Busan Paik Hospital, Inje University, Busan, Republic of Korea

31 ¹¹ Department of Biomedical Sciences of Cells & Systems, Cognitive Neurosciences, University of
32 Groningen, University Medical Center Groningen (UMCG), Groningen, The Netherlands

33 ¹² New York University School of Medicine, New York, NY, USA

34 ¹³ Manhattan Psychiatric Center, New York, NY, USA

35 ¹⁴ Department of Psychiatry and Psychotherapy, Hospital of the University of Munich, Munich.
36 Germany

37 ¹⁵ Medical Park Chiemseeblick, Bernau-Felden, Germany

38 ¹⁶ Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY,
39 USA

40 ¹⁷ School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

41 ¹⁸ Neuroscience Research Australia, Sydney, NSW, Australia

42 † shared last authorship

43

44 ***Corresponding author**

45 Marine Mondino, PsyR2 team, Centre Hospitalier le Vinatier, batiment 416, 1st floor, 95 boulevard
46 Pinel, 69678 Bron, Cedex BP 30039, FRANCE

47 email: marine.mondino@ch-le-vinatier.fr

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51 **Abstract**

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

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

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

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

71

72 **Key words:** tDCS, psychosis, neuromodulation

73 **Introduction**

74 Lack of patient insight into the illness is a key characteristic of many psychiatric disorders, including
75 bipolar disorder,¹ obsessive-compulsive disorder,² and dementias.³ Among patients with
76 schizophrenia, the estimated prevalence of poor insight, corresponding to a general unawareness of
77 illness, can be up to 50%.^{4,5} Insight deficit includes lack of awareness of the symptoms of the illness,
78 the need for and willingness to undergo treatment, and the consequences of the illness on the patient's
79 life.⁶ Poor insight has been regularly associated with negative attitudes toward medication⁷ and
80 nonadherence to antipsychotic treatment.⁸⁻¹¹ Treatment nonadherence in schizophrenia represents a
81 heavy economic cost, estimated between \$13.92 and \$18.36 million a year in the United States,¹² since
82 it increases the risk of relapse, rehospitalization rates, and suicide attempts.^{12,13} Poor insight is directly
83 associated with a higher risk of relapse,¹⁴ which further emphasizes the importance of fostering better
84 insight into the illness. Unfortunately, available treatments such as antipsychotic medication and
85 psychotherapy provide either little or no improvement in patients' insight into their illness.¹⁵

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

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

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

110

111 **Methods**

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

115 *Literature search and selection criteria*

116 Two authors (OA and MM) searched independently for articles in the PubMed and ScienceDirect
117 databases with no restriction of date for eligible studies using the following keywords: (“tDCS” OR
118 “transcranial direct current stimulation”) AND (“PANSS” OR “positive and negative syndrome
119 scale”) AND “schizophrenia”). The search was conducted between November 2020 and March 2021.

120 In ScienceDirect, research was refined using *research articles*, *book chapters* and *other* limits.

121 Selected studies met the following inclusion criteria: (1) inclusion of patients with schizophrenia or
122 schizoaffective disorder; (2) comparison between active and sham stimulation; and (3) assessment of
123 symptoms before and after tDCS sessions using the PANSS. The selection procedure was repeated on
124 the full text of eligible studies. We excluded studies that were not RCTs, that combined tDCS with a
125 therapy other than antipsychotic treatments, and that did not offer at least 10 sessions of tDCS. This

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

129 *Data extraction and main outcome*

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

136 *Quality and risk of bias assessments*

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

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

143 *Statistical analysis*

144 All statistical analyses were performed with R software, version 4.1.2 (R Core Team, 2021), using the
145 *metafor*, *meta* and *dmetar* packages. The significant α level was set at 0.05. Hedges' g effect size
146 (ESg) along with the 95% confidence interval was computed based on mean (SD) scores of G12. The
147 overall ESg was pooled from each study using a random-effects model and was interpreted according
148 to Cohen's guidelines (0.2=small; 0.5=medium; 0.8=large effect).³⁶ Global heterogeneity significance
149 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 \geq 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 (I²=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 ($\text{average} \geq 3$) and those with on average an absence of or minimal lack of insight
204 ($\text{average} < 3$, $Q=0.62$, $P=0.43$).

205 *Sensitivity analyses*

206 No outlier study could be identified by the QQ plot (Supplementary Figure 3) but the study of Chang
207 and colleagues²³ 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 adherence³⁸ and compliance with treatment.⁵⁷ Improvements in insight
234 could also benefit patients' quality of life, as insight improvements correlate with reductions in
235 symptoms⁵⁷ 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 disorders¹⁻³, 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 excitability¹⁸ 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 inhibition¹⁸ 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 insight⁶⁵ 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 quality³³ 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 variability⁷⁶. 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 questioned⁷⁷. Efforts should be made to improve
357 blinding and sham procedures and their evaluation through the development of new methods.

358

359 *Conclusion*

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

367

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370

371 **Contributors:** MM and OA had full access to all the data in the study and take responsibility for the
372 integrity of the data and the accuracy of the data analysis. MM and JB conceived and designed the
373 study and shared last authorship. OA, MB, JB, and MM contributed to the acquisition, analysis, or
374 interpretation of data. OA drafted the manuscript. All authors contributed to the critical revision of the
375 manuscript for important intellectual content. OA, JB, and MM contributed to the statistical analysis.

376

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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).

^aJadad scores correspond to the average of the scores given by the author OA and by the main author of the associated article.

^bKoops 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.

^cChang 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 |

^aChang et al. (2020) used a bi-anodal montage targeting the left and right dorsolateral prefrontal cortex with extracephalic cathodes. ^bTotal charge per

session(C/cm²) = stimulation intensity (A)/electrode size (cm²) x duration (s). ^cTotal charge per tDCS regimen (C/cm²) = stimulation intensity (A)/electrode size (cm²) x duration (s) x number of sessions.