J Neural Transm (2016) 123:1159–1172
DOI 10.1007/s00702-016-1558-x

PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - REVIEW ARTICLE

The effect of the interval-between-sessions on prefrontal transcranial direct current stimulation (tDCS) on cognitive outcomes: a systematic review and meta-analysis

Josefien Dedoncker[1,2] · Andre R. Brunoni[3] · Chris Baeken[1,2,4] · Marie-Anne Vanderhasselt[1,2,4,5]

Received: 26 January 2016 / Accepted: 15 April 2016 / Published online: 4 May 2016

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 1 h to up to 1 week (i.e. cathodal tDCS) or 2 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

Electronic supplementary material The online version of this article (doi:10.1007/s00702-016-1558-x) contains supplementary material, which is available to authorized users.

✉ Josefien Dedoncker
josefien.dedoncker@gmail.com

[1] Department of Psychiatry and Medical Psychology, University Hospital Ghent (UZ Ghent), Ghent University, 1K12F, De Pintelaan 185, 9000 Ghent, Belgium

[2] Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, Ghent, Belgium

[3] Service of Interdisciplinary Neuromodulation, Laboratory of Neurosciences (LIM-27), Department and Institute of Psychiatry, University of São Paulo, São Paulo, Brazil

[4] Faculty of Medicine and Pharmacy, Department of Psychiatry, University Hospital Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium

[5] Department of Experimental Clinical and Health Psychology, Ghent University, Ghent, Belgium

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, 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, 2012; Nelson et al. 2014; Nozari and Thompson-Schill 2013), memory and verbal processing (Fertonani et al. 2010, 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 et al. 2009; Boggio et al. 2006; Dockery et al. 2009; Filmer et al. 2013; Fregni et al. 2005; Gladwin et al. 2012a; Hammer et al. 2011; Harty et al. 2014; Hoy et al. 2014; Jo et al. 2009; Keshvari et al. 2013; Leite et al. 2011, 2013; Mulquiney et al. 2011; Penolazzi et al. 2010; Plewnia et al. 2013; Saidmanesh et al. 2012; Vanderhasselt et al. 2013a, b; 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 hammer 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 1 h (Fertonani et al. 2010; Fregni et al. 2005; Gladwin et al. 2012b; Knechtel et al. 2014a, b), to up to 2 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).

Materials 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.

Analyses were performed on the same dataset as reported in the recent meta-analysis by Dedoncker et al. (2016), examining the effects of DLPFC-targeted tDCS on cognition in healthy volunteers and psychiatric patients. In this latter meta-analysis, the role of stimulation parameters (e.g., density, duration, etc.) on these DLPFC-tDCS effects was explored, but as in the present paper the general effects on behavioral measures are first described. Therefore, in the current paper, main effects of tDCS on RT and ACC in the general population, and in healthy vs. neuropsychiatric populations separately, are reported without going into much detail. We refer to Dedoncker et al. (2016) for detailed analyses and a specific discussion of the results.

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. "48–72 h") or the minimum IBS length (e.g. "at least 48 h") that was used, the minimum length was used in our analysis (i.e. 48 h 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, five 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 s (Fregni et al. 2005; Mylius et al. 2012) up to 2 min and 45 s (Andrews et al. 2011; Hoy et al. 2013, 2014). However, in three studies tDCS was given with a placebo stimulator (Keeser et al. 2011; Balconi and Canavesio 2014; Balconi and Vitaloni 2013), while in one 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, 2014; Nieratschker et al. 2014; Plewnia et al. 2013; Teo et al. 2011; Turi et al. 2015; Wolkenstein and Plewnia 2013; Wolkenstein et al. 2014) or the person delivering tDCS was not the person analyzing the data (Kang et al. 2009, 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 min (Beeli et al. 2008) to 2 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 et al. 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 (see Dedoncker et al. 2016). 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) (see Dedoncker et al. 2016), 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 0.03–0.18, $p < 0.01$, Fig. 3a), i.e., participants responded significantly more correct after active vs. sham non-invasive brain stimulation (see Dedoncker et al. 2016). When splitting the data over the three task types an increase in the percentage of accurate responses in executive functioning tasks

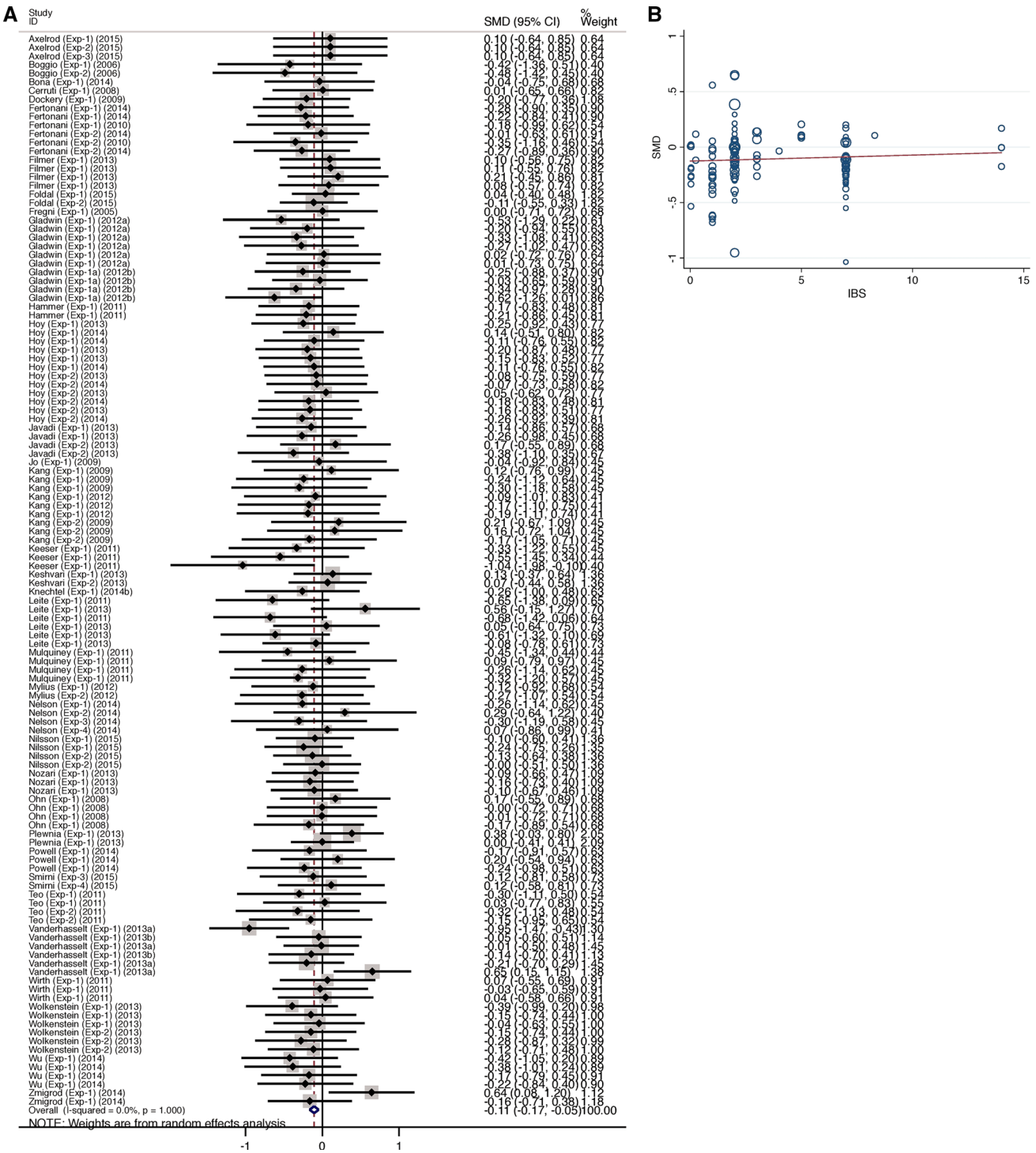


Fig. 1 **a** *Forest plot* showing the effect sizes from the comparison between anodal vs. sham tDCS for reaction time (RT) from the Hedges g' random effects model. *Positive* values indicate an increase in reaction time following transcranial direct current stimulation (tDCS). *Negative* values indicate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

following anodal tDCS (Cohen's d 0.08, 95 % CI 0.01–0.16, $p < 0.05$) 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

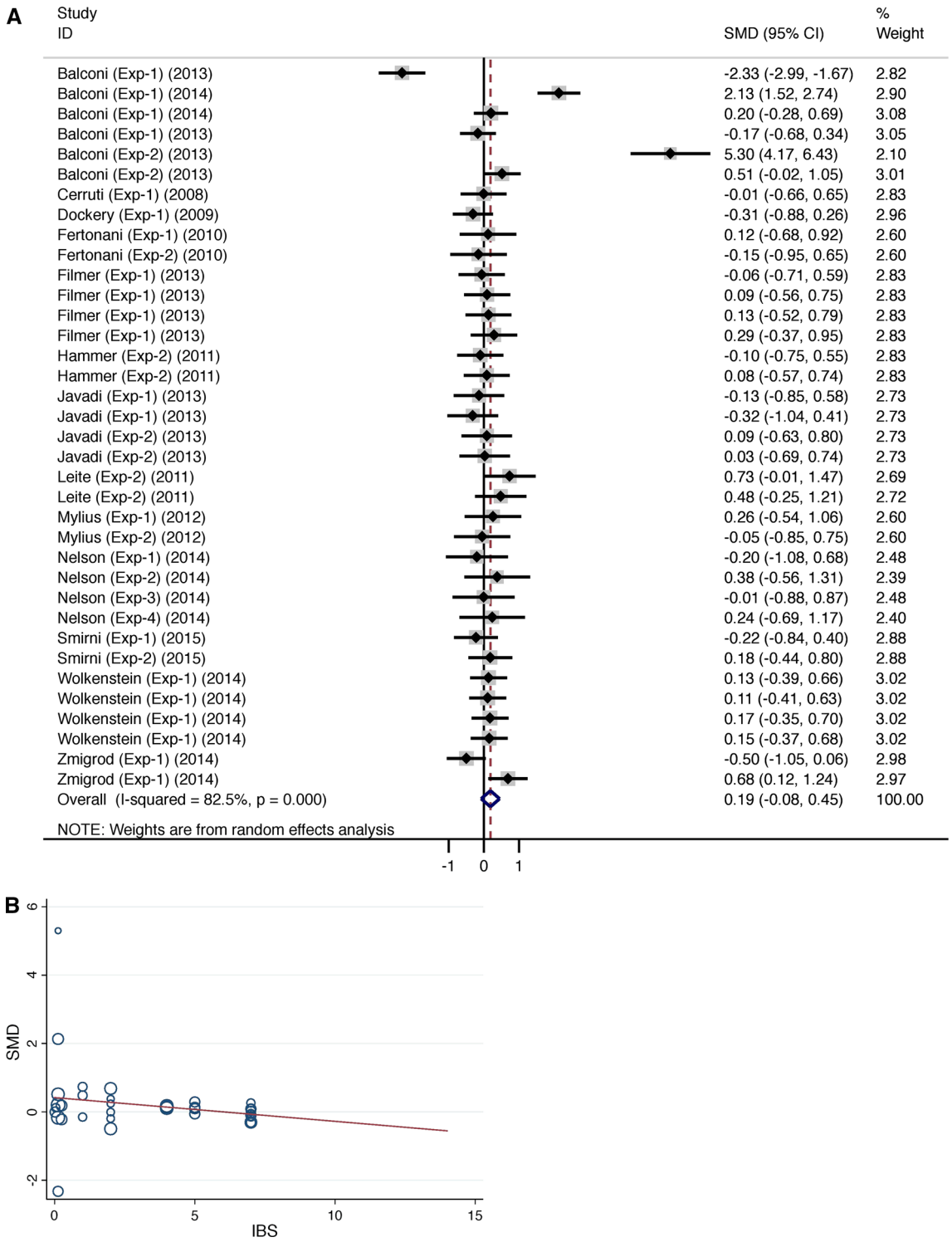
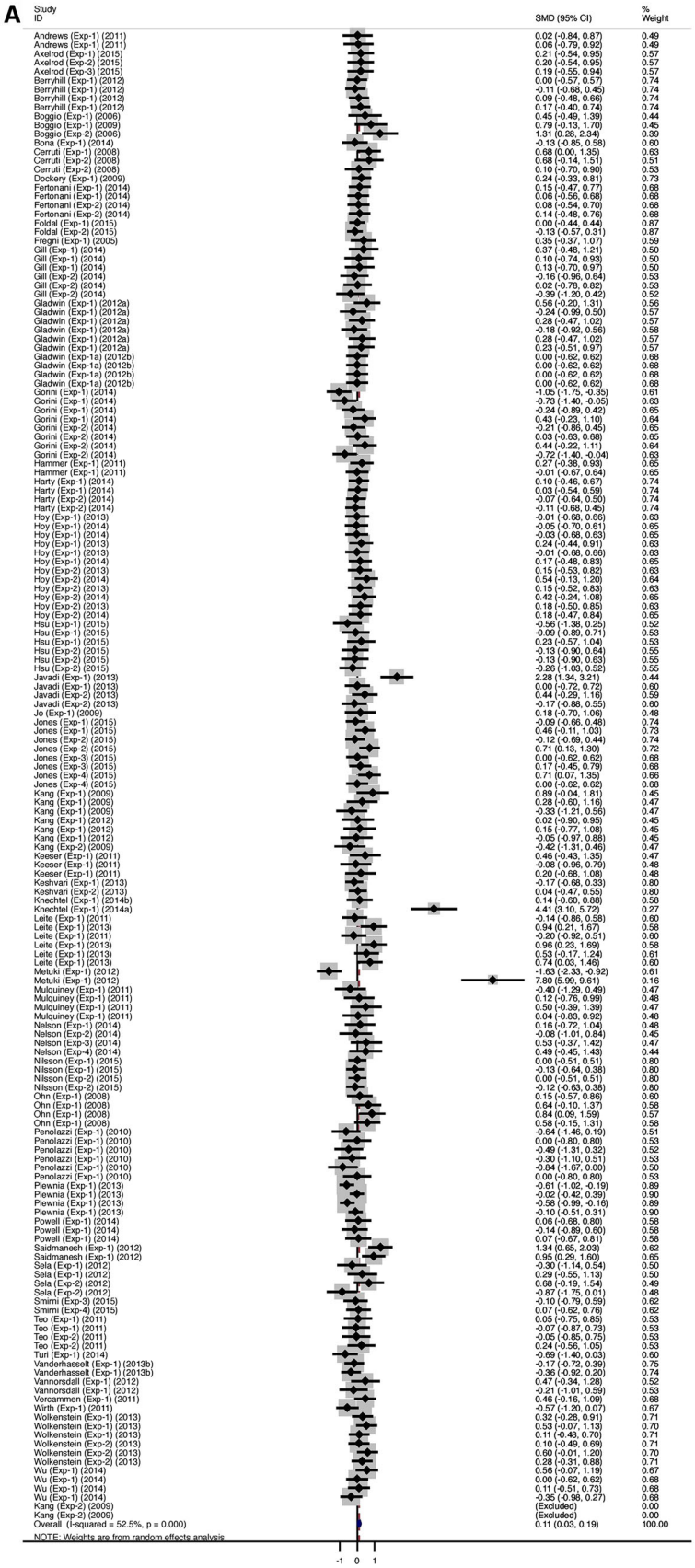


Fig. 2 **a** *Forest plot* showing effect sizes from the comparison between cathodal vs. sham tDCS for reaction time (RT) from the Hedges g' random effects model. *Positive* values indicate an increase in reaction time following transcranial direct current stimulation (tDCS). *Negative* values indicate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


A
Study ID
SMD (95% CI)
% Weight
Andrews (Exp-1) (2011) 0.02 (-0.84, 0.87) 0.49
Andrews (Exp-1) (2011) 0.06 (-0.79, 0.92) 0.49
Axelrod (Exp-1) (2015) 0.21 (-0.54, 0.95) 0.57
Axelrod (Exp-2) (2015) 0.20 (-0.54, 0.95) 0.57
Axelrod (Exp-3) (2015) 0.19 (-0.55, 0.94) 0.57
Berryhill (Exp-1) (2012) 0.00 (-0.57, 0.57) 0.74
Berryhill (Exp-1) (2012) -0.11 (-0.68, 0.45) 0.74
Berryhill (Exp-1) (2012) 0.09 (-0.48, 0.66) 0.74
Berryhill (Exp-1) (2012) 0.17 (-0.40, 0.74) 0.74
Boggio (Exp-1) (2006) 0.45 (-0.49, 1.39) 0.44
Boggio (Exp-1) (2009) 0.79 (-0.13, 1.70) 0.45
Boggio (Exp-2) (2006) 1.31 (0.28, 2.34) 0.39
Bona (Exp-1) (2014) -0.13 (-0.85, 0.58) 0.60
Cerruti (Exp-1) (2008) 0.68 (0.00, 1.35) 0.63
Cerruti (Exp-2) (2008) 0.68 (-0.14, 1.51) 0.51
Cerruti (Exp-2) (2008) 0.10 (-0.70, 0.90) 0.53
Dockery (Exp-1) (2009) 0.24 (-0.33, 0.81) 0.73
Fertonani (Exp-1) (2014) 0.15 (-0.47, 0.77) 0.68
Fertonani (Exp-1) (2014) 0.06 (-0.56, 0.68) 0.68
Fertonani (Exp-2) (2014) 0.08 (-0.54, 0.70) 0.68
Fertonani (Exp-2) (2014) 0.14 (-0.48, 0.76) 0.68
Foldal (Exp-1) (2015) 0.00 (-0.44, 0.44) 0.87
Foldal (Exp-2) (2015) -0.13 (-0.57, 0.31) 0.87
Fregni (Exp-1) (2005) 0.35 (-0.37, 1.07) 0.59
Gill (Exp-1) (2014) 0.37 (-0.48, 1.21) 0.50
Gill (Exp-1) (2014) 0.10 (-0.74, 0.93) 0.50
Gill (Exp-1) (2014) 0.13 (-0.70, 0.97) 0.50
Gill (Exp-2) (2014) -0.16 (-0.95, 0.64) 0.53
Gill (Exp-2) (2014) 0.02 (-0.78, 0.82) 0.53
Gill (Exp-2) (2014) -0.39 (-1.20, 0.42) 0.52
Gladwin (Exp-1) (2012a) 0.56 (-0.20, 1.31) 0.56
Gladwin (Exp-1) (2012a) -0.24 (-0.99, 0.50) 0.57
Gladwin (Exp-1) (2012a) 0.28 (-0.47, 1.02) 0.57
Gladwin (Exp-1) (2012a) -0.18 (-0.92, 0.56) 0.58
Gladwin (Exp-1) (2012a) 0.28 (-0.47, 1.02) 0.57
Gladwin (Exp-1) (2012a) 0.23 (-0.51, 0.97) 0.57
Gladwin (Exp-1a) (2012b) 0.00 (-0.62, 0.62) 0.68
Gladwin (Exp-1a) (2012b) 0.00 (-0.62, 0.62) 0.68
Gladwin (Exp-1a) (2012b) 0.00 (-0.62, 0.62) 0.68
Gladwin (Exp-1a) (2012b) 0.00 (-0.62, 0.62) 0.68
Gorini (Exp-1) (2014) -1.05 (-1.75, -0.35) 0.61
Gorini (Exp-1) (2014) -0.73 (-1.40, -0.05) 0.63
Gorini (Exp-1) (2014) -0.24 (-0.89, 0.42) 0.65
Gorini (Exp-1) (2014) 0.43 (-0.23, 1.10) 0.64
Gorini (Exp-2) (2014) -0.21 (-0.86, 0.45) 0.65
Gorini (Exp-2) (2014) 0.03 (-0.63, 0.68) 0.65
Gorini (Exp-2) (2014) 0.44 (-0.22, 1.11) 0.64
Gorini (Exp-2) (2014) -0.72 (-1.40, -0.04) 0.63
Hammer (Exp-1) (2011) 0.27 (-0.38, 0.93) 0.65
Hammer (Exp-1) (2011) -0.01 (-0.67, 0.64) 0.65
Harty (Exp-1) (2014) 0.10 (-0.46, 0.67) 0.74
Harty (Exp-1) (2014) 0.03 (-0.54, 0.59) 0.74
Harty (Exp-2) (2014) -0.07 (-0.64, 0.50) 0.74
Harty (Exp-2) (2014) -0.11 (-0.68, 0.45) 0.74
Hoy (Exp-1) (2013) -0.01 (-0.68, 0.66) 0.63
Hoy (Exp-1) (2014) -0.05 (-0.70, 0.61) 0.65
Hoy (Exp-1) (2014) -0.03 (-0.68, 0.63) 0.65
Hoy (Exp-1) (2013) 0.24 (-0.44, 0.91) 0.63
Hoy (Exp-1) (2013) -0.01 (-0.68, 0.66) 0.63
Hoy (Exp-1) (2014) 0.17 (-0.48, 0.83) 0.65
Hoy (Exp-2) (2013) 0.15 (-0.53, 0.82) 0.63
Hoy (Exp-2) (2014) 0.54 (-0.13, 1.20) 0.64
Hoy (Exp-2) (2013) 0.15 (-0.52, 0.83) 0.63
Hoy (Exp-2) (2014) 0.42 (-0.24, 1.08) 0.65
Hoy (Exp-2) (2013) 0.18 (-0.50, 0.85) 0.63
Hoy (Exp-2) (2014) 0.18 (-0.47, 0.84) 0.65
Hsu (Exp-1) (2015) -0.56 (-1.38, 0.25) 0.52
Hsu (Exp-1) (2015) -0.09 (-0.89, 0.71) 0.53
Hsu (Exp-1) (2015) 0.23 (-0.57, 1.04) 0.53
Hsu (Exp-2) (2015) -0.13 (-0.90, 0.64) 0.55
Hsu (Exp-2) (2015) -0.13 (-0.90, 0.63) 0.55
Hsu (Exp-2) (2015) -0.26 (-1.03, 0.52) 0.55
Javadi (Exp-1) (2013) 2.28 (1.34, 3.21) 0.44
Javadi (Exp-1) (2013) 0.00 (-0.72, 0.72) 0.60
Javadi (Exp-2) (2013) 0.44 (-0.29, 1.16) 0.59
Javadi (Exp-2) (2013) -0.17 (-0.88, 0.55) 0.60
Jo (Exp-1) (2009) 0.18 (-0.70, 1.06) 0.48
Jones (Exp-1) (2015) -0.09 (-0.66, 0.48) 0.74
Jones (Exp-1) (2015) 0.46 (-0.11, 1.03) 0.73
Jones (Exp-2) (2015) -0.12 (-0.69, 0.44) 0.74
Jones (Exp-2) (2015) 0.71 (0.13, 1.30) 0.72
Jones (Exp-3) (2015) 0.00 (-0.62, 0.62) 0.68
Jones (Exp-3) (2015) 0.17 (-0.45, 0.79) 0.68
Jones (Exp-4) (2015) 0.71 (0.07, 1.35) 0.66
Jones (Exp-4) (2015) 0.00 (-0.62, 0.62) 0.68
Kang (Exp-1) (2009) 0.89 (-0.04, 1.81) 0.45
Kang (Exp-1) (2009) 0.28 (-0.60, 1.16) 0.47
Kang (Exp-1) (2009) -0.33 (-1.21, 0.56) 0.47
Kang (Exp-1) (2012) 0.02 (-0.90, 0.95) 0.45
Kang (Exp-1) (2012) 0.15 (-0.77, 1.08) 0.45
Kang (Exp-1) (2012) -0.05 (-0.97, 0.88) 0.45
Kang (Exp-2) (2009) -0.42 (-1.31, 0.46) 0.47
Keeser (Exp-1) (2011) 0.46 (-0.43, 1.35) 0.47
Keeser (Exp-1) (2011) -0.08 (-0.96, 0.79) 0.48
Keeser (Exp-1) (2011) 0.20 (-0.68, 1.08) 0.48
Keshvari (Exp-1) (2013) -0.17 (-0.88, 0.33) 0.80
Keshvari (Exp-2) (2013) 0.04 (-0.47, 0.55) 0.80
Knechtel (Exp-1) (2014b) 0.14 (-0.60, 0.88) 0.58
Knechtel (Exp-1) (2014a) 4.41 (3.10, 5.72) 0.27
Leite (Exp-1) (2011) -0.14 (-0.86, 0.58) 0.60
Leite (Exp-1) (2013) 0.94 (0.21, 1.67) 0.58
Leite (Exp-1) (2011) -0.20 (-0.92, 0.51) 0.60
Leite (Exp-1) (2013) 0.96 (0.23, 1.69) 0.58
Leite (Exp-1) (2013) 0.53 (-0.17, 1.24) 0.61
Leite (Exp-1) (2013) 0.74 (0.03, 1.46) 0.60
Metuki (Exp-1) (2012) -1.63 (-2.33, -0.92) 0.61
Metuki (Exp-1) (2012) 7.80 (5.99, 9.61) 0.16
Mulquiney (Exp-1) (2011) -0.40 (-1.29, 0.49) 0.47
Mulquiney (Exp-1) (2011) 0.12 (-0.76, 0.99) 0.48
Mulquiney (Exp-1) (2011) 0.50 (-0.39, 1.39) 0.47
Mulquiney (Exp-1) (2011) 0.04 (-0.83, 0.92) 0.48
Nelson (Exp-1) (2014) 0.16 (-0.72, 1.04) 0.48
Nelson (Exp-2) (2014) -0.08 (-1.01, 0.84) 0.45
Nelson (Exp-3) (2014) 0.53 (-0.37, 1.42) 0.47
Nelson (Exp-4) (2014) 0.49 (-0.45, 1.43) 0.44
Nilsson (Exp-1) (2015) 0.00 (-0.51, 0.51) 0.80
Nilsson (Exp-1) (2015) -0.13 (-0.64, 0.38) 0.80
Nilsson (Exp-2) (2015) 0.00 (-0.51, 0.51) 0.80
Nilsson (Exp-2) (2015) -0.12 (-0.63, 0.38) 0.80
Ohn (Exp-1) (2008) 0.15 (-0.57, 0.86) 0.60
Ohn (Exp-1) (2008) 0.64 (-0.10, 1.37) 0.58
Ohn (Exp-1) (2008) 0.84 (0.09, 1.59) 0.57
Ohn (Exp-1) (2008) 0.58 (-0.15, 1.31) 0.58
Penolazzi (Exp-1) (2010) -0.64 (-1.46, 0.19) 0.51
Penolazzi (Exp-1) (2010) 0.00 (-0.80, 0.80) 0.53
Penolazzi (Exp-1) (2010) -0.49 (-1.31, 0.32) 0.52
Penolazzi (Exp-1) (2010) -0.30 (-1.10, 0.51) 0.53
Penolazzi (Exp-1) (2010) -0.84 (-1.67, 0.00) 0.50
Penolazzi (Exp-1) (2010) 0.00 (-0.80, 0.80) 0.53
Plewnia (Exp-1) (2013) -0.61 (-1.02, -0.19) 0.89
Plewnia (Exp-1) (2013) -0.02 (-0.42, 0.39) 0.90
Plewnia (Exp-1) (2013) -0.58 (-0.99, -0.16) 0.89
Plewnia (Exp-1) (2013) -0.10 (-0.51, 0.31) 0.90
Powell (Exp-1) (2014) 0.06 (-0.68, 0.80) 0.58
Powell (Exp-1) (2014) -0.14 (-0.89, 0.60) 0.58
Powell (Exp-1) (2014) 0.07 (-0.67, 0.81) 0.58
Saidmanesh (Exp-1) (2012) 1.34 (0.65, 2.03) 0.62
Saidmanesh (Exp-1) (2012) 0.95 (0.29, 1.60) 0.65
Sela (Exp-1) (2012) -0.30 (-1.14, 0.54) 0.50
Sela (Exp-1) (2012) 0.29 (-0.55, 1.13) 0.50
Sela (Exp-2) (2012) 0.68 (-0.19, 1.54) 0.49
Sela (Exp-2) (2012) -0.87 (-1.75, 0.01) 0.48
Smirni (Exp-3) (2015) -0.10 (-0.79, 0.59) 0.62
Smirni (Exp-4) (2015) 0.07 (-0.62, 0.76) 0.62
Teo (Exp-1) (2011) 0.05 (-0.75, 0.85) 0.53
Teo (Exp-1) (2011) -0.07 (-0.87, 0.73) 0.53
Teo (Exp-2) (2011) -0.05 (-0.85, 0.75) 0.53
Teo (Exp-2) (2011) 0.24 (-0.56, 1.05) 0.53
Turi (Exp-1) (2014) -0.69 (-1.40, 0.03) 0.60
Vanderhasselt (Exp-1) (2013b) -0.17 (-0.72, 0.39) 0.75
Vanderhasselt (Exp-1) (2013b) -0.36 (-0.92, 0.20) 0.74
Vannorsdall (Exp-1) (2012) 0.47 (-0.34, 1.28) 0.52
Vannorsdall (Exp-1) (2012) -0.21 (-1.01, 0.59) 0.53
Vercammen (Exp-1) (2011) 0.46 (-0.16, 1.09) 0.68
Wirth (Exp-1) (2011) -0.57 (-1.20, 0.07) 0.67
Wolkenstein (Exp-1) (2013) 0.32 (-0.28, 0.91) 0.71
Wolkenstein (Exp-1) (2013) 0.53 (-0.07, 1.13) 0.70
Wolkenstein (Exp-1) (2013) 0.11 (-0.48, 0.70) 0.71
Wolkenstein (Exp-2) (2013) 0.10 (-0.49, 0.69) 0.71
Wolkenstein (Exp-2) (2013) 0.60 (-0.01, 1.20) 0.70
Wolkenstein (Exp-2) (2013) 0.28 (-0.31, 0.88) 0.71
Wu (Exp-1) (2014) 0.56 (-0.07, 1.19) 0.67
Wu (Exp-1) (2014) 0.00 (-0.62, 0.62) 0.68
Wu (Exp-1) (2014) 0.11 (-0.51, 0.73) 0.68
Wu (Exp-1) (2014) -0.35 (-0.98, 0.27) 0.68
Kang (Exp-2) (2009) (Excluded) 0.00
Kang (Exp-2) (2009) (Excluded) 0.00
Overall (I-squared = 52.5%, p = 0.000) 0.11 (0.03, 0.19) 100.00
NOTE: Weights are from random effects analysis
-1
0
1
B
SMD
IBS
-2
0
2
4
6
8
0
5
10
15

◀**Fig. 3** **a** *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. **b** *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)

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) (see Dedoncker et al. 2016). 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).

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 (for a detailed meta-analysis) 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).

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

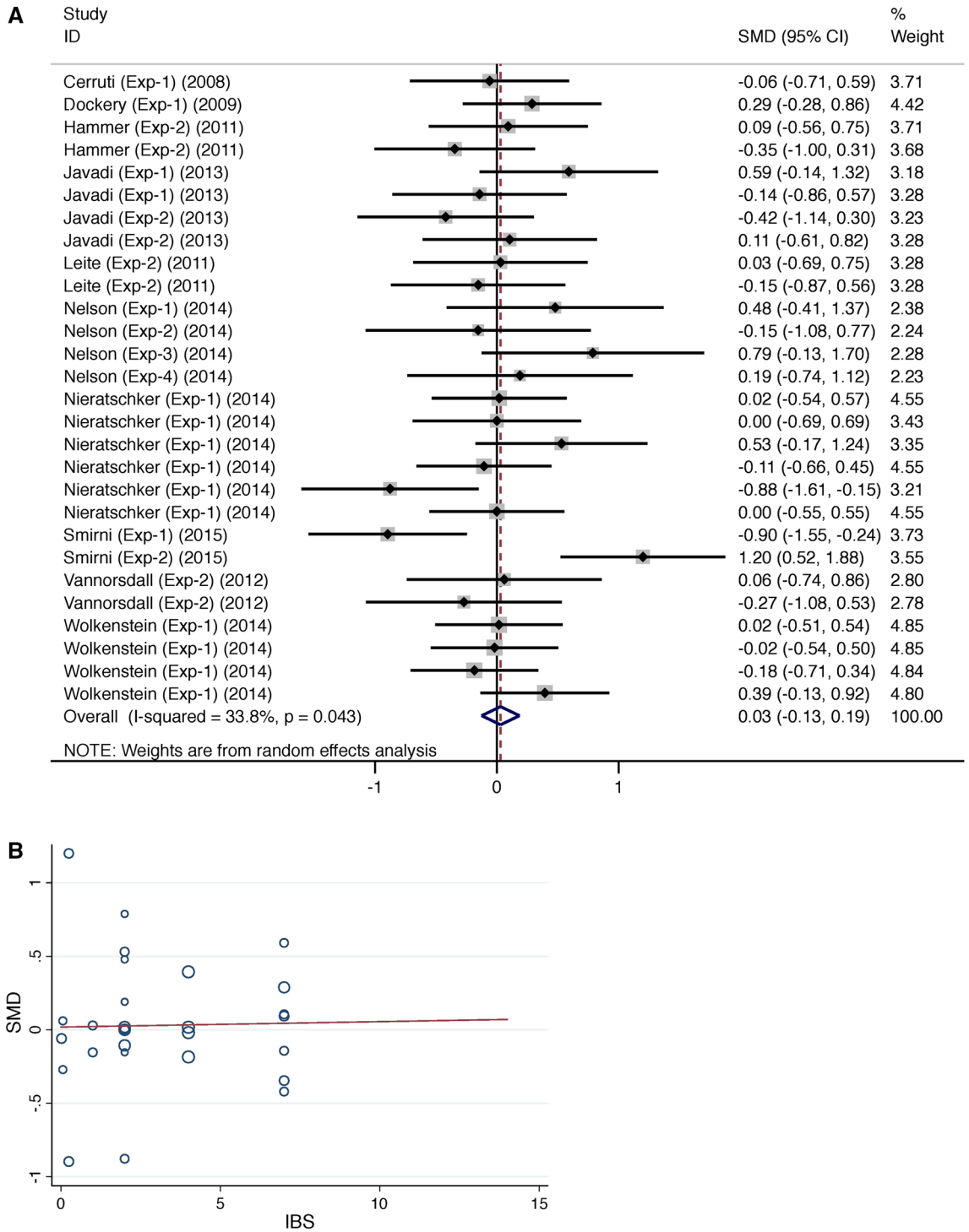


Fig. 4 **a** *Forest plot* showing effect sizes from the comparison between cathodal vs. sham tDCS for accuracy rates (ACC) from the Hedges g' random effects model. *Positive* values indicate an increase in accuracy rates following transcranial direct current stimulation (tDCS). *Negative* values indicate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

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

Table 1 Results of additional meta-regressions

	Anodal tDCS				Cathodal tDCS			
	RT		ACC		RT		ACC	
	Coef. (SE)	*p* value	Coef. (SE)	*p* value	Coef. (SE)	*p* value	Coef. (SE)	*p* value
Age	−0.001 (0.002)	0.76	0.001 (0.002)	0.72	−0.007 (0.05)	0.90	0.006 (0.022)	0.79
Healthy vs. patients[a]	0.047 (0.080)	0.58	−0.15 (0.11)	0.19	–	–	–	–
% Female	−0.0004 (0.002)	0.81	0.002 (0.002)	0.33	−0.006 (0.009)	0.51	−0.005 (0.005)	0.30

Coefficient (SE) and *p* values are provided. The coefficient represents the regression coefficient of each regression

ACC accuracy, *Coef* coefficient, *RT* response time, *SE* standard error

[a] Meta-regression of the variable "Healthy vs. Patients" could not be performed for cathodal tDCS trials, since only healthy participants were included (i.e. collinearity)

subjects are able to compare between both sessions in a short interval. Nonetheless, our results show that a large IBS (i.e., more than 1 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 × task type; polarity × condition; polarity × condition × 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).

Acknowledgments M.A.V. (FWO08/PDO/168) is a postdoctoral research fellow of the Research Foundation Flanders (FWO). A.R.B. is supported by the following grants: 2013 NARSAD Young Investigator from the Brain & Behavior Research Foundation (Grant Number 20493), 2012 FAPESP Young Researcher from the São Paulo State Foundation (Grant Number 20911-5) and National Council for Scientific and Technological Development (CNPq, Grant Number 470904). This work was also supported by the Ghent University Multidisciplinary Research Partnership "The integrative neuroscience of behavioral control".

Compliance with ethical standards

Conflict of interest There were no conflicts of interest.

References

Andrews SC, Hoy KE, Enticott PG et al (2011) Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 4(2):84–89

Axelrod V, Rees G, Lavidor M, Bar M (2015) Increasing propensity to mind-wander with transcranial direct current stimulation. PNAS 112(11):3314–3319

Balconi M, Canavesio Y (2014) The contribution of dorsolateral prefrontal cortex and temporoparietal areas in processing instrumental versus functional semantic violations in action representation. J Clin Exp Neuropsychol 36(7):701–715

Balconi M, Vitaloni S (2013) Dorsolateral pFC and the representation of the incorrect use of an object: The transcranial direct current stimulation effect on n400 for visual and linguistic stimuli. J Cogn Neurosci 26(2):305–318

Beeli G, Casutt G, Baumgartner T, Jäncke L (2008) Modulating presence and impulsiveness by external stimulation of the brain. Behav Brain Funct 4(1):1

Berryhill M, Jones K (2012) tDCS selectively improves working memory in older adults with more education. Neurosci Lett 521(2):148–151

Boggio PS, Ferrucci R, Rigonatti SP et al (2006) Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 249(1):31–38

Boggio PS, Khoury LP, Martins DC et al (2009) Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J Neurol Neurosur Ps 80(4):444–447

Bona S, Silvanto J (2014) Accuracy and confidence of visual short-term memory do not go hand-in-hand: behavioral and neural dissociations. PLoS One 9(3):e90808

Brunoni AR, Vanderhasselt MA (2014) Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cognit 86:1–9

Brunoni AR, Nitsche MA, Bolognini N et al (2012) Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimul 5(3):175–195

Cerruti C, Schlaug G (2009) Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci 21(10):1980–1987

Cohen R, Sparling-Cohen Y, O'Donnell B (1993) The neuropsychology of attention. Plenum Press, New York

Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA (2016) A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. Brain Stimul. doi:10.1016/j.brs.2016.04.006

Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C (2009) Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 29(22):7271–7277

Falleti MG, Maruff P, Collie A, Darby DG (2006) Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-min, 1 week and 1 month test–retest intervals. J Clin Exp Neuropsychol 28(7):1095–1112

Fertonani A, Rosini S, Cotelli M et al (2010) Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 208(2):311–318

Fertonani A, Brambilla M, Cotelli M, Miniussi C (2014) The timing of cognitive plasticity in physiological aging: a tDCS study of naming. Front Aging Neurosci 6(131):10–3389

Filmer HL, Mattingley JB, Dux PE (2013) Improved multitasking following prefrontal tDCS. Cortex 49(10):2845–2852

Fregni F, Boggio PS, Nitsche M et al (2005) Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 166(1):23–30

Gill J, Shah-Basak PP, Hamilton R (2014) It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul 8(2):253–259

Gladwin TE, den Uyl TE, Wiers RW (2012a) Anodal tDCS of dorsolateral prefontal cortex during an implicit association test. Neurosci Lett 517(2):82–86

Gladwin TE, den Uyl TE, Fregni FF, Wiers RW (2012b) Enhancement of selective attention by tDCS: interaction with interference in a Sternberg Task. Neurosci Lett 512(1):33–37

Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G (2014) Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front Hum Neurosci 8:661

Hammer A, Mohammadi B, Schmicker M, Saliger S, Münte TF (2011) Errorless and errorful learning modulated by transcranial direct current stimulation. BMC Neurosci 12(1):72

Harty S, Robertson IH, Miniussi C et al (2014) Transcranial direct current stimulation over right dorsolateral prefrontal cortex enhances error awareness in older age. J Neurosci 34(10):3646–3652

Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions, vol 5. Wiley-Blackwell, Chichester

Horvath JC, Carter O, Forte JD (2014) Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). Front Syst Neurosci 8:2

Horvath JC, Forte JD, Carter O (2015) Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul 8(3):535–550

Hoy KE, Emonson MR, Arnold SL et al (2013) Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia 51(9):1777–1784

Hoy KE, Arnold SL, Emonson MR et al (2014) An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr Res 155(1):96–100

Hsu WY, Zanto TP, Anguera JA et al (2015) Delayed enhancement of multitasking performance: effects of anodal transcranial direct current stimulation on the prefrontal cortex. Cortex 69:175–185

Jacobson L, Koslowsky M, Lavidor M (2012) tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 216(1):1–10

Javadi AH, Cheng P (2013) Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. Brain Stimul 6(4):668–674

Jo JM, Kim YH, Ko MH et al (2009) Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehab 88(5):404–409

Jones K, Gözenman F, Berryhill ME (2015) The strategy and motivational influences on the beneficial effect of neurostimulation: a tDCS and fNIRS study. Neuroimage 105:238–247

Kang EK, Baek MJ, Kim SY, Paik NJ (2009) Non-invasive cortical stimulation improves post-stroke attention decline. Restor Neurol Neurosci 27(6):647–652

Kang EK, Kim DY, Paik NJ (2012) Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. J Rehabil Med 44(4):346–350

Keeser D, Padberg F, Reisinger E et al (2011) Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA). NeuroImage 55(2):644–657

Keshvari F, Pouretemad HR, Ekhtiari H (2013) The polarity-dependent effects of the bilateral brain stimulation on working memory. Basic Clin Neurosci 4(3):224

Knechtel L, Schall U, Cooper G et al (2014a) Transcranial direct current stimulation of prefrontal cortex: an auditory event-related potential and proton magnetic resonance spectroscopy study. Neurol Psychiatry Brain Res 20(4):96–101

Knechtel L, Thienel R, Cooper G et al (2014b) Transcranial direct current stimulation of prefrontal cortex: an auditory event-related potential study in schizophrenia. Neurol Psychiatry Brain Res 20(4):102–106

Leite J, Carvalho S, Fregni F, Gonçalves OF (2011) Task-specific effects of tDCS-induced cortical excitability changes on cognitive and motor sequence set shifting performance. PLoS One 6(9):e24140

Leite J, Carvalho S, Fregni F et al (2013) The effects of cross-hemispheric dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS) on task switching. Brain Stimul 6(4):660–667

Liberati A, Altman DG, Tetzlaff J et al (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151(4):W-65

Liebetanz D, Nitsche MA, Tergau F, Paulus W (2002) Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 125(10):2238–2247

Metuki N, Sela T, Lavidor M (2012) Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. Brain Stimul 5(2):110–115

Miyake A, Friedman NP, Emerson MJ et al (2000) The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 41(1):49–100

Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB (2011) Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clin Neurophysiol 122(12):2384–2389

Mylius V, Jung M, Menzler K et al (2012) Effects of transcranial direct current stimulation on pain perception and working memory. Eur J Pain 16:974–982

Nelson JT, McKinley RA, Golob EJ et al (2014) Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 85:909–917

Nieratschker V, Kiefer C, Giel K et al (2014) The COMT Val/Met polymorphism modulates effects of tDCS on response inhibition. Brain Stimul 8(2):283–288

Nilsson J, Lebedev AV, Lövdén M (2015) No significant effect of prefrontal tDCS on working memory performance in older adults. Front Aging Neurosci 7:230

Nitsche MA, Paulus W (2000) Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 527(3):633–639

Nitsche MA, Paulus W (2001) Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 57(10):1899–1901

Nitsche MA, Nitsche MS, Klein CC et al (2003) Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 114(4):600–604

Nitsche MA, Cohen LG, Wassermann EM et al (2008) Transcranial direct current stimulation: state of the art 2008. Brain Stimul 1(3):206–223

Nitsche MA, Bikson M, Bestmann S (2015) On the use of meta-analysis in neuromodulatory non-invasive brain stimulation. Brain Stimul 8(3):66

Nozari N, Thompson-Schill SL (2013) More attention when speaking: does it help or does it hurt? Neuropsychologia 51(13):2770–2780

Ohn SH, Park CI, Yoo WK et al (2008) Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. NeuroReport 19(1):43–47

Penolazzi B, Di Domenico A, Marzoli D et al (2010) Effects of transcranial direct current stimulation on episodic memory related to emotional visual stimuli. PLoS One 5(5):e10623

Plewnia C, Zwissler B, Längst I et al (2013) Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/Met polymorphism. Cortex 49(7):1801–1807

Powell TY, Boonstra TW, Martin DM et al (2014) Modulation of cortical activity by transcranial direct current stimulation in patients with affective disorder. PLoS One 9(6):e98503

Price AR, Hamilton RH (2015) A re-evaluation of the cognitive effects from single-session transcranial direct current stimulation. Brain Stimul 8(3):663–665

Purpura DP, McMurtry JG (1965) Intracellular activities and evoked potential changes during polarization of motor cortex. J Neurophysiol 28(1):166–185

Saidmanesh M, Pouretemad HR, Amini A et al (2012) Effects of transcranial direct current stimulation on working memory in patients with non-fluent aphasia disorder. Res J Biol Sci 7(7):290–296

Sela T, Ivry RB, Lavidor M (2012) Prefrontal control during a semantic decision task that involves idiom comprehension: a

transcranial direct current stimulation study. Neuropsychologia 50(9):2271–2280

Smirni D, Turriziani P, Mangano GR et al (2015) Modulating memory performance in healthy subjects with transcranial direct current stimulation over the right dorsolateral prefrontal cortex. PLoS One 10(12):e0144838

Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB (2011) Investigating the role of current strength in tDCS modulation of working memory performance in healthy controls. Front Psychiatry 2(45.10):1–6

Tremblay S, Lepage JF, Latulipe-Loiselle A et al (2014) The uncertain outcome of prefrontal tDCS. Brain Stimul 7(6):773–783

Turi Z, Mittner M, Opitz A et al (2015) Transcranial direct current stimulation over the left prefrontal cortex increases randomness of choice in instrumental learning. Cortex 63:145–154

Vanderhasselt MA, Brunoni AR, Loeys T et al (2013a) Nosce te ipsum–Socrates revisited? Controlling momentary ruminative self-referent thoughts by neuromodulation of emotional working memory. Neuropsychologia 51(13):2581–2589

Vanderhasselt MA, De Raedt R, Brunoni AR et al (2013b) tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. PLoS One 8(5):e62219

Vannorsdall TD, Schretlen DJ, Andrejczuk M et al (2012) Altering automatic verbal processes with transcranial direct current stimulation. Front Psychiatry 3:1–6

Vercammen A, Rushby JA, Loo C et al (2011) Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr Res 131(1):198–205

Wirth M, Rahman RA, Kuenecke J et al (2011) Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. Neuropsychologia 49(14):3989–3998

Wolkenstein L, Plewnia C (2013) Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol Psychiat 73(7):646–651

Wolkenstein L, Zeiller M, Kanske P, Plewnia C (2014) Induction of a depression-like negativity bias by cathodal transcranial direct current stimulation. Cortex 59:103–112

Wu YJ, Tseng P, Chang CF et al (2014) Modulating the interference effect on spatial working memory by applying transcranial direct current stimulation over the right dorsolateral prefrontal cortex. Brain Cognition 91:87–94

Zmigrod S, Colzato LS, Hommel B (2014) Evidence for a role of the right dorsolateral prefrontal cortex in controlling stimulus-response integration: a transcranial direct current stimulation (tDCS) study. Brain Stimul 7(4):516–520