Number of words: 8,534 / Number of tables: 4 / Number of figures: 1 / Online-only supplemental materials: 1

Evidence-based Umbrella Review of Cognitive Effects of Prefrontal tDCS

Running title: Umbrella review on tDCS and cognition

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation approach which has been increasingly used as an investigational tool in neuroscience. In social and affective neuroscience research, the prefrontal cortex has been primarily targeted, since this brain region is critically involved in complex psychobiological processes subserving both "hot" and "cold" domains. Although several studies have suggested that prefrontal tDCS can enhance neuropsychological outcomes, meta-analyses have reported conflicting results. Therefore, we aimed to assess the available evidence by performing an umbrella review (UR). We evaluated the effects of prefrontal active vs. sham tDCS on different domains of cognition among healthy and neuropsychiatric individuals. AMSTAR-2 was employed to evaluate the quality of systematic reviews and meta-analyses and the GRADE system was employed to grade the quality of evidence. PubMed/MEDLINE, PsychINFO and the Cochrane Database of Systematic Reviews were searched, and 11 meta-analyses were included resulting in 55 comparisons. Only 16 comparisons reported significant effects favoring tDCS, but 13 of them had either a very low or low quality of evidence. Systematic reviews were rated as having critically low and low quality. Among several reasons to explain these findings, the lack of consensus and reproducibility in tDCS research is discussed.

Keywords

Umbrella review; non-invasive brain stimulation; cognition; psychology; psychiatry; reproducibility.

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that consists on the application of weak, electric currents over the scalp (Brunoni *et al.*, 2012). Since the seminal study of Nitsche and Paulus (2000), which showed that tDCS promoted polarity-dependent changes in motor cortical excitability according to the parameters of stimulation, the technique has been investigated as a clinical and research tool in neuropsychology (Shin *et al.*, 2015) and neuropsychiatry (Moffa *et al.*, 2018; Brunoni *et al.*, 2019).

For these conditions, the prefrontal cortex (PFC) has been the preferential target of tDCS, since it is the brain region primarily involved in more complex psychological processes, including cognitive and emotional domains (Shin *et al.*, 2015). In fact, several studies have investigated the effects of prefrontal tDCS on neuropsychological outcomes, such as working memory (Oliveira *et al.*, 2013), cognitive control (Wolkenstein and Plewnia, 2013), vigilance to threat (Ironside *et al.*, 2016), and rumination (Kuhn *et al.*, 2012), mostly showing significant results. Nonetheless, non-significant results have also been found, with a recent meta-analysis suggesting that the net tDCS effects on cognition are null (Horvath *et al.*, 2015). Several reasons could explain these heterogeneous findings, such as differences in tDCS montage, stimulation parameters and anatomical and functional individualities (Brunoni *et al.*, 2012; Bikson *et al.*, 2018; Chase *et al.*, 2019). Issues in the design of tDCS studies also harm their internal validity, such as underpowered sample sizes (Medina and Cason, 2017) and methodological challenges in effective sham blinding (Fonteneau *et al.*, 2019). To a broader extent, biases in cognitive sciences have been increasingly more common, with contradictory and non-replicable findings (Ioannidis *et al.*, 2014). For instance, an attempt to reproduce the findings of 100 experimental and correlation studies in

psychological science, using high-powered designs, was able to replicate approximately one-third of the them (Open Science Collaboration, 2015), which is suggestive of a "reproducibility crisis" on the field.

Recently, umbrella reviews (URs) have been introduced as a new meta-analytical modality in evidence-based synthesis (Fusar-Poli and Radua, 2018). They are reviews of previous systematic reviews and meta-analyses that use standardized methods to assess and compare the evidence of included studies. Examples of these methods include performing a systematic review of the literature, using common effect sizes, assessing heterogeneity, grading the quality of evidence and presenting new research avenues based on the assessed evidence (Fusar-Poli and Radua, 2018). In fact, they represent a higher level of evidence than meta-analyses that can also present biases and reach discrepant conclusions (Ioannidis, 2009). For these reasons, URs are becoming increasingly in the biomedical field (Fusar-Poli and Radua, 2018) as a method to synthesize highest-quality evidence. Considering the discrepant findings of meta-analyses examining the effects of tDCS on "hot" and "cold" cognition, an UR could be useful to critically assess the quality and availability of the evidence. Notwithstanding, no such study has been performed so far.

Therefore, our aim was to perform an UR of meta-analyses that examined the effects of prefrontal tDCS on cognition. Our study is important to provide critical, high-quality evidence of a commonly used tDCS application in neuropsychology, which can help better guiding and tailoring new studies according to our findings.

METHODS

Search strategy and inclusion criteria for the UR

The protocol for this systematic review was pre-registered at PROSPERO (CRD42020140779). The electronic databases of PubMed, PsycINFO, and the Cochrane Database of Systematic Reviews (CDSR) were searched on April, 2019 for relevant references. Search strategies were tailored for each database and detailed descriptions can be found on the supplemental material. The search strategy was limited to meta-analyses in each one of the databases. The references section of review articles and meta-analyses were carefully read to look for additional references. No language restrictions were applied. No further efforts were made to search for unpublished research.

Titles and abstracts of references were screened by two independent reviewers (ARB, LCF) to identify those that were eligible for inclusion. Inclusion criteria were determined through the PICO (population, intervention, control and outcome) format; specifically, meta-analyses had to evaluate the comparative effects of prefrontal tDCS against sham tDCS on cognitive domains in healthy or neuropsychiatric individuals. No restrictions were made regarding age; diagnoses, i.e. any neuropsychiatric disorder was eligible for inclusion, e.g. depression, attention-deficit hyperactivity disorder, eating disorders, Parkinson's disease, etc.; polarity of tDCS, i.e. anodal tDCS (a-tDCS) and cathodal tDCS (c-tDCS) were eligible; number of treatment sessions; timing of outcome measurement, i.e. online and offline designs, when the study outcomes were measured during and after tDCS session, respectively, were eligible; cognitive domains, i.e. any cognitive domain reported in the eligible meta-analysis were included in the UR. Only

meta-analyses were eligible for our UR as we were interested on the effect sizes of tDCS interventions over the prefrontal cortex.

Data extraction, methodological quality assessment and appraisal of the evidence

Data were extracted by two independent reviewers (ARB, LCF); any disagreement was solved through discussing and obtaining more information from study investigators. For each comparison from eligible meta-analyses, the following data were extracted: first author, year of publication, cognitive domain, cognitive tasks, number of studies included, pooled effect sizes – either standardized mean difference (SMD) or Hedges' g – with their 95% confidence intervals (95% CIs) and I^2 values. If the Q-statistic was provided, I^2 was calculated as recommended by the Cochrane Handbook of Systematic Reviews of Interventions. Data were extracted in Summary of Finding (SoF) tables from the GRADEpro GDT (Grading of Recommendations, Assessment, Development and Evaluation Guideline Development Tool). The GRADEpro GDT can be accessed through the link www.gradepro.org and is the official GRADE working group software for the production of SoF tables. SoF tables are tabular presentations of key information about relevant outcomes of health care interventions. For this UR, separate SoF tables were created for healthy and neuropsychiatric populations, as well as for a-tDCS, c-tDCS and tDCS.

The GRADE approach was employed (The GRADE Working Group, 2013) to rate the quality of evidence of every comparison from each eligible meta-analysis. The GRADE approach is a system for rating the quality of evidence in systematic reviews and/or meta-analysis, providing four grades depending on the certainty that the true effect is close to the effect size estimate: high, moderate, low and very low. It considers five reasons to possibly rate down, and three to possibly rate up, the quality of evidence. Factors that rate down quality of evidence are (a) risk of bias (RoB); (b) inconsistency

of results (c) indirectness of evidence, (d) imprecision and (e) publication bias. Factors that rate up the quality of evidence are (a) large magnitude of effect, (b) dose-response gradient and (c) effect of plausible residual confounding. A GRADE checklist to aid in the consistency and reproducibility of the GRADE approach was also employed (Meader *et al.*, 2014). Quality of evidence was evaluated at the comparison-level based on what was reported in each meta-analysis, and information from the trials included in each meta-analysis were not retrieved. A strict approach was employed to grade the quality of evidence to avoid validating results that were not of the highest possible quality. For instance, if statistical test for heterogeneity and/or I^2 values were not reported, the quality of evidence was downgraded due to serious inconsistency regardless of the distribution of effect sizes and 95% CI – those could only contribute to rate down further the quality of evidence due to very serious inconsistency. For RoB, a meta-analysis was considered to have not properly examined RoB if it did not perform a quality assessment of the included studies, i.e. if it did not check for methodological procedures that minimize biases, such as proper randomization, allocation concealment, blinding, attrition, and incomplete or selective reporting, as described in the Cochrane guidelines for Risk of Bias assessment (Higgins *et al.*, 2011; Sterne *et al.*, 2019); quality of evidence was systematically rated down due to serious RoB if RoB was not properly examined. For publication bias, if meta-analyses did not evaluate publication bias either through funnel plot asymmetry or statistical criteria, quality of evidence was rated down due to strong suggestion of publication bias. Additionally, adjusted effect sizes, e.g. through the trim-and-fill method, were not considered a solution to the identified publication bias as these are simulations with issues of their own (Guyatt *et al.*, 2011) and quality of evidence was downgraded regardless of whether such imputation approaches were employed or not; similarly, considering recommendations from the

Cochrane Handbook of Systematic Reviews of Interventions, the fail-safe number was not considered an adequate assessment of publication bias when employed alone. For comparisons which included individuals with different neuropsychiatric disorders, quality of evidence was systematically rated down due to serious indirectness.

The methodological quality of each included meta-analysis was rated with the A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2) (Shea *et al.*, 2017), a 16-item tool employed to help in the evaluation of the reporting quality of systematic reviews. A detailed description of the AMSTAR 2 methodology can be found at the online-only supplemental material. The online AMSTAR-2 checklist available at https://amstar.ca/Amstar_Checklist.php was employed to apply the AMSTAR-2 methodology to each meta-analysis included in the UR.

RESULTS

Study selection and included meta-analysis

Figure 1 illustrates the PRISMA flowchart representing the selection of studies for this UR. Of the 40 references excluded through screening of titles and abstracts, 16 were excluded as prefrontal tDCS was not the intervention studied (Rodriguez-Martin *et al.*, 2002; Rodriguez-Martin *et al.*, 2003; Medical Advisory Secretariat, 2004; Phillips and McFerran, 2010; Poulet *et al.*, 2010; Hoekstra *et al.*, 2011; Meng *et al.*, 2011; Baldo *et al.*, 2012; Hobson *et al.*, 2012; Hilton *et al.*, 2013; Li *et al.*, 2014; Dougall *et al.*, 2015; Luvizutto *et al.*, 2015; Stevens *et al.*, 2016; Pievani *et al.*, 2017; Hsu *et al.*, 2018), 16 were excluded as the outcome evaluated was not a cognitive function (O'Connell *et al.*, 2010; Luedtke *et al.*, 2012; Tsoi *et al.*, 2013; Brunoni *et al.*, 2014; Vaseghi *et al.*, 2014; Brunoni *et al.*, 2015; Cruccu *et al.*, 2016; Elsner *et al.*, 2016; Hou *et al.*, 2016;

McMillan *et al.*, 2016; Zhu *et al.*, 2017; Aleman *et al.*, 2018; Kennedy *et al.*, 2018; Machado *et al.*, 2018; Mutz *et al.*, 2018; Soares-Weiser *et al.*, 2018) and 8 studies were excluded as they were not meta-analyses (Micoulaud Franchi *et al.*, 2015; Martin *et al.*, 2016; Palm *et al.*, 2016; Hall *et al.*, 2017; Katz *et al.*, 2017; Bieck *et al.*, 2018; Lee *et al.*, 2018; Rubia, 2018; Boayue *et al.*, 2019). Of the nine references excluded through reading the full text, two reported results also presented in another paper which was already included in the UR (Dedoncker *et al.*, 2016a; Hall *et al.*, 2017), three did not report results from an independent comparison between active and sham prefrontal tDCS (Jansen *et al.*, 2013; Brunoni and Vanderhasselt, 2014; Song *et al.*, 2018) and four did not carry out meta-analyses (Khalighinejad *et al.*, 2016; Lupi *et al.*, 2017; Greenwood *et al.*, 2018; Schluter *et al.*, 2018).

Therefore, only 11 articles were included in this UR (Horvath *et al.*, 2015; Price *et al.*, 2015; Dedoncker *et al.*, 2016b; Hill *et al.*, 2016; Mancuso *et al.*, 2016; Lowe *et al.*, 2017; Nilsson *et al.*, 2017; Bell and DeWall, 2018; Imburgio and Orr, 2018; Mostafavi *et al.*, 2018; Salehinejad *et al.*, 2019). These 11 meta-analyses yielded 55 comparisons distributed across the 12 cognitive domains; specifically, working memory, [long-term] memory, set shifting, response inhibition, language, aggression, overeating/food cravings, emotional and implicit bias, honesty, rumination, impulsivity and risk-taking were the cognitive domains reported in these meta-analyses and were therefore included in our UR. The respective tasks for each one of these cognitive domains are depicted in Table 1. Of the 55 comparisons, 41 (~75%) were carried out among exclusively healthy individuals and another 7 (~13%) were carried out among a mixed population of healthy and neuropsychiatric individuals; therefore, only 7 comparisons (~13%) were carried out among exclusively neuropsychiatric individuals. Table 2 illustrates the methodological quality assessment of each meta-analysis while

Table 3 describes the characteristics and quality of evidence assessment of each comparison among healthy (Table 3A), neuropsychiatric (Table 3B) and both healthy and neuropsychiatric (Table 3C) individuals.

Anodal tDCS

Working memory

Six meta-analyses (Horvath *et al.*, 2015, Hill *et al.*, 2016, Mancuso *et al.*, 2016, Nilsson *et al.*, 2017, Imburgio and Orr, 2018, Salenijehad *et al.* 2019) resulting in 13 comparisons, 10 among healthy and 3 among neuropsychiatric individuals, evaluated the effects of prefrontal a-tDCS on working memory performance. AMSTAR-2 quality assessment indicated that these reviews varied from critically low to low quality.

Among healthy individuals, all 10 comparisons targeted the DLPFC; in 7 comparisons, both offline and online designs were included; besides, in 8 comparisons, only single-session design studies were included whereas in the remaining 2 multiple sessions design with adjuvant working memory training studies were included.

The mean number of studies and individuals in the single-session design comparisons were 16.25 (range 8-32) and 457.5 (range 167-914), respectively. Of these 8 comparisons, 4 reported a significant effect favoring a-tDCS (ES = 0.56, 95% CI [0.19, 0.93], $p < 0.01$; ES = 0.17, 95% CI [0.03, 0.30], p = not reported; ES = 0.15, 95% CI [0.02, 0.28], p = 0.02; ES = -0.15, 95% CI [-0.29, -0.01], p = 0.003), but GRADE assessment of quality of evidence indicated moderate and low certainty that the true effect is close to these estimates as quality of evidence was rated down to “moderate” due to serious RoB (RoB was either not assessed or there was evidence of significant unclear RoB regarding randomization, allocation concealment and blinding) for all four comparisons and to “low” due to the serious imprecision (relatively small number of

trials [N = 10] and individuals [n = 354]) for one of these comparisons and due to the strong suggestion of publication bias (funnel plot asymmetry was identified) for another comparison. The remaining 4 comparisons yielded non-significant findings, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed), to "low" due to the strong suggestion of publication bias (publication bias was either not assessed or funnel plot asymmetry was identified) and to "very low" due to the serious imprecision (relatively small number of trials [N = 8] and individuals [n = 283/ 167]) for all five comparisons.

The mean number of studies and individuals in the 2 multiple-session design comparisons with adjuvant working memory training were 8.5 (range 7-10) and 275.5 (range 266 – 285), respectively. Only one comparison reported a small significant effect favoring a-tDCS (ES = 0.29, 95% CI [0.06, 0.52], p not reported), but GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to the strong suggestion of publication bias (funnel plot asymmetry was identified), to "low" due to serious RoB (RoB was not assessed) and to "very low" due to serious imprecision (relatively small number of trials [N = 10] and individuals [n = 285]). The remaining comparison yielded a non-significant effect, and GRADE assessment of quality of evidence indicated low certainty that the true effect is close to this estimate; quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed) and to "low" due to serious imprecision (relatively small number of trials [N = 7] and individuals [n = 266] included).

Among neuropsychiatric individuals, all three comparisons targeted the DLPFC in a single-session design and included both an offline and online design. The mean

number of studies and individuals included in these comparisons were 12 (range 8 – 16) and 491 (range 232 – 860), respectively. None of the three comparisons yielded significant effects, and GRADE assessment of quality of evidence indicated low and very low certainty that the true effect is close to these estimates. Quality of evidence was rated down to "moderate" due to serious RoB (there was evidence of significant unclear RoB regarding randomization, allocation concealment and/or blinding) for the three comparisons and to "low" due to serious indirectness (data included was from a sample with diverse neuropsychiatric individuals) for two comparisons and due to the strong suggestion of publication bias (publication bias was not evaluated) for the other comparison. Quality of evidence was rated down further to "very low" due to serious imprecision (relatively small number of trials [N = 8] and individuals [n = 232]) for one of these comparisons and due to serious inconsistency (effect size estimates from individual studies varied considerably with relatively little overlap of CIs) for another of these comparisons.

[Long-term] memory

One meta-analysis (Horvath *et al.*, 2015) resulting in one comparison among healthy individuals evaluated the effects of prefrontal a-tDCS on [long-term] memory. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison targeted the DLPFC and only included an online design. A small number of trials (N = 3) and individuals (n = 104) were included. No significant effects were reported, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "low" due to very serious imprecision (relatively small number of trials [N = 3]

and individuals [n = 104]; extremely large 95% CI [-0.87, 2.94]) and to "very low" due to the strong suggestion of publication bias (publication bias was not evaluated).

Set shifting and response inhibition

Three meta-analyses (Horvath *et al.*, 2015, Imburgio and Orr, 2018, Salehinejad *et al.* 2019) resulting in 8 comparisons, 7 among healthy and 1 among neuropsychiatric individuals, evaluated the effects of prefrontal a-tDCS on set shifting and response inhibition. AMSTAR-2 quality assessment indicated that these reviews were of critically low quality. Among healthy individuals, 2 comparisons evaluated set shifting whereas the remaining 5 evaluated response inhibition; among neuropsychiatric individuals, only response inhibition was evaluated.

For set shifting, both comparisons among healthy individuals targeted the DLPFC; one included offline and online designs whereas the other only included offline designs. The mean number of studies and individuals in both comparisons were 8 (range 3 – 13) and 430 (range 212 – 648). None of the two comparisons yielded significant effects, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed) and to "low" due to serious inconsistency (either heterogeneity was not assessed statistically or was considerable [I^2 = 69.92%]) for both comparisons; quality of evidence was rated down further to "very low" due to the strong suggestion of publication bias (publication bias was not assessed) for one comparison and due to serious imprecision (effect size estimate with wide 95% CI [-0.68, 0.59]) for the other comparison. For response inhibition, of the 5 comparisons among healthy individuals, 3 targeted the DLPFC and 2 the IFG; 1 included offline and online designs, whereas 4 only included offline designs. The mean number of studies

and individuals in these five comparisons were 3.83 (range 2 – 13) and 141 (range 55 – 616). None of these five comparisons yielded significant effects and GRADE assessment of quality of evidence indicated low and very low certainty that the true effect is close to these estimates. Quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed) and to "low" due to serious inconsistency (either heterogeneity was not assessed statistically or effect size estimates from individual studies varied considerably with relatively little overlap of CIs) for all five comparisons; quality of evidence was rated down further to "very low" due to strong suggestion of publication bias (publication bias was not assessed) for four comparisons.

For response inhibition, the comparison among neuropsychiatric individuals targeted the DLPFC and IFG and included offline and online designs. The number of trials and individuals included were 34 and 1404, respectively; only individuals with attention-deficit hyperactivity disorder were included. This comparison reported a small significant effect favoring a-tDCS (ES = 0.23, 95% CI [0.07 – 0.40], p = 0.0065), and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious RoB (there was evidence of significant unclear RoB in blinding outcome assessment), to "low" due to serious inconsistency (effect size estimates from individual studies varied considerably) and to "very low" due to the strong suggestion of publication bias (publication bias was not assessed).

Memory/attention/executive functioning

One meta-analysis (Dedoncker *et al.*, 2016) resulting in 6 comparisons, 2 among healthy, 2 among neuropsychiatric and 2 among both healthy and neuropsychiatric individuals, evaluated the effects of prefrontal a-tDCS on memory/attention/executive

functioning. AMSTAR-2 quality assessment indicated that this review was of low quality.

Among healthy individuals, both comparisons targeted the DLPFC and included offline and online designs. The mean number of trials and individuals included were 116.5 (range 102 – 131) and 3942.5 (range 3470 - 4415), respectively. One of the two comparisons reported a small significant effect favoring a-tDCS (ES = – 0.10, 95% CI [-0.16, -0.04], $p < 0.01$) and GRADE assessment of quality of evidence indicated moderate certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious RoB (only 6/61 studies included in the Dedoncker *et al.,* 2016 meta-analysis had a low risk of allocation concealment bias). The remaining comparison reported a non-significant effect, and GRADE assessment of quality of evidence also indicated moderate certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious RoB (only 6/61 studies included in the Dedoncker *et al.,* 2016 meta-analysis had a low risk of allocation concealment bias).

Among neuropsychiatric individuals, both comparisons targeted the DLPFC and included offline and online designs. The mean number of trials and individuals included were 26 (range 22-30) and 802 (range 660 – 944), respectively. One of these comparisons reported a small significant effect favoring a-tDCS (ES = 0.22, 95% CI [0.04, 0.40], $p < 0.05$), but GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious RoB (only 6/61 studies included in the Dedoncker *et al.,* 2016 meta-analysis had a low risk of allocation concealment bias), to "low" due to serious indirectness (data included was from a sample with diverse neuropsychiatric individuals) and to "very low" due to serious inconsistency ($I^2 = 42.5\%$). The remaining

comparison reported a non-significant effect, and GRADE assessment of quality of evidence indicated low certainty that the true effect is close to its estimate as quality of evidence was rated down to "moderate" due to serious RoB (only 6/61 studies included in the Dedoncker *et al.,* 2016 meta-analysis had a low risk of allocation concealment bias) and to "low" due to serious indirectness (data included was from a sample with diverse neuropsychiatric individuals).

Among both healthy and neuropsychiatric individuals, both comparisons targeted the DLPFC and included both offline and online designs. The mean number of trials and individuals included were 144.5 (range 124 – 165) and 4,744.5 (range 4,130 – 5,359), respectively. The two comparisons reported small significant effects favoring a-tDCS (ES = 0.18, 95% CI [0.03, 0.18], $p < 0.01$; ES = – 0.11, 95% CI [-0.17, -0.05], $p < 0.01$) and GRADE assessment of quality of evidence indicated very low and low certainty that the true effect is close to these estimates as quality of evidence was rated down to "moderate" due to serious RoB (only 6/61 studies included in the Dedoncker *et al.,* 2016 meta-analysis had a low risk of allocation concealment bias) and to "low" due to serious indirectness for both comparisons (data included was from a sample with diverse neuropsychiatric individuals); quality of evidence was rated down further to "very low" due to serious inconsistency ($I^2 = 52.5\%$) for one comparison.

Language

Two meta-analyses (Horvath *et al.*, 2015 and Price *et al.*, 2015) resulting in five comparisons, all among healthy individuals, evaluated the effects of prefrontal a-tDCS on language. AMSTAR-2 quality assessment indicated that these reviews were of critically low quality. All 5 comparisons targeted the lPFC/DLPFC; 3 included only offline designs whereas the remaining 2 included only online designs.

For the 3 offline comparisons, the mean number of studies and individuals included were 4 (range 3-7) and 115.3 (range 58 – 208). Only one comparison yielded a small-to-moderate significant effect favoring a-tDCS (ES = 0.48, 95% CI [0.35, 0.92], p not reported), but GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious imprecision (small number of studies [N = 3] and individuals [n = 80] included), to "low" due to strong suggestion of publication bias (publication bias was not assessed) and to "very low" due to serious inconsistency (heterogeneity was not assessed statistically). The remaining two offline comparisons did not yield significant effects, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down due to serious imprecision (small number of studies [N = 2, 7] and individuals [n = 58, 208] included), to "low" due to strong suggestion of publication bias (publication bias was not assessed) and to "very low" due to serious inconsistency (heterogeneity was not assessed statistically) for both comparisons.

For the 2 online comparisons, the mean number of studies and individuals included were 3 (range 3 – 3) and 100 (range 100 – 100). None of the two comparisons yielded significant findings, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down due to significant imprecision (small number of studies and individuals included), to "low" due to strong suggestion of publication bias (publication bias was not assessed) and to "very low" due to significant inconsistency (heterogeneity was not assessed statistically).

Aggression

One meta-analysis (Bell and DeWall, 2018) resulting in one comparison among healthy individuals evaluated the effects of prefrontal a-tDCS on aggression. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison evaluated a-tDCS, targeted the DLPFC and included both an offline and an online design. The number of studies and individuals included were 6 and 339, respectively. The comparison yielded a non-significant finding, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed), to "low" due to serious imprecision (relatively small number of studies and individuals included) and to "very low" due to serious inconsistency (effect size estimates from individual studies varied considerably with relatively little overlap of CIs)

Overeating

One meta-analysis (Bell and DeWall, 2018) resulting in one comparison among healthy individuals evaluated the effects of prefrontal a-tDCS on overeating. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison targeted the DLPFC and included both offline and online designs. The number of trials and individuals included were 6 and 339, respectively. This comparison reported a small treatment effect favoring a-tDCS (ES = -0.25, 95% CI [-0.49, -0.01], p = 0.03), and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate, as quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed), to "low" due to serious imprecision (relatively small number of trials and individuals included) and to "very low" due to strong suggestion of publication (funnel plot asymmetry was identified).

Emotional and implicit bias

Two meta-analyses (Horvath *et al.*, 2015, Bell and DeWall, 2018) resulting in five comparisons among healthy individuals evaluated the effects of prefrontal a-tDCS on emotional and implicit bias; AMSTAR-2 quality assessment indicated that these reviews were of critically low quality. All comparisons targeted the DLPFC; four only included an online design and one included both an offline and an online design. Four of them only evaluated emotional bias whereas one of them included both emotional and implicit bias measures. The mean number of studies and individuals included were 3.2 (range 2 - 7) and 169 (range 88 – 447), respectively. One of the comparisons, the one which included mixed outcomes, reported a small significant effect favoring a-tDCS (ES = -0.25, 95% CI [-0.48, -0.03], p = 0.02). GRADE assessment of quality of evidence indicated low certainty that the true effect is close to this estimate; quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed) and to "low" due to serious imprecision (relatively small number of trials [N = 7] and individuals [n = 447] included). The remaining four comparisons yielded non-significant findings, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down to "moderate" due to serious inconsistency (heterogeneity was not assessed statistically), to "low" due to serious RoB (RoB was not assessed) and to "very low" due to strong suggestion of publication bias (publication bias was not assessed).

Honesty

One meta-analysis (Bell and DeWall, 2018) resulting in one comparison among healthy individuals evaluated the effects of prefrontal a-tDCS on honesty. AMSTAR-2

quality assessment indicated that this review was of critically low quality. The comparison evaluated a-tDCS, targeted the DLPFC and included both an online and an offline design. The number of studies and individuals included were 4 and 322, respectively. The comparison yielded a non-significant finding, and GRADE assessment of quality of evidence indicated low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious imprecision (relatively small number of trials and individuals included) and to "low" due to serious RoB (RoB was not assessed).

Rumination

One meta-analysis (Horvath *et al.*, 2015) resulting in one comparison among healthy individuals evaluated the effects of prefrontal a-tDCS on rumination. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison targeted the DLPFC and included only online designs. The number of studies and individuals included were 2 and 126, respectively. The comparison yielded a non-significant finding, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious inconsistency (heterogeneity was not assessed statistically), to "low" due to serious RoB (RoB was not assessed) and to "very low" due to strong suggestion of publication bias (publication bias was not assessed).

Impulsivity

One meta-analysis (Bell and DeWall, 2018) resulting in one comparison among healthy individuals evaluated the effects of prefrontal a-tDCS on impulsivity. AMSTAR-2 quality assessment indicated that this review was of critically low quality.

The comparison evaluated a-tDCS, targeted the DLPFC and included both an offline and an online design. The number of studies and individuals included were 9 and 676, respectively. The comparison yielded a non-significant finding and GRADE assessment of quality of evidence indicated low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed) and to "low" due to serious inconsistency (effect size estimates from individual studies varying considerable with relatively little overlap of CIs).

Risk-taking

Two meta-analyses (Horvath *et al*., 2015, Bell and DeWall, 2018) resulting in two comparisons, all among healthy individuals, evaluated the effects of prefrontal a-tDCS on risk-taking. AMSTAR-2 quality assessment indicated that these reviews were of critically low quality. Both comparisons targeted the DLPFC and while one only included online designs, the other one included both offline and online designs. The number of studies and individuals included were 8 (range 3-13) and 376 (range 76 – 676), respectively. One of the comparisons yielded a small, significant effect in favor of a-tDCS (ES = -0.36, 95% CI [-0.65, -0.07], p = 0.01), but GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to due to strong suggestion of publication bias (funnel plot asymmetry was identified), to "low" due to serious RoB (RoB was not assessed) and to "very low" due to serious inconsistency (I^2 = 65.5%). The remaining comparison yielded non-significant findings, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to serious inconsistency (heterogeneity was not assessed), to "low" due to serious RoB

(RoB was not assessed) and to "very low" due to strong suggestion of publication bias (publication bias was not assessed).

Cathodal tDCS

[Long-term] memory

One meta-analysis (Horvath *et al.*, 2015) resulting in one comparison among healthy individuals evaluated the effects of prefrontal c-tDCS on [long-term] memory. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison targeted the DLPFC and only included online designs. A small number of trials (N = 3) and individuals (n = 103) were included. No significant effects were reported, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to strong suggestion of publication bias (publication bias was not assessed), to "low" due to the serious heterogeneity (heterogeneity was not accessed statistically) and to "very low" due to serious RoB (RoB was not assessed).

Response inhibition

One meta-analysis (Salehinejad *et al.*, 2019) resulting in one comparison among neuropsychiatric individuals evaluated the effects of prefrontal c-tDCS on response inhibition. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison targeted the DLPFC and included both offline and online designs. A small number of trials (N = 13) and individuals (N = 468) were included. No significant effects were reported, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate, as quality of evidence was rated down to "moderate" due to serious RoB (there was evidence of

significant unclear RoB in blinding outcome assessment), to "low" due to serious inconsistency (effect size estimates from individual studies varied considerably with relatively little overlap of CIs) and to "very low" due to the strong suggestion of publication bias (publication bias was not assessed).

Memory/attention/executive functioning

One meta-analysis (Dedoncker *et al.*, 2016) resulting in two comparisons among both healthy and neuropsychiatric individuals evaluated the effects of prefrontal c-tDCS on memory/attention/executive functioning. AMSTAR-2 quality assessment indicated that this review was of low quality. The two comparisons included a mean number of studies and individuals of 32 (range 28 – 36) and 1,062 (range 942 – 1,182), respectively. None of them yielded significant effects and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down to "moderate" due to serious RoB (only 6/61 studies included in the Dedoncker *et al.*, 2016 meta-analysis had a low risk of allocation concealment bias) and to "very low" due to very serious inconsistency (I^2 = 82.5% or I^2 = 33.8% with effect size estimates from individual studies varying considerable with relatively little overlap of CIs) for both comparisons.

Emotional bias

One meta-analysis (Horvath *et al.*, 2015) resulting in two comparison among healthy individuals evaluated the effects of prefrontal c-tDCS on emotional bias. AMSTAR-2 quality assessment indicated that this review was of critically low quality. Both comparisons targeted the DLPFC and included online designs. The mean number of studies and individuals included were 2 (range 2 – 2) and 88 (range 88 – 88),

respectively. None of the comparisons reported significant effects, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates; quality of evidence was rated down to "moderate" due to serious inconsistency (heterogeneity was not assessed statistically), to "low" due to serious RoB (RoB was not assessed) and to "very low" due to strong suggestion of publication bias (publication bias was not assessed).

Risk taking

One meta-analysis (Horvath *et al.*, 2015) resulting in one comparison among healthy individuals evaluated the effects of prefrontal c-tDCS on risk taking. AMSTAR-2 quality assessment indicated that this review was of critically low quality. The comparison targeted the DLPFC and only included online designs. A small number of trials (N = 3) and individuals (n = 126) were included. No significant effects were reported, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to strong suggestion of publication bias (publication bias was not assessed), to "low" due to the serious heterogeneity (heterogeneity was not accessed statistically) and to "very low" due to serious RoB (RoB was not assessed).

tDCS

Three comparisons from two meta-analyses (Mostafavi *et al.*, 2018; Lowe *et al.*, 2017) did not report separate effect sizes for c-tDCS and a-tDCS, but rather analyzed results from both c-tDCS and a-tDCS together. All of these three comparisons evaluated the effects of prefrontal t-DCS on food cravings, targeted the DLPFC and included a

mixed population of healthy and neuropsychiatric individuals. The mean number of studies and individuals included were 7.66 (range 4 – 13) and 264 (range 145 – 416), respectively. Two comparisons yielded moderate-to-large significant effects (ES = -0.54, 95% CI [-0.85, -0.24], $p < 0.001$; ES = -0.78, 95% CI [-1.12, -0.44], $p < 0.001$), but GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to these estimates as quality of evidence was rated down to "moderate" due to serious RoB (RoB was not assessed), to "low" due to serious indirectness (data included was from a sample with diverse neuropsychiatric individuals) and to "very low" due to serious imprecision (small number of studies [N = 4] and individuals [n = 145] included) for one comparison and due to serious inconsistency ($I^2 = 71.4\%$) for the other comparison. The remaining comparison yielded non-significant findings, and GRADE assessment of quality of evidence indicated very low certainty that the true effect is close to this estimate as quality of evidence was rated down to "moderate" due to strong suggestion of publication bias (funnel plot asymmetry was identified) and to " very low" due to the very serious imprecision (effect size estimates with wide 95% CI [-0.80, 0.29] and a small number of trials and individuals included).

DISCUSSION

This study provides a critical assessment of the available evidence regarding the effects of prefrontal tDCS on cognition. We identified previously published meta-analyses on the topic through a systematic literature search and rated the quality of meta-analyses included as well as of each included comparison evaluating the effects of either a-tDCS, c-tDCS or tDCS on several cognitive domains among either healthy or neuropsychiatric individuals. Our UR included 11 meta-analyses which were of either low (n = 2) or critically low (n = 9) quality. Our UR also included 55 comparisons, of

which 41 (~75%) were exclusively among healthy individuals; therefore, only 25% of the included comparisons also involved individuals with different neuropsychiatric disorders, which were frequently collapsed together without abiding by diagnostic boundaries. Of the 55 available comparisons between active tDCS and sham tDCS, only 16 reported significant findings. Among healthy individuals, a significant effect favoring a-tDCS was reported for working memory (ES = 0.56, 0.29, 0.17, 0.15 [accuracy], -0.15 [reaction time]), memory/attention/executive functioning (ES = -0.10), language (ES = 0.48), overeating (ES = -0.25), emotional and implicit bias (ES = -0.25) and risk-taking (ES = -0.36). Among neuropsychiatric individuals, a significant effect favoring a-tDCS was reported for response inhibition (ES = 0.26) and memory/attention/executive functioning (ES = 0.22). Among both healthy and neuropsychiatric individuals, a significant effect favoring tDCS was reported for memory/attention/executive functioning (ES = 0.18 [accuracy], -0.11 [reaction time]) and food cravings (ES = -0.54, -0.78). However, of these 16 significant effects, GRADE assessment of quality of evidence indicated that only 3 of them had moderate quality, while the remaining 13 had either low (n = 4) or very low (n = 9) quality. Of the 39 non-significant effects, GRADE assessment of quality of evidence indicated that only 1 of them had moderate quality, while the remaining 38 had either low (n = 7) or very low (n = 31) quality. When taken together, these findings highlight that, although several meta-analyses evaluating the effects of prefrontal tDCS on cognition have been carried out, they do not provide any definitive conclusion due to the low certainty of evidence.

In our UR, most of the included meta-analyses were rated as of low or critically low quality according to AMSTAR-2 methodology. Some of the

identified weaknesses of the included meta-analyses were likely the result of continuing changes in the best practices for reporting meta-analysis. For instance, Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) (Moher *et al.*, 2009) guidelines and the first international registry for systematic reviews (PROSPERO) (Page *et al.*, 2018) were made available only in 2009 and 2011, respectively. It is reasonable to suppose that these innovations take some time to be implemented; in this context, the lack of *a priori* publication of a protocol might be, to some extent, understandable for the meta-analyses, especially the oldest ones. Editorial policies might also contribute to explain why lists of excluded studies were not frequently reported given most journals usually determine word-limits that might be considered relatively stringent for meta-analyses. Nevertheless, other weaknesses likely cannot be better explained by external factors. Among these, perhaps most importantly is the fact that few meta-analyses evaluated the RoB of the trials included in their analyses. RoB assessments are necessary to evaluate the internal validity of randomized trials, i.e. whether it answers the proposed research question 'correctly'. Without a proper assessment of RoB, meta-analyses have limited capability to draw accurate conclusions from their findings.

Additionally, although we have considered meta-analyses statistics as adequate for the 11 included studies, it should be noted that some meta-analyses frequently included, in the same model, data from two different experiments carried out with the same participants, which might be troubling as these data are likely not independent from one another (Peters and Mengersen, 2008). For instance, Hoy *et al.*, (2013) developed a cross-over trial to evaluate the effects of a-tDCS on working memory as measured by 10-minute blocks of n-back, 5 minutes each of 2-back and 3-back. In this trial, participants underwent 20-minute a-tDCS sessions, either 1mA, 2mA or sham, 1

week apart from one another to avoid carry-over effects. Participants also underwent the 10-minute blocks of n-back immediately, 20 minutes and 40 minutes after stimulation, totaling six trials of n-back, three 2-back and three 3-back, per week of stimulation. Although it seems reasonable to consider data from this trial as non-independent, particularly data from the same stimulation strength, which were all collected within one hour after the a-tDCS session, the meta-analysis by Hill *et al.,* (2016) included data of each stimulation strength from Hoy *et al.,* (2016) as six independent trials. Similarly, Dedoncker *et al.,* (2016) included data of each stimulation strength from Hoy *et al.,* (2016) as three independent trials, although it did not consider differences in 2-back and 3-back. Although the 1-week difference between active and sham tDCS might be enough to avoid carry-over effects, it likely is not an adequate time period to consider their data as independent.

Additionally, methodological issues with the trials included in the meta-analyses have also to be taken in consideration. For instance, some of the meta-analyses in our UR (Dedoncker *et al.,* 2016; Hill *et al.,* 2016) included mostly crossover single-session within-subject design trials in which active and sham tDCS were administered to the same individual separated by a period of time. This approach has several advantages, such as the relatively smaller cost and number of individuals required to complete the study. Yet, there are also important caveats to consider; importantly, the order of administration of active and sham tDCS can likely influence the outcomes of the study if an appropriate washout is not carefully respected. Although a large number of trials employed a large washout period, others have employed smaller periods (Boggio *et al.,* 2006; Gladwin *et al.,* 2012) which could have had carry-over effects.

Besides, many trials from meta-analyses in our UR frequently did not acknowledge how investigators involved with recruitment of subjects and treatment administration were blinded to the order of treatments of each subject. In fact, some trials even acknowledged employing a single-blind design, in which only the subjects who were receiving the treatment were unaware of the order of treatment administration. A recent report reinforced the need to improve blinding procedures in tDCS research, particularly when employing a single-session design (Bikson *et al.*, 2018). Double-blinding in tDCS studies can be achieved by using specific tDCS research devices in which active/sham stimulation is delivered according to a 6-digit code inputted in a keypad, guaranteeing that neither subjects nor researchers are aware of the allocation group. This method was employed in recent tDCS trials (Brunoni *et al.*, 2017; Sampaio-Junior *et al.*, 2018). Although this would be the preferable method, in some scenarios specific research-tailored tDCS devices are not available. In such contexts, it is advisable that tDCS operators are instructed to not interact further with the subjects, and critically not when assessing study outcomes. Such approach has also been employed successfully in previous tDCS studies (Brunoni *et al.*, 2013).

Additionally, sample sizes included in each individual trial were usually critically small, limiting the statistical power of comparison, and active and sham tDCS methodology varied considerably. Variation in the position and size of electrodes might influence how much current passes through different brain regions (Chase *et al.*, 2019); the use of different sham parameters for stimulation likely adds more variability and makes it increasingly difficult to compare results across different trials (Fonteneau *et al.*, 2019). Recently, several guidelines establishing adequate procedures for tDCS research have been published (Brunoni *et al.*, 2011; Woods *et al.*, 2016). The

understanding of the effects of prefrontal tDCS on cognition is likely going to improve when trials adopt these procedures.

Future trials designed to evaluate the cognitive effects of prefrontal tDCS could also benefit from including a bigger number of individuals with neuropsychiatric disorders besides only healthy volunteers. In this UR, most of the comparisons evaluated (~ 75%) were generated with data from trials which only included healthy volunteers; given healthy individuals are more likely to have normal cognitive functioning, studies which only included such participants might have been unable to detect a treatment effect in favor of tDCS due to the fact that there was a small room for improvement in cognitive functioning among healthy volunteers. Cognitive impairment is widely recognized in several neuropsychiatric disorders such as depression, bipolar disorder and schizophrenia (Millan *et al.*, 2012; Bortolato *et al.*, 2015; Bortolato *et al.*, 2016), and it is likely that by giving preference to such populations future studies would be better equipped to detect treatment effects of tDCS regarding cognitive functioning, although it should be noted that effect sizes were mostly similar between comparisons performed among healthy and neuropsychiatric individuals, as well as among mixed samples.

Future meta-analysis evaluating the cognitive effects of prefrontal tDCS could also benefit from establishing separate comparison for individuals with different neuropsychiatric disorders. By collapsing individuals with different neuropsychiatric conditions in the same group, such approach includes subjects with distinct conditions which might limit the external validity of the findings identified in the meta-analysis. Although transdiagnostic approaches are useful under the Research Domain Criteria (RDoC) framework (Insel *et al.*, 2013) that

sustains that dysfunctions in cognitive domains occurring in psychiatric disorders should be investigated together in order to develop interventions specifically tailored for such dysfunctions, and not to the disorders per se, at the current moment it would likely be more clinically informative to have separate effect sizes for each neuropsychiatric disorder.

Our UR has several important strengths. A comprehensive search for eligible references was carried out. Considerable efforts were made to collect as much data as possible, and emails were sent to several authors asking for additional information. We were also able to include the vast majority – if not all – cognitive outcomes evaluated in prefrontal tDCS trials. Yet, this UR also has some limitations. We did not include reviews which did not report a separate comparison between active tDCS and sham tDCS, which might have limited – although to a little extent – the outcomes included. We did not carry out a quantitative analysis. We applied the GRADE criteria to meta-analyses without considering the information reported by individual trials; different results could have been obtained if we had done a careful examination of each trial included in each comparison from each meta-analysis, e.g. we could have assessed RoB instead of immediately downgrading for serious RoB if authors did not report RoB in their meta-analyses. However, we chose to apply the quality assessment criteria at the meta-analysis level as meta-analysis constitute one of the highest levels of evidence and are frequently employed by researchers and clinicians as a guide to future research/intervention; by highlighting the issues with available evidence from meta-analyses in this field, we clearly indicate there is actually an evidence of absence, and no definitive conclusions regarding whether a-tDCS, c-tDCS or tDCS are either effective or ineffective in improving cognitive functioning can be made. Additionally, we did not examine unpublished meta-analyses, which could have added new

information to our findings. However, in contrast with pre-registration of clinical trials, pre-registration of systematic reviews and meta-analyses is still on its infancy and, in most journals, optional; therefore, there is no standard procedure for checking for unpublished meta-analyses yet. Lastly, since most meta-analyses did not perform sensitivity analyses on the range of parameters that possible influence the effects of tDCS such as single vs. multi-session, online vs. offline stimulation and others, we could not report separate findings in our UR, and future research should look further into this when data is available.

In conclusion, although a significant volume of trials and meta-analyses have been performed to provide an assessment of the effects of prefrontal tDCS on cognition, poor quality of trials and meta-analyses does not allow to take definitive conclusion as to whether tDCS is effective in improving cognitive function among healthy and neuropsychiatric individuals. At the moment, trials employing better methodology are warranted. Researchers aiming at developing future trials to evaluate the effects of tDCS on cognition should abide by the increasing recommendations from guidelines to enable the reproducibility of their experiments and the comparison of their findings with those from other researchers. Researchers aiming at synthetizing data of the cognitive effects of tDCS on cognition should also abide by the recommendations currently available in guiding formularies such as the PRISMA statement to ensure transparency and to provide more reliable estimates of effect.

Funding

There are no funders to report for this submission.

Declaration of Interest

The authors declare no conflicts of interest.

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Figure legend:

Figure 1. PRISMA flowchart depicting study selection results.

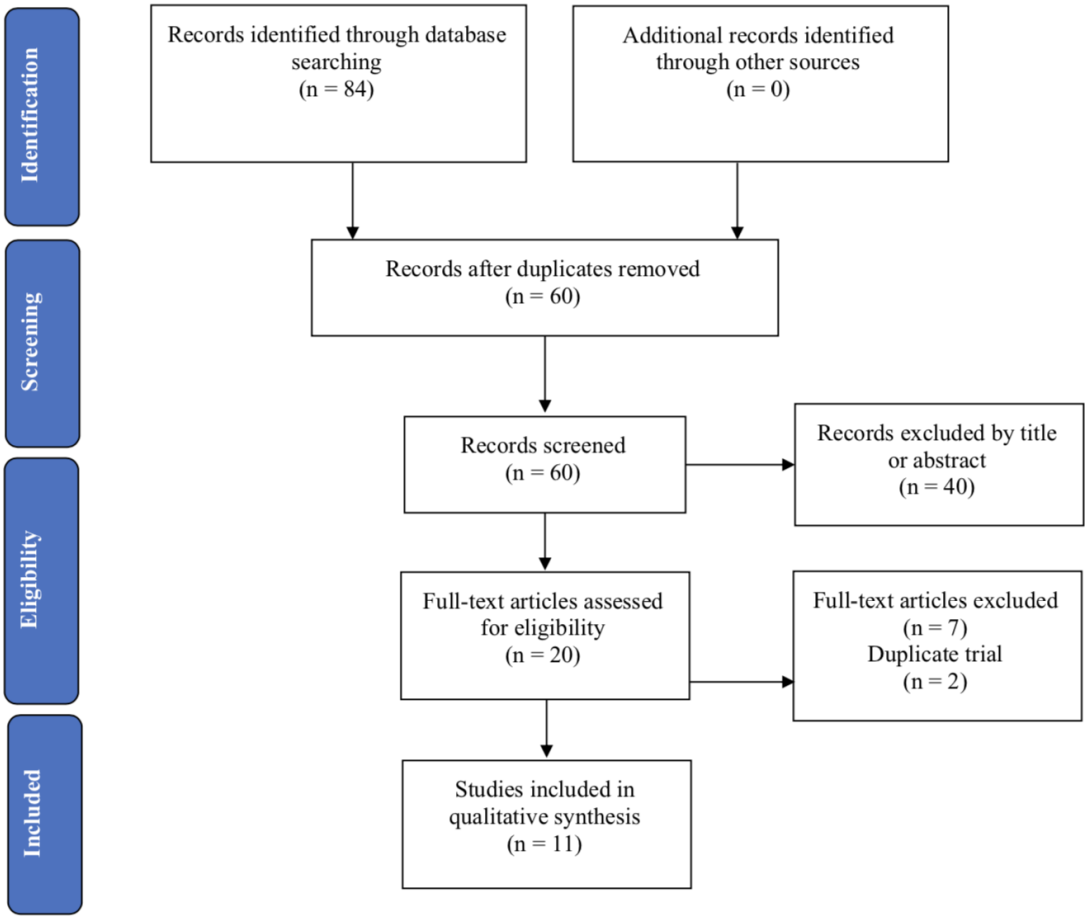

Table 1. Description of the outcomes and tasks included in the umbrella review for each cognitive domain

Cognitive domain:	Outcomes and respective tasks:	Meta-analysis investigating each outcome:
Working memory	Accuracy, reaction time, d' values and working memory index in a multitude of working memory tasks such as 0-back, 1-back, 2-back, 3-back, n-back, Sternberg, Stroop, digit-span task, block tapping task, paced auditory serial addition test, operation word span, working memory scale, Tower of London	Horvath et al., 2015, Dedoncker et al., 2016, Hill et al., 2016, Mancuso et al., 2016, Nilsson et al., 2017, Imburgio and Orr, 2018, Salenijehad et al. 2019
[Long-term] memory	Accuracy in the recognition memory task and the long-term verbal memory task	Horvath et al., 2015, Dedoncker et al., 2016
Set shifting	Switch cost, resumption lag and errors in the task sequence learning, affective financial management, cognitive and motor set shifting task and the paced auditory serial addition test	Horvath et al., 2015, Dedoncker et al., 2016, Imburgio and Orr, 2018, Salehinejad et al. 2019
Response inhibition	Incongruent reaction time, flanker effect, accuracy and stop signal reaction time in the Stroop, Flanker, Stop Signal task, go/no-go task, Simon	Horvath et al., 2015, Dedoncker et al., 2016, Imburgio and Orr, 2018, Salehinejad et al. 2019
Language	Accuracy and number of words in verbal fluency tasks	Horvath et al., 2015 and Price et al., 2015
Aggression	Aggression score in the Taylor aggression paradigm and negative affect state after a frustrating task	Bell and DeWall, 2018
Overeating/food cravings	Subjective report of food	Bell and DeWall, 2018/

	and sweet cravings, visual analog scale scores, food-craving questionnaire scores	Mancuso et al., 2016 and Lowe et al., 2017
Emotional andimplicit bias	Negativity rating after viewing both neutral and negative valence pictures, judgment score of a moral dilemma	Horvath et al., 2015, Bell and DeWall, 2018
Honesty	Lying or reaction time in trust/truth games	Bell and DeWall, 2018
Rumination	Rumination scores on the Rumination Response Scale	Horvath et al., 2015
Impulsivity	Error rate, errors in easy condition and errors on incorrect trials in the Stroop, sentence completion task, cognitive reflection test	Bell and DeWall, 2018
Risk-taking	Number of pumps, high risk choices, riskiness in gains, number of low-probability/high-reward choices in the balloon analogue risk task, Columbia card task and gambling tasks (e.g. Iowa Gambling Task)	Horvath et al., 2015, Bell and DeWall, 2018

Table 2. Methodological quality assessment of the included systematic reviews using the AMSTAR 2 tool

	Salehinejad *et al.* 2019	Bell and De Wall 2018	Imburgio and Orr, 2018	Mostafavi *et al.* 2018	Lowe *et al.* 2017	Nilsson *et al.* 2017	Dedoncker *et al.* 2016b	Hill *et al.* 2016	Mancuso *et al.* 2016	Horvath *et al.* 2015	Price *et al.* 2015
1. PICO for research question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Protocol determined a priori	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**
3. Inclusion criteria explained	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Comprehensive literature search	**Yes**	**Yes**	**Partially yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**
5. Study selection in duplicate	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes
6. Data extraction in duplicate	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes
7. List of the excluded studies	**No**	**No**	**No**	**No**	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**
8. Thorough description of included trials	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
9. Risk	**Yes**	**No**	**No**	**No**	**Yes**	**No**	**Yes**	**Yes**	**No**	**No**	**No**

of bias (RoB) assessed					**s**			**s**			
10. Included studies' funding sources	No	No	No	No	No	No	No	No	No	No	No
11. Meta-analysis statistics adequate	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
12. Considered impact of RoB in studies effect sizes	No	-	-	-	No	-	No	No	-	-	-
13. Discussed RoB	**Yes**	**-**	**-**	**-**	**Yes**	**-**	**Yes**	**Yes**	**-**	**-**	**-**
14. Discussed heterogeneity findings	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
15. Examined publication bias?	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**
16. Disclosures	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No

Bold indicates critical domains.

Table 3 Characteristics of included comparisons of the effects of tDCS over the prefrontal cortex on different domains of cognition among healthy individuals

Identification	Intervention	Target	Task	Outcome	Effect size (95% CI)	p-value	N studies	n individuals (active vs. sham)	Heterogeneity (I^2 value)	Publication bias	GRADE certainty
(A) WORKING MEMORY (WM)											
Imburgio and Orr, 2018	a-tDCS (offline and online)	DLPFC	3-back, WAIS-WM, Sternberg, delayed-response working memory	Accuracy, working memory index	**0.56 (0.19 – 0.93)**	**<0.01**	10	354 (177 vs. 177)	0%	Not suggested	**Low**
Nilsson et al., 2017	a-tDCS (offline and online) + cognitive training	DLPFC	n-back, Sternberg, digit-span task, Corsi block tapping task, Stroop and others	Accuracy, reaction time and d' values	0.07 (-0.21 – 0.34)	0.64	7	266 (131 vs. 135)	0%	Not suggested	Low
Mancuso et al., 2016	a-tDCS + cognitive training	lDLPFC	n-back, PASAT, Sternberg,OSPAN, digit-span task, block	Accuracy and Reaction time	**0.29 (0.06 – 0.5**	**Not reported**	10	285 (144 vs. 141)	0%	Funnel plot asymmetry identified	**Very low**

	a-tDCS (offline and online)		tapping task and others		**2) 0.17 (0.03 – 0.30)**	Not reported	23	768 (385 vs. 383)			**Low**
		rDLPFC			0.04 (-0.19 – 0.27)	Not reported	8	283 (144 vs. 139)			Very low
Hill et al., 2016	a-tDCS (offline and online)	DLPFC	n-back, Sternberg and digit-span task	Accuracy	**0.15 (0.02 – 0.28)**	**0.02**	32	914 (459 vs. 455)	0%	Not suggested	**Moderate**
				Reaction time	**-0.15 (-0.29 – -0.01)**	**0.003**	28	814 (407 vs. 407)			
Horvath et al., 2015	a-tDCS (offline)	lDPFC	digit-span task, Sternb	Accuracy	0.17 (-	0.151	13	293 (140 vs. 153)	Not evaluated	Not evaluated	Very low

		erg, 0-back, 1-back, 2-back, 3-back,		0.06 – 0.40)							
	a-tDCS (online)			0.29 (-0.04 – 0.62)	0.089	8	167 (83 vs. 84)				
			Reaction time	-0.10 (-0.37 – 0.17)	0.474						
[LONG-TERM] MEMORY											
Horvath et al., 2015	a-tDCS (online)	lDLPFC	Recognition memory task, long term verbal memory	Accuracy	1.03 (-0.87 – 2.94)	0.235	3	104 (52 vs. 52)	Not evaluated	Not evaluated	Very low
	c-tDCS (online)				-0.81 (-2.1	0.23					

					4 – 0.51)						
SET SHIFTING											
Hovarth et al., 2015	a-tDCS (offline)	lDLPFC	PASAT, cognitive and motor set shifting tasks	Errors	0.03 (-0.27 – 0.32)	0.836	3	212 (106 vs. 106)	Not evaluated	Not evaluated	Very low
Imburgio and Orr, 2018	a-tDCS (offline and online)	DLPFC	Task sequence learning, affective financial management	Switch cost, resumption lag	-0.04 (-0.68 – 0.59)	0.552	13	648 (324 vs. 324)	69.92 %	Not suggested	Very low
RESPONSE INHBITION											
Hovarth et al., 2015	a-tDCS (offline)	IFG	Stop signal task	Stop signal reaction time	-0.17 (-0.72 – 0.36)	0.548	2	55 (21 vs. 34)	Not evaluated	Not evaluated	Very low
					-0.48 (-1.0	0.12					

					9 – 0.13)						
		rDLPFC	Stroop	Completion time	0.49 (-0.06 – 0.98)	0.082	3	60 (30 vs. 30)			
		lDLPFC			0.56 (-1.60 – 0.48)	0.291					
Imburgio and Orr, 2018	a-tDCS (offline and online)	DLPFC	Stroop, flanker, stop signal task, cognitive reflection test, go/no-go level 3, Simon	Incongruent reaction time, flanker, effect, stop signal reaction time, accuracy	-0.10 (-0.45 – 0.24)	0.55	13	616 (308 vs. 308)	11.49%	Not suggested	Low
MEMORY/ATTENTION/EXECUTIVE FUNCTIONING											
Dedoncker et al., 2016b	a-tDCS (offline and online)	DLPFC	Digit span from WAIS II, SART, detection	Accuracy	0.04 (-0.02 –	0.19	13 1	4415 (2208 vs. 2207)	24%	Not suggested	Moderate

			task: picture and sentence, go/no-go, 2-back, 3-back, n-back, EAT, GDT, BART, IAT, Sternberg, PASAT, CPT, TOL, RAT and others	Reaction time	0.11) **-0.10 (-0.16 - -0.04)**	**< 0.01**	102	3470 (1735 vs. 1735)	0%	Not suggested	**Moderate**
LANGUAGE											
Price et al., 2015	a-tDCS (offline)	lPFC	Verbal fluency	Accuracy	**0.48 (0.04 – 0.92)**	**Not reported**	3	80 (40 vs. 40)	Not evaluated	Not evaluated	**Very low**
	a-tDCS (online)	lPFC			0.33 (-0.06 – 0.73)			100 (50 vs. 50)			
Horvath et al., 2015	a-tDCS (offline)	lDLPFC	Verbal fluency	Number of words	0.23 (-0.	0.16	7	208 (104 vs. 104)	Not evaluated	Not evaluated	Very low

				0.09 – 0.55)							
	a-tDCS (online)			0.35 (-0.22 – 0.91)	0.226	3	100 (50 vs. 50)				
	a-tDCS (offline)	Novel language learning	Accuracy	-0.01 (-0.50 – 0.48)	0.416	2	58 (29 vs. 29)				
AGRESSION											
Bell and DeWall, 2018	a-tDCS (offline and online)	DLPFC	Taylor aggression paradigm, frustrating task (PASAT), essay criticism paradigm	Total aggression, PANAS negative affect, anger and state rumination	-0.17 (-0.44 – 0.09)	0.19	6	339 (170 vs. 169)	29.48 %	Not suggested	Very low
OVEREATING											
Bell and DeWall,	a-tDCS (offline	DLPFC	-	Calories eaten, desire to eat	**-0.25**	**0.03**	7	326 (163 vs. 163)	17.69 %	Funnel plot asy	**Very low**

2018	and online)			high calorie foods, food cravings, appetite for sweets, sweet craving	**(-0.49 - -0.01)**					mmetry identified	
EMOTIONAL AND IMPLICIT BIAS											
Horvath et al., 2015	a-tDCS (online)	lDLPFC	Negative valence pictures	Negativity rating	-0.17 (-0.52 – 0.18)	0.333	3	134 (59 vs. 75)	Not evaluated	Not evaluated	Very low
			Neutral valence pictures		0.01 (-0.42 – 0.45)	0.957	2	88 (36 vs. 52)			
		rDLPFC	Negative valence pictures		-0.19 (-1.20 – 0.81)	0.709		88 (43 vs. 45)			
			Neutral valence		0.1	0.575					

			picture s	2 (-0.30 – 0.54)						
	c-tDCS (online)	lDLPFC	Negative valence pictures	0.03 (-0.54 – 0.60)	0.915	2	88 (36 vs. 52)			
			Neutral valence pictures	0.37 (-0.06 – 0.81)	0.094					
Bell and DeWall, 2018	a-tDCS (offline and online)	DLPFC	Moral dilemma value judgement score; affective biasing task with emotional go/no-go; race IAT	**-0.25 (-0.48 - -0.03)**	**0.02**	7	447 (224 vs. 223)	12.79 %	Not suggested	**Low**

HONESTY										
Bell and DeWall, 2018	a-tDCS (offline and online)	DLPFC	Selection trials, trust game, truth response (personal information)	Reaction time, lying	0.06 (-0.16 – 0.28)	0.57	4	322 (162 vs. 160)	0%	Not suggested	Low
RUMINATION										
Horvath et al., 2015	a-tDCS (offline)	DLPFC	-	Rumination Response Scale	-0.01 (-0.36 – 0.34)	0.95	2	126 (61 vs. 65)	Not evaluated	Not evaluated	Very low
IMPULSIVITY										
Bell and DeWall, 2018	a-tDCS (offline and online)	DLPFC	Stroop, sentence completion task, CRT problem solving task	Error rate, errors in easy condition, errors on incorrect trials	-0.02 (-0.21 – 0.16)	0.70	9	676 (338 vs. 338)	33.17%	Not suggested	Low
RISK TAKING										
Horvath et al., 2015	a-tDCS (online)	DLPFC	BART, risk task, gambling task	Number of low-probability/high-reward choices	-0.67 (-2.39 –	0.451	3	76 (38 vs. 38)	Not evaluated	Not evaluated	Very low

					1.06)						
	c-tDCS (online)				-1.70 (-3.61–0.22)	0.082		126 (61 vs. 65)			
Bell and DeWall, 2018	a-tDCS (offline and online)	DLPFC	BART, Columbia Card Task, Iowa Gambling Task	Number of pumps, high risk choice, riskiness in gains	**-0.36 (-0.65 – -0.07)**	**0.01**	13	676 (338 vs. 338)	65.50 %	Funnel plot asymmetry identified	**Very low**
(B) WORKING MEMORY											
Hill et al., 2016	a-tDCS (offline and online)	DLPFC	n-back, Sternberg and digit-span task	Accuracy	0.11 (-0.07–0.29)	0.24	15	860 (430 vs. 430)	10 %	Not suggested	Low
				Reaction time	-0.14 (-0.39–	0.26	8	232 (126 vs. 126)	0%		Very low

					0.11)						
Salehinejad et al., 2019	a-tDCS (online and offline)	DLPFC	Digit span, corsi cube, 1-back, 2-back, quantified behavior	Amount, accuracy, reaction time, quantified behavior score	0.12 (-0.32 – 0.55)	0.5996	16	382 (191 vs. 191)	0%	Not evaluated	Very low
RESPONSE INHIBITION											
Salehinejad et al., 2019	a-tDCS (offline and online)	DLPFC + rIFG	Go/no-go, stop signal task, CPT, Flanker, Stroop,	Reaction time, accuracy, true positive errors, false positive errors, omission errors, commission errors, correct responses, etc.	**0.26 (0.07 – 0.44)**	**0.0079**	34	1404 (702 vs. 702)	0%	Not evaluated	**Very low**
	c-tDCS (offline and online)				0.09 (-0.19 – 0.37)	0.53	13	468 (234 vs. 234)	0%	Not evaluated	Very low
MEMORY/ATTENTION/EXECUTIVE FUNCTIONING											
Dedoncker et al., 2016b	a-tDCS (offline and online)	DLPFC	Digit span from WAIS II, SART, detection task: picture and sentenc	Accuracy	**0.22 (0.04 – 0.40)**	**< 0.05**	30	944 (472 vs. 472)	42.5%	Not suggested	**Very low**
				Reaction time	-0.	0.065	22	660 (330	0%	Not sugg	Low

			e, go/no-go, 2-back, 3-back, n-back, EAT, GDT, BART, IAT, Sternberg, PASAT, CPT, TOL, RAT and others		15 (-0.30 – 0.01)			vs. 330)		tested	
(C) MEMORY/ATTENTION/EXECUTIVE FUNCTIONING											
Dedoncker et al., 2016b	a-tDCS (offline and online)	DLPFC	Digit span from WAIS II, SART, detection task: picture and sentence, go/no-go, 2-back, 3-back, n-back, EAT, GDT, BART, IAT, Sternberg, PASAT, CPT, TOL, RAT and others	Accuracy	**0.18 (0.03 – 0.18)**	**< 0.01**	165	5359 (2680 vs. 2679)	52.50%	Not suggested	**Very low**
				Reaction time	**-0.11 (-0.17 - -0.05)**	**< 0.01**	124	4130 (2065 vs. 2065)	0%		**Low**
	c-tDCS (offline and online)			Accuracy	0.03 (-0.1	0.70	28	942 (471 vs. 471)	33.8%	Not suggested	Very low

	e)		others		3 – 0.19)						
				Reaction time	0.18 (-0.07 – 0.44)	0.16	36	1182 (591 vs. 591)	82.5%		Very low
FOOD CRAVINGS											
Lowe et al., 2017	tDCS	DLPFC	-	Visual analog scale, Food Craving Questionnaire	-0.25 (-0.80 – 0.29)	0.3647	4	114 (57 vs. 57)	Not reported	Funnel plot asymmetry identified	Very low
Mostafavi et al., 2018	tDCS	DLPFC	-	Food Craving Questionnaire	**-0.54 (-0.85 – -0.24)**	**<0.001**	4	145 (72 vs. 73)	0%	Not suggested	**Very low**
				Visual analog scale	**-0.78 (-1.12**	**<0.001**	13	416 (208 vs. 208)	71.4%		

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a-tDCS: anodal tDCS, c-tDCS: cathodal tDCS, DLPFC: dorsolateral prefrontal cortex, rDLPFC: right dorsolateral prefrontal cortex, lDLPFC: lateral dorsolateral prefrontal cortex, IFG: inferior frontal gyrus, lPFC: left prefrontal cortex, PASAT: paced auditory serial addition test, OSPAN: operation span, WAIS-WM: Wechsler Adult Intelligence Scale Working Memory, SART: Sustained attention to respond task, TOL: Tower of London, RAT: Remote associates test, GDT: Game of dice task, BART: Balloon analog risk task, EAT: Error awareness task, IAT: Implicit association test, CRT: cognitive. reflection test, PANAS: Positive and negative affect schedule. Values in bold represent significant comparisons.

Table 4. Description of the main findings in the umbrella review for each cognitive domain

Cognitive domain:	Findings from the umbrella review:
Working memory	**5 comparisons among healthy individuals indicated significant benefit of a-tDCS for working memory, but there was at best moderate certainty that the true effect is close to the estimates from the meta-analyses.** 5 comparisons among healthy individuals indicated no benefit of a-tDCS for working memory. 3 comparisons among neuropsychiatric individuals indicated no benefit of a-tDCS for working memory.
[Long-term] memory	2 comparisons among healthy individuals indicated no benefit of either a-tDCS or c-tDCS for [long-term] memory improvement.
Set shifting	2 comparisons among healthy individuals indicated no benefit of a-tDCS for set shifting.
Response inhibition	5 comparisons among healthy individuals indicated no benefit of a-tDCS for response inhibition. **1 comparison among neuropsychiatric individuals indicated a significant benefit of a-tDCS for response inhibition. but there was very low certainty that the true effect is close to the estimate from the meta-analysis.** 1 comparison among neuropsychiatric individuals indicated no benefit of c-tDCS for response inhibition.
Language	**1 comparison among healthy individuals indicated a significant benefit of a-tDCS for language performance, but there was very low certainty that the true effect is close to the estimate from the meta-analysis.** 4 comparisons among healthy individuals indicated no benefit of a-tDCS for language performance.
Aggression	1 comparison among healthy individuals indicated no benefit of a-tDCS for aggression.

Overeating/Food cravings	**1 comparison among healthy individuals indicated significant benefit of a-tDCS for overeating, but there was very low certainty that the true effect is close to the estimate from the meta-analysis.** **2 comparisons among mixed samples of healthy and neuropsychiatric individuals indicated a significant benefit of tDCS for food cravings, but there was very low certainty that the true effect is close to the estimates from meta-analyses.** 1 comparison among mixed samples of healthy and neuropsychiatric individuals indicated no benefit of tDCS for food cravings.
Emotional and implicit bias	**1 comparison among healthy individuals indicated a significant benefit of a-tDCS for emotional bias and implicit bias, but there was low certainty that the true effect is close to the estimate from the meta-analysis.** 6 comparisons among healthy individuals indicated no benefit of a-tDCS or c-tDCS for emotional bias.
Honesty	1 comparison among healthy individuals indicated no benefit of a-tDCS for honesty.
Rumination	1 comparison among healthy individuals indicated no benefit of a-tDCS for rumination.
Impulsivity	1 comparison among healthy individuals indicated no benefit of a-tDCS for impulsivity.
Risk-taking	**1 comparison among healthy individuals indicated significant benefit of a-tDCS for risk-taking, but there was very low certainty that the true effect is close to the estimate from the meta-analysis.** 2 comparisons among healthy individuals indicated no benefit of either a-tDCS or c-tDCS for risk-taking.