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The Effect of the Interval-Between-Sessions on Prefrontal Transcranial Direct Current Stimulation (tDCS) on Cognitive Outcomes: A Systematic Review and Meta-Analysis.

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ABSTRACT

Recently, there has been wide interest in the effects of transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) on cognitive functioning. However, many methodological questions remain unanswered. One of them is whether the time interval between active and sham-controlled stimulation sessions, i.e. the Interval Between Sessions (IBS), influences DLPFC tDCS effects on cognitive functioning. Therefore, a systematic review and meta-analysis was performed of experimental studies published in PubMed, Science Direct, and other databases from the first data available to February 2016. Single session sham-controlled within-subject studies reporting the effects of tDCS of the DLPFC on cognitive functioning in healthy controls and neuropsychiatric patients were included. Cognitive tasks were categorized in tasks assessing memory, attention, and executive functioning. Evaluation of 188 trials showed that anodal vs. sham tDCS significantly decreased response times and increased accuracy, and specifically for the executive functioning tasks, in a sample of healthy participants and neuropsychiatric patients (although a slightly different pattern of improvement was found in analyses for both samples separately). The effects of cathodal vs. sham tDCS (45 trials), on the other hand, were not significant. IBS ranged from less than one hour to up to one week (i.e. cathodal tDCS) or two weeks (i.e. anodal tDCS). This IBS length had no influence on the estimated effect size when performing a meta-regression of IBS on reaction time and accuracy outcomes in all three cognitive categories, both for anodal and cathodal stimulation. Practical recommendations and limitations of the study are further discussed.

Keywords:

Cognition, dorsolateral prefrontal cortex, meta-analysis, noninvasive brain stimulation, systematic review, transcranial direct current stimulation.

Abbreviations:

ACC, accuracy; DC, direct current; DLPFC, dorsolateral prefrontal cortex; ER, error rate; ES, effect size; IBS, interval between sessions; mA, micro-Ampère; NIBS, non-invasive brain stimulation; NMDA, N-Methyl-D-Aspartate; RT, response time; SD, standard deviation; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation.

INTRODUCTION

In recent years, researchers have become increasingly interested in the effects of transcranial direct current stimulation, a non-invasive brain stimulation (NIBS) technique. tDCS operates by means of the delivery of a low-intensity direct current (e.g. 1-2 mA) via an anodal electrode and a cathodal electrode attached to the scalp surface. This way, tDCS modulates spontaneous cortical activity. More specifically, anodal stimulation increases motor cortical excitability (Nitsche and Paulus 2000; Nitsche and Paulus 2001; Purpura and McMurtry 1965), whereas cathodal stimulation decreases motor cortical activity (Nitsche and Paulus 2000; Nitsche et al. 2003). Nevertheless, the neurophysiology of tDCS is more complex, particularly for brain areas other than the motor cortex. Not only synaptic processes have been demonstrated to be involved (e.g. NMDA-receptor dependent changes in synaptic strength; Liebetanz et al. 2002), non-synaptic processes and prolonged neurochemical changes may be of importance as well (Brunoni et al. 2012). The dorsolateral prefrontal cortex (DLPFC) is one of the most frequently targeted stimulation sites in tDCS studies. Studies have shown that tDCS has modulatory effects on attention (Gladwin et al. 2012b; Kang et al. 2009; Kang et al. 2012; Nelson et al. 2014; Nozari and Thompson-Schill 2013), memory and verbal processing (Fertonani et al. 2010; Fertonani et al. 2014; Metuki et al. 2012; Sela et al. 2012; Vannorsdall et al. 2012; Wirth et al. 2011), and executive functioning (including working memory; Andrews et al. 2011; Berryhill and Jones 2012; Boggio and Khoury 2009; Boggio et al. 2006; Dockery et al. 2009; Filmer et al. 2013; Fregni et al. 2005; Gladwin et al. 2012a; Hammer and Mohammadi 2011; Harty et al. 2014; Hoy et al. 2014; Jo et al. 2009; Keshvari et al. 2013; Leite et al. 2011; Leite et al. 2013; Mulquiney and Hoy 2011; Penolazzi et al. 2010; Plewnia et al. 2013; Saidmanesh et al. 2012; Vanderhasselt et al. 2013a; Vanderhasselt et al. 2013b; Wu et al. 2014; Zmigrod et al. 2014); for a meta-analysis of the effects of tDCS on working memory, see Brunoni and Vanderhasselt (2014), among others.

However, some recent systematic reviews have suggested otherwise, i.e. that tDCS effects may be mixed and contradictory (Tremblay et al. 2014), or even absent (Horvath et al. 2015; however, see also Price and Hamilton 2015). One reason for such findings is that tDCS presents a number of fundamental methodological issues (Horvath et al. 2014), and that this heterogeneity could hamper the internal validity of the growing body of research conducted on the area. Particularly, little is known regarding the influence of the time between the administration of an active and a sham stimulation in within-subject, single-session, sham-controlled tDCS studies. Often, the time of the Interval Between Sessions (IBS) is chosen empirically, with lengths varying between less than one hour (Fertonani et al. 2010; Fregni et al. 2005; Gladwin et al. 2012b; Knechtel et al. 2014a; Knechtel et al. 2014b), to up to two weeks (Ohn et al. 2008). Although studies on motor cortical

excitability showed that the after-effects of tDCS may last several hours (Nitsche et al. 2008), no such systematic exploration for cognitive measures has been conducted yet. Comprehension of the IBS length-effect would, however, greatly impact on tDCS cognition research. If, for instance, the length has little-to-no effect on cognitive outcome measures, the study duration could be shortened (i.e. days instead of weeks). This would be advantageous as, with a large IBS, other subject variables (e.g. menstrual cycle, mood, stress) can vary more compared to a short IBS. To date however, the IBS length has been increasing steadily, which can introduce noise to the study. Furthermore, studies can become more standardized if a universal IBS is used in future studies.

Therefore, our aim is to evaluate whether the effects of tDCS applied to the DLPFC on cognitive outcome measures is influenced by the length of the IBS. To this end, we performed a systematic review and meta-analysis of tDCS studies using cross-over, single session, sham-controlled designs that investigate the effects of DLPFC neuromodulation on cognitive measures in healthy volunteers and neuropsychiatric patients. Our main focus is on the effects of tDCS on neuropsychological functioning. Therefore, only studies investigating DLPFC are included in the systematic review. Accordingly, studies targeting other brain regions (e.g. motor cortex) and investigating the effects of neuromodulation on other functions (e.g. movement) were not included. Given that anodal tDCS and cathodal tDCS have opposing effects on cortical excitability, respectively increasing and decreasing activity in the neural tissue being stimulated, analyses were performed for each polarity separately. Anodal prefrontal tDCS is expected to decrease response times and increase the percentage of correct responses, whereas cathodal prefrontal tDCS is expected to increase response times and decrease accuracy (although, see Jacobson et al. 2012).

MATERIAL AND METHODS

We conducted a systematic review and meta-analysis according to the recommendations of the Cochrane group guidelines (Higgins and Green 2008), including the following procedures: literature review, selection of eligible articles according to predefined inclusion and exclusion criteria, assessment of quality of the included studies, data extraction of outcomes and other relevant variables, and a quantitative synthesis and meta-analysis of the results. This report follows PRISMA guidelines (Liberati et al. 2009). Discrepancies were resolved by consensus.

Literature review. The first step was a literature search of following databases: PubMed, Web of Science, Google Scholar and Science Direct. Published articles were searched from the first data available to 5 February 2016 (incl. articles available online-only). We used the following key words: (1) (“transcranial direct current stimulation” OR “tDCS”) and (“dorsolateral prefrontal cortex” OR “DLPFC”), and (2) “transcranial” OR “transcranial direct current stimulation” OR “tDCS” OR “direct current stimulation”. We also looked for additional references in retrieved articles and reviews. Subsequently, we checked each article according to our inclusion criteria.

Eligibility criteria. The included studies had to: (a) be written in English; (b) have a single-session within-subject design; (c) be randomized and sham-controlled; (d) enroll either healthy volunteers or neuropsychiatric patients; (e) perform transcranial direct current stimulation on dorsolateral prefrontal cortex; (f) provide data (in the article or upon request) of the mean and standard deviation (SD) on cognitive measures. Furthermore, case studies, studies on preconditioning, reviews, duplicates and unrelated studies were excluded.

Quality assessment. We used the Cochrane risk of bias tool that assesses the following criteria (according to the Cochrane guidelines; Higgins and Green 2008): (a) sequence generation – whether randomization and/or counterbalancing was performed; (b) allocation concealment – if the method for randomization was concealed properly; (c) blinding participants – whether subjects and/or investigators were blind to the allocation group and if a reliable sham method was used; (d) incomplete outcome data – whether all data was obtained by the researchers; (e) selective outcome reporting – whether the authors reported on the results for all the pre-specified primary objectives.

Data extraction. From each article, we extracted data of sample characteristics (i.e. extraction of the sample size, whether subjects were healthy volunteers or not, gender, age), study design (i.e. randomization and/or counterbalancing, blinding, how missing data were handled, interval-between-sessions), characteristics of tDCS intervention (i.e. for sham and active stimulation, the site of anodal and/or cathodal stimulation), and characteristics of the cognitive task (i.e. type). IBS length was operationalized differently across studies. When the exact or average IBS length was not reported (or not communicated personally), and rather the authors described an IBS interval (e.g. “48h-72h”) or the minimum IBS length (e.g. “at least 48h”) that was used, the minimum length was used in our analysis (i.e. 48h in the examples above). IBS lengths were subsequently converted to days (d) when necessary. Finally, we extracted data on perceived blinding and adverse effects.

For the cognitive outcomes, we extracted the following data: (a) mean RT and standard deviation (SD) of RT; (b) percentage of correct responses and the corresponding SD, and; (c) percentage of errors and the corresponding SD. Data post-tDCS was always extracted and, if available, data pre-tDCS was extracted as well. However, due to a small amount of trials measuring error percentages, and a small amount of studies testing the cognitive outcomes at baseline (pre-tDCS), we could not include these data in the analyses.

For data reduction of the cognitive outcomes, cognitive tasks were categorized in three different task types according to specific theoretical models: (1) Memory: all memory tasks not assessing working memory were classified in this category; We did not specify a language category since these tasks mostly measure memory processes (e.g. semantic memory, object recognition, picture naming, among others). (2) Attention: tasks assessing sustained attention (e.g. detection task) and divided attention (e.g. dual auditory and visual discrimination task), among others were included in the attention category (Cohen et al. 1993). However, it must be mentioned that all tasks included in this meta-analysis measure attention to a certain degree; and (3) Executive functioning: according to Miyake et al. (2000) tasks that evaluate shifting, inhibition and updating (i.e. working memory) can be considered executive functioning tasks. Therefore, working memory tasks (e.g. n-back) were classified in this category.

Quantitative analysis. All analyses were performed using Stata software version 12 (Statacorp, TX, USA). First, we categorized all experiments as either anodal tDCS (+ reference), cathodal tDCS (+ reference), or bi-frontal tDCS (e.g. simultaneous stimulation of the left and the right DLPFC). Bi-hemispheric trials were then mostly allocated to the anodal tDCS category as many authors indicate a shift of neural activity towards the hemisphere under anodal stimulation. However, in one study in which bi-frontal stimulation was used, Nelson et al. (2014) specifically make a distinction between an anodal condition and a cathodal condition. In this case, we follow this distinction made by the authors. In order to meta-analyze the results across studies, an effect size had to be estimated for each trial comparing the effects of either anodal tDCS and sham tDCS, or cathodal tDCS and sham tDCS on the cognitive outcomes. Therefore, for each outcome, we calculated the standardized mean difference (SMD) and the pooled standard deviation for each comparison. Cohen's d was used as measure of effect size (ES). Subsequently, the effect sizes needed to be pooled into a measure of the effect size across studies. A random-effects model was used to measure the pooled effect size, weighted by the inverse variance method. To answer our research question, the effect size of the difference between active tDCS (anodal vs. cathodal) and sham tDCS across studies was then plotted against the IBS length of each study using meta-regression techniques. The Chi-square test was used to assess heterogeneity for each outcome. Egger's test and

Begg's funnel plot were used to assess risk of publication bias. Meta-regression was used to assess heterogeneity and identify moderators influencing the results. The following variables were meta-regressed: age (continuous), clinical condition (healthy vs. psychiatric patients), gender (% females), and laterality (left vs. right). Only one variable was meta-regressed at a time.

RESULTS

Overview. We obtained 3119 references on Science Direct, Web of Science, Google Scholar and PubMed using our specific search criteria. However, 3018 studies were excluded after title and abstract review for reasons described earlier (cf. methods, eligibility criteria). In total, 101 articles were more closely inspected. However, following a full-text evaluation, another 40 references were further excluded due to ineligibility (for an overview, see Online Resource 1). For example, either the reports did not assess cognitive outcome measures, the studies used a variant of tDCS (e.g. a three- or four-electrode setup, intermittent tDCS, slow oscillatory tDCS), the studies did not evaluate single sessions, or the studies were excluded for other reasons (e.g. no overall RT, accuracy or error rates were reported, a subliminal face paradigm was used, stimulation effects were analyzed simultaneously for DLPFC and parietal cortex stimulation, and not for DLPFC separately). Finally, 5 eligible studies were excluded due to the requested data not being provided by the authors. In sum, 61 studies were included in the review (for a flow-chart, see Online Resource 2). However, some studies reported more than one experiment (e.g. different samples), while many reported more than one comparison (e.g. tDCS in different samples, diverse outcome facets). Therefore, each experiment/comparison was considered a different dataset (total amount of trials, $n=233$; anodal tDCS studies, $n=188$ trials; cathodal tDCS studies, $n=45$ trials; see Online Resource 3).

Quality assessment. Quality assessment showed that all studies have a crossover single-session within-subject design. Furthermore, in 14 reports there was a random allocation of subjects to the different stimulation conditions, while in 27 studies stimulation conditions were counterbalanced across subjects. In the remainder of the studies, randomization as well as counterbalancing was used. Unfortunately, in only 6 out of 61 studies there was a low risk of allocation concealment bias (i.e. almost all studies did not report if and how concealment took place). In most studies, sham stimulation was performed by turning off the electric current shortly after stimulation onset. The length of the active period of stimulation during the sham session differed between studies, ranging from 5 seconds (Fregni et al. 2005; Mylius et al. 2012) up to 2 minutes and 45 seconds

(Andrews et al. 2011; Hoy et al. 2013; Hoy et al. 2014). However, in 3 studies tDCS was given with a placebo stimulator (Keeser et al. 2011; Balconi and Canavesio 2014; Balconi and Vitaloni 2014), while in 1 study, the stimulator was turned off for the entire session (Beeli et al. 2008). Regarding blinding, 47 out of the 61 studies were single-blind. The other 14 studied used a double-blind design. To this end, the tDCS apparatus was either turned off automatically by entering a code prior to tDCS administration (Hoy et al. 2013; Hoy et al. 2014; Nieratschker et al. 2014; Plewnia et al. 2013; Teo et al. 2011; Turi et al. 2014; Wolkenstein and Plewnia 2013; Wolkenstein et al. 2014) or the person delivering tDCS was not the person analyzing the data (Kang et al. 2009; Kang et al. 2012). In the remaining 3 studies, the procedure for double blinding was not mentioned (Gill et al. 2014; Powell et al. 2014; Sela et al. 2012). The time period in between the active stimulation session and the sham stimulation session ranged from 3.5 minutes (Beeli et al. 2008) to two weeks (Ohn et al. 2008). However, there is a large variety in the lengths of IBS. The risk of incomplete outcome data and selective outcome reporting were generally low across studies. Only two studies have a high risk of incomplete outcome data (Cerruti and Schlaug 2009; Dockery et al. 2009) and three studies have a high risk of selective outcome reporting (Cerruti and Schlaug 2009; Javadi and Cheng 2013; Kang et al. 2012). To date, researchers investigating the effects of tDCS are advised to evaluate the occurrence of adverse effects as well. Of the studies included in this review, however, only 35 of the 61 studies report having evaluated side effects or adverse effects (i.e. either in the article or upon request). Most studies only included right-handed participants. Other exclusion criteria were more diverse. Clinical samples of the included studies were on a stable dose (Hoy et al. 2014; Kang et al. 2012; Knechtel et al. 2014a; Powell et al. 2014; Vercammen et al. 2011; Wolkenstein and Plewnia 2013) or did not take psychiatric medication (Boggio et al. 2006; Gorini and Lucchiari 2014). Psychiatric interviews and/or questionnaires were used to screen patients. In summary, the procedures that were used for including and excluding subjects, and for randomization, counterbalancing, sham stimulation, and sham blinding suggest overall good quality of the studies (Cochrane risk of bias, Online Resource 4).

Main results. Only response time (RT) data and data on the percentage of accurate responses (i.e. accuracy; ACC) are included in the analysis. Data on the percentage of erroneous responses was not included due to small amount of trials (n=44; 18.88% of the trials reported the percentage of errors). Furthermore, baseline data was not included in the analysis for the same reason (n=65; 27.89% of the trials reported baseline data) as most studies (73.77%) did not perform a baseline assessment.

Response times. For anodal tDCS (N of RT trials = 124) Cohen's d for the pooled random-effects standardized mean difference (SMD) was -0.107 (95% CI -0.17 to -0.05, $p < 0.01$, Fig. 1a). Overall,

participants were faster in responding after anodal vs. sham non-invasive brain stimulation. In sub-analyses for the three task categories separately, the significant effect of anodal tDCS on RT was found for executive functioning tasks only (Cohen's d -0.0117, 95% CI -0.17 to -0.05, $p < 0.01$). No significant effects of anodal tDCS on RT were found for memory tasks (Cohen's d -0.108, 95% CI -0.27 to 0.05, $p = 0.19$) and attention tasks (Cohen's d -0.04, 95% CI -0.21 to 0.13, $p = 0.61$). No significant heterogeneity was observed ($I^2 = 0\%$; $\chi^2(123) = 73.24$, $p = 1$). Meta-regression analysis showed no significant effect of laterality (left vs. right anodal stimulation) on the effect sizes ($\beta = 0.05$, $SE = 0.046$, $p = 0.25$). More importantly, there was no significant effect of IBS on the effect size ($\beta = 0.005$, $SE = 0.009$, $p = 0.58$; Fig. 1b). Cathodal tDCS (N of RT trials = 36) had no significant effect on overall RT (Cohen's d 0.18, 95% CI -0.07 to 0.44, $p = 0.16$; Fig. 2a), nor was a significant effect found when splitting the data over memory tasks (Cohen's d -0.04, 95% CI -0.28 to 0.19, $p = 0.71$), attention tasks (Cohen's d 0.42, 95% CI -0.24 to 1.09, $p = 0.21$) and executive functioning tasks (Cohen's d 0.12, 95% CI -0.07 to 0.31, $p = 0.21$). However, significant heterogeneity was observed for the overall analysis ($I^2 = 82.50\%$; $\chi^2(35) = 199$, $p < 0.01$), as well as specifically for the attention sub-category ($I^2 = 82.50\%$; $\chi^2(13) = 178$, $p < 0.01$). Meta-regression analysis showed no significant effect of laterality (left vs. right cathodal stimulation) on the effect sizes ($\beta = -0.03$, $SE = 0.26$, $p = 0.91$). Finally, there was no significant effect of the IBS on the effect sizes ($\beta = -0.069$, $SE = 0.06$, $p = 0.26$; Fig. 2b). Although for the cathodal vs. sham analyses all effects are non-significant, it is interesting to notice that anodal tDCS decreases RT, while cathodal tDCS tends to increase RT. Statistical testing for the anodal tDCS trials and the cathodal tDCS trials using Egger's test for small-study effects showed no effect of bias and the funnel plot showed only a few outliers (Online Resource 5a and 5b for anodal and cathodal tDCS trials respectively). Percentage of correct responses. In this analysis we identified two important significant outliers that were excluded as they presented large, positive effect sizes (Knechtel (Exp-1) and Metuki (Exp-1)) – these studies presented Cohen's d three standard deviations above of the mean and, since our aim was to explore stimulation parameters through meta-regressions, these studies would be influential points in our slopes. Interestingly Egger's test was significant before ($p < 0.01$) but not after the exclusion of the outliers ($p = 0.18$). For anodal tDCS (N of ACC trials = 165), significant heterogeneity was observed ($I^2 = 52.50\%$; $\chi^2(164) = 344.9$, $p < 0.01$). The pooled random-effects standardized mean difference (SMD) gave a Cohen's d of 0.18 (95% CI 0.03 to 0.18, $p < 0.01$, Fig. 3a), i.e., participants responded significantly more correct after active vs. sham non-invasive brain stimulation. When

splitting the data over the three task types an increase in the percentage of accurate responses in executive functioning tasks following anodal tDCS (Cohen's d 0.08, 95% CI 0.01 to 0.16, $p < 0.05$) was found. No significant effects of anodal tDCS vs. sham were found for memory tasks (Cohen's d 0.18, 95% CI -0.11 to 0.47, $p = 0.22$) and attention tasks (Cohen's d 0.15, 95% CI -0.29 to 0.34, $p = 0.10$). Further, meta-regression analysis showed no effect of laterality (left vs. right anodal tDCS) on the effect sizes ($\beta = -0.03$, SE = 0.05, $p = 0.61$). Finally, IBS length did not influence the effect size ($\beta = 0.01$, SE = 0.014, $p = 0.46$; Fig. 3b). Cathodal tDCS vs. sham (N of ACC trials = 28) did not influence overall accuracy (Cohen's d 0.03, 95% CI -0.13 to 0.19, $p = 0.70$; Fig. 4a). No significant effects of cathodal tDCS vs. sham were found for memory tasks (Cohen's d 0.01, 95% CI -0.39 to 0.43, $p = 0.93$), attention tasks (Cohen's d 0.26, 95% CI -0.05 to 0.58, $p = 0.10$), and executive functioning tasks (Cohen's d -0.03, 95% CI -0.20 to 0.13, $p = 0.71$). Significant heterogeneity was observed in the general analysis ($I^2 = 33.8\%$; $\chi^2(27) = 40.79$), as well as the sub-analysis for attention tasks ($I^2 = 66.50\%$; $\chi^2(8) = 23.8$, $p < 0.01$). Meta-regression analysis demonstrated a significant influence of laterality (left vs. right cathodal tDCS) on the effect sizes ($\beta = 0.27$, SE = 0.13, $p < 0.05$), i.e. cathodal tDCS applied to the right DLPFC is associated with greater increases in accuracy than cathodal tDCS to the left DLPFC. However, no effect of IBS length on effect sizes was found ($\beta = 0.004$, SE = 0.03, $p = 0.91$; Fig. 4b). Statistical testing using Egger's test for small-study effects for the anodal tDCS trials (after exclusion of outliers) and cathodal tDCS trials showed no effect of bias and funnel plot showed no outliers (Online Resource 5c and 5d for anodal and cathodal tDCS trials respectively).

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Meta-regression. We ran additional meta-regressions in order to identify possible moderators of our results (Table 1). No variable was associated with the RT results as well as the ACC results. However, even though the condition to which participants belonged (i.e. healthy participants vs. neuropsychiatric patients) did not influence anodal tDCS effects on RT and ACC, we ran the meta-analyses and meta-regressions once more for the two populations separately. As the available tDCS research in neuropsychiatric patients only investigated the effects of anodal tDCS, but not cathodal tDCS, on cognitive outcomes, analyses could only be performed for anodal tDCS trials. In summary, for healthy participants as well as neuropsychiatric patients, IBS length did not moderate the effects of anodal tDCS on cognitive outcomes (for a detailed description of the results, see Online Resource 6).

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DISCUSSION

The aim of this review was to systematically assess whether the effects of DLPFC tDCS on cognitive functioning are influenced by the length of the interval between stimulation sessions. To this end, we performed a meta-analysis of 61 tDCS studies (233 trials) using cross-over, single session, sham-controlled designs, investigating the effects of DLPFC neuromodulation on cognitive measures. Analyses were performed separately for anodal tDCS (188 trials) and cathodal tDCS (45 trials), as both stimulation types have opposing effects on cortical activity. Furthermore, cognitive tasks that were used in the studies included in the meta-analysis were categorized into three categories: memory, attention and executive functioning. By means of this categorization, we attempted to decrease the heterogeneity of the data and decrease the type I error.

Anodal vs. sham tDCS influenced RT and accuracy on cognitive tasks for all three categories. More specific analyses showed that anodal tDCS decreased RT and increased the percentage of correct responses only in executive functioning tasks. Cognitive functioning was not influenced by anodal tDCS in the two other cognitive task categories (attention and memory; although slightly differing patterns of improvement following anodal tDCS were found for healthy vs. neuropsychiatric samples, see Online Resource 6). In contrast to the effects with anodal neuromodulation, analyses for cathodal tDCS yielded no results. In other words, cathodal vs. sham tDCS did not influence RT or accuracy across the three cognitive tasks, nor did it influence RT or accuracy when analyzing the task types separately.

For these anodal and cathodal effects of tDCS, IBS length does not influence the effect of prefrontal tDCS on cognitive functioning. Moreover, when response times and accuracy rates were analyzed separately for the three different cognitive task types (i.e. memory, attention, executive functioning), no significant effects were found. Lastly, separate analyses for healthy participants and neuropsychiatric patients also yielded no significant effects of the IBS length on anodal tDCS effects on cognition. Thus, our results demonstrate that the effect sizes of studies are independent from a long or short IBS. However, it may be beneficial to use moderate IBS lengths instead of really short IBS lengths (e.g. within the same day), considering issues such as practice effects, blinding and performance decay when cognitive-demanding tasks are applied in a short interval. Performing the same test in a short interval may lead to an increased performance due to practice effects (Falleti et al. 2006). However, if the interval is sufficiently long, these practice effect might decrease. Also, it might be possible that a very short IBS (i.e., within the same day) might lead to a more vulnerable blinding, as subjects are able to

compare between both sessions in a short interval. Nonetheless, our results show that a large IBS (i.e., more than one week) is not particularly more beneficial than a shorter (within the same week) interval. Consequently, we conclude that the IBS does not significantly contribute to the cognitive tDCS effects over the DLPFC. However, considering issues such as the study length, patients' adherence and intra-circadian biological rhythms we suggest that future tDCS trials opt to use relatively short IBS. However, this recommendation may not hold true for applying tDCS over non-DLPFC areas.

The anodal/cathodal tDCS effects on cognition are partly in line with the results of a recent meta-analysis. Brunoni and Vanderhasselt (2014) showed that tDCS decreased RTs, although it had no effect on accuracy. Differences in the inclusion criteria could explain the contradictory results considering the accuracy outcome between the current meta-analysis and the meta-analysis of Brunoni and Vanderhasselt (2014). Particularly, their meta-analysis assessed only the n-back task performance whereas the present meta-analysis was much more inclusive, evaluating working memory and other executive functions. In a different meta-analysis, Horvath et al. (2015) concluded that tDCS does not influence cognitive outcomes. Similar to the present study, Horvath et al. (2015) evaluated sham-controlled single-session tDCS data for a variety of cognitive outcomes. However, the authors used different categories and classified the tasks differently without basing their decision on a model or theory. Most importantly, the analyses were run differently as Horvath et al. (2015) made separate meta-analyses for each considered category (e.g. most meta-analyses included only three experiments or less). This way, the statistical power of their analyses was significantly decreased. Caution is therefore warranted when interpreting their results (for editorial replies, see Nitsche et al. 2015; Price and Hamilton 2015). In our study we have split all the data over three different task types without making subdivisions, but performed the meta-analyses on the totality of the studies. We also ran an omnibus meta-analysis for each cognitive outcome measure (RT and accuracy rate) for all tasks together, thereby including 188 trials for anodal tDCS and 45 trials for cathodal tDCS. The evaluation of such a large amount of trials, especially for anodal tDCS studies, adds to the firmness of the conclusion made by our systematic review. Moreover, our results are in line with previous research investigating the effects of tDCS neuromodulation on cognition, only showing a significant influence of anodal tDCS on cognition, and no effect of prefrontal cathodal tDCS (Jacobson et al. 2012).

This study has several limitations. First, the heterogeneity test was significant in trials investigating the effects of anodal and cathodal tDCS on accuracy, and trials investigating the influence of cathodal tDCS on RT, which can be attributed to methodological diversity in the original studies (Higgins and Green 2008). Because the tDCS technique has relatively low focality (i.e. neighboring brain regions such as the anterior temporal lobe region or

the premotor area might be influenced by DLPFC-tDCS; Nitsche et al. 2008), modulating cognitive abilities through DLPFC (i.e. tertiary association cortex) tDCS stimulation encompasses a wide array of cognitive functions, and research teams use diverse parameter settings, it could be expected that the data would be heterogeneous (Jacobson et al. 2012; Tremblay et al. 2014). Nonetheless, we used a random-effects model to account for such heterogeneity in our analyses and performed several sub-analyses to decrease variability even more (e.g. polarity; polarity x task type; polarity x condition; polarity x condition x task type). Furthermore, there was significant publication bias for the accuracy data, although the exclusion of the outliers identified in the funnel plot did not impact on our findings. Lastly, approximately half of the studies in this meta-analysis involved online data. Results of online tasks should be interpreted with caution because effects of tDCS might be occurring only several minutes following the end of tDCS stimulation, and not directly (Price and Hamilton 2015).

To conclude, the present study makes several noteworthy contributions to the field of neuromodulation. First, the study evaluated many trials (i.e. 188 trials on anodal tDCS data, 45 trials on cathodal tDCS data, and 233 trials in total), ensuring high power of the analysis and thus adding weight to the conclusion that IBS length has no effect on the modulation of cognitive outcomes by tDCS. We did not find an association between IBS and tDCS cognitive effects. We suggest that further studies should use relatively short IBS considering that some biological variables can change in the course of weeks. Furthermore, our study provides additional evidence with respect to the effect of tDCS on cognitive outcomes itself (i.e. significant difference anodal tDCS vs. sham for accuracy and RT, although slightly different effects are found for healthy vs. neuropsychiatric patients; but no significant influence of cathodal tDCS; see also Jacobson et al. 2012).

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FIGURE CAPTIONS

Fig. 1a Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Reaction Time (RT) from the Hedges g' random effects model. Positive values indicate an increase in reaction time following transcranial direct current stimulation (tDCS). Negative values indicate a decrease in reaction time following tDCS. Error bars: 95% confidence interval

Fig. 1b Plot of the meta-regression of the IBS length (in days) to the effect size (ES) for Reaction Time (RT) in anodal tDCS trials. The weight given each study is indicated by the diameter of the circle. The estimated slope of this curve shows no significant effects of IBS length on the effect sizes for RT results (IBS, Interval-Between-Sessions; SMD, Standard Mean Difference)

Fig. 2a Forest Plot showing effect sizes from the comparison between cathodal vs. sham tDCS for Reaction Time (RT) from the Hedges g' random effects model. Positive values indicate an increase in reaction time following transcranial direct current stimulation (tDCS). Negative values indicate a decrease in reaction time following tDCS. Error bars: 95% confidence interval

Fig. 2b Plot of the meta-regression of the IBS length (in days) to the effect size (ES) for Reaction Time (RT) in cathodal tDCS trials. The weight given each study is indicated by the diameter of the circle. The estimated slope of this curve shows no significant effects of IBS length on the effect sizes for RT results (IBS, Interval-Between-Sessions; SMD, Standard Mean Difference)

Fig. 3a Forest Plot showing effect sizes from the comparison between anodal vs. sham tDCS for Accuracy Rates (ACC) from the Hedges g' random effects model. Positive values indicate an increase in accuracy rates following transcranial direct current stimulation (tDCS). Negative values indicate a decrease in accuracy rates following tDCS. Error bars: 95% confidence interval

Fig. 3b Plot of the meta-regression of the IBS length (in days) to the effect size (ES) for Accuracy Rates (ACC) in anodal tDCS trials. The weight given each study is indicated by the diameter of the circle. The estimated slope of this curve shows no significant effects of IBS length on the effect sizes for ACC results (IBS, Interval-Between-Sessions; SMD, Standard Mean Difference)

Fig. 4a Forest Plot showing effect sizes from the comparison between cathodal vs. sham tDCS for Accuracy Rates (ACC) from the Hedges g' random effects model. Positive values indicate an increase in accuracy rates following transcranial direct current stimulation (tDCS). Negative values indicate a decrease in accuracy rates following tDCS. Error bars: 95% confidence interval

Fig. 4b Plot of the meta-regression of the IBS length (in days) to the effect size (ES) for Accuracy Rates (ACC) in cathodal tDCS trials. The weight given each study is indicated by the diameter of the circle. The estimated slope of this curve shows no significant effects of IBS length on the effect sizes for ACC results (IBS, Interval-Between-Sessions; SMD, Standard Mean Difference)

TABLE CAPTIONS

Table 1 Results of additional meta-regressions. Coefficient (SE) and p-values are provided. The coefficient represents the regression coefficient of each regression