Accepted for publication in *Brain Stimulation*

***Note*: This is an uncorrected version of an author's manuscript accepted for publication.*Copyediting, typesetting, and review of the resulting proofs will be undertaken on this manuscript before final publication. During production and pre-press, errors may be discovered that could affect the content.**

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

Josefien Dedoncker [a,b*], Andre R. Brunoni [c*], Chris Baeken [a,b,d], Marie-Anne Vanderhasselt [a,b,d,e]

(*) Both authors equally contributed to this work.

[a] Ghent University, University Hospital Ghent (UZ Ghent), Department of Psychiatry and Medical Psychology, Ghent, Belgium

[b] Ghent University, Ghent Experimental Psychiatry (GHEP) lab, Ghent, Belgium

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

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

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

*Corresponding authors: Josefien Dedoncker, MSc; Ghent University Hospital, 1K12F, De Pintelaan 185, 9000 Ghent, Belgium; E-mail: josefien.dedoncker@gmail.com; Tel: +32471520825; Andre Russowsky Brunoni, MD, PhD; Interdisciplinary Center for Applied Neuromodulation; Av. Professor Lineu Prestes, 2565, 3o andar, CEP 05508-000; São Paulo (SP), Brazil; E-mail: brunoni@usp.br; Tel/Fax: +55 11 3091-9241.

ACKNOWLEDGEMENTS

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”. There were no conflicts of interest.

ABSTRACT

Background: Research into the effects of transcranial direct current stimulation of the dorsolateral prefrontal cortex on cognitive functioning is increasing rapidly. However, methodological heterogeneity in prefrontal tDCS research is also increasing, particularly in technical stimulation parameters that might influence tDCS effects.

Objective: To systematically examine the influence of technical stimulation parameters on DLPFC-tDCS effects.

Methods: We performed a systematic review and meta-analysis of tDCS studies targeting the DLPFC published from the first data available to February 2016. Only single-session, sham-controlled, within-subject studies reporting the effects of tDCS on cognition in healthy controls and neuropsychiatric patients were included.

Results: Evaluation of 61 studies showed that after single-session a-tDCS, but not c-tDCS, participants responded faster and more accurately on cognitive tasks. Sub-analyses specified that following a-tDCS, healthy subjects responded faster, while neuropsychiatric patients responded more accurate. Importantly, different stimulation parameters affected a-tDCS effects, but not c-tDCS effects, on accuracy in healthy samples vs. patients: increased current density and density charge resulted in improved accuracy in healthy samples, most prominently in females; for neuropsychiatric patients, task performance during a-tDCS resulted in stronger increases in accuracy rates compared to task performance following a-tDCS.

Conclusions: Healthy participants respond faster, but not more accurate on cognitive tasks after a-tDCS. However, increasing the current density and/or charge might be able to enhance response accuracy, particularly in females. In contrast, online task performance leads to greater increases in response accuracy than offline task performance in neuropsychiatric patients. Possible implications and practical recommendations are discussed.

Keywords: Cognition; dorsolateral prefrontal cortex; meta-analysis; noninvasive brain stimulation; stimulation parameters; transcranial direct current stimulation.

Abbreviations: ACC, accuracy; DLPFC, dorsolateral prefrontal cortex; ER, error rate; ES, effect size; IBS, interval between sessions; mA, micro-Ampère; NIBS, non-invasive brain stimulation; rTMS, repetitive transcranial magnetic stimulation; RT, response time; SD, standard deviation; SMD, standardized mean difference; tDCS, transcranial direct current stimulation; WM, working memory.

1. INTRODUCTION

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (NIBS) technique that modulates spontaneous cortical activity using a low-intensity direct current (e.g. 1-2mA) [1]. First studies evaluated tDCS effects over the motor cortex [2,3]; although more recent research has also focused on its effects over the dorsolateral prefrontal cortex (DLPFC), particularly to treat psychiatric disorders [4] and to modulate cognitive performance [5–8]. These cognitive results can be useful to predict treatment outcome. For instance, a study in patients with major depression disorder suggested that the effects of repetitive transcranial magnetic stimulation (rTMS), another NIBS technique, on attentional control predicted the antidepressant response [9].

Nonetheless, although some studies showed that tDCS over the DLPFC is able to improve cognitive performance in both healthy and neuropsychiatric samples [10,11], recent meta-analyses revealed that the results are mixed – e.g., one study found that tDCS improves reaction time (RT) but not accuracy [12] in the n-back task [13]; whereas Hill et al. observed only modest benefits of tDCS on cognition following a single-session or repeated-sessions of anodal tDCS [14]. Importantly, in both meta-analyses the data were not analyzed separately for healthy participants and neuropsychiatric patients. However, another meta-analysis by Horvath et al. in healthy samples only, claimed that there is no evidence of cognitive effects of single-session anodal tDCS [15].

Possibly, these heterogeneous findings are associated to the diversity of stimulation parameters applied, such as stimulation polarity, position of reference electrode, session duration, current intensity and density, and the use of “offline” vs. “online” protocols [1]. There is an urgent need to better investigate whether these parameters influence on tDCS effects [16,17]. Therefore, we aimed to evaluate DLPFC-tDCS effects on cognition considering several methodological parameters that might influence the outcomes. We performed an exploratory review and meta-analysis of tDCS studies using single-session, sham-controlled within-subject designs that evaluate the effects of DLPFC stimulation on cognitive outcomes in healthy participants and neuropsychiatric patients. Because the intrapersonal variation is smaller in crossover as compared to parallel trials [18], only within-subject studies were included as this type of design has an increased power to detect small effects. Such approach also decreases overall meta-analysis heterogeneity. The study importance is to identify parameters particularly related to tDCS cognitive outcomes in order to design further, and more efficient, studies.

2. MATERIAL AND METHODS

The meta-analysis was conducted according to the recommendations of the Cochrane group guidelines [19] and the report follows the PRISMA guidelines [20]. Discrepancies were resolved by consensus.

2.1. Literature review

Articles published from the first data available to 5 February 2016 were selected based on a search of the PubMed, Web of Science, Google Scholar and Science Direct databases using the following key words: (1) "dorsolateral prefrontal cortex" OR "DLPFC", and (2) "transcranial" OR "transcranial direct current stimulation" OR "tDCS" OR "direct current stimulation". We also searched for additional references in retrieved articles and reviews. Subsequently, we checked each article according to our inclusion criteria.

2.2. Eligibility criteria

The included articles had to be single-session, sham-controlled and randomized within-subject studies, written in English. Further, the studies investigated the effects of tDCS on DLPFC in healthy participants or neuropsychiatric patients. We included all studies targeting the DLPFC. Nonetheless, as tDCS focality is relatively low and the nature the current stimulation pattern is diffuse, stimulation over other brain areas might also indirectly stimulate the DLPFC. However, including all tDCS studies that placed the electrodes over other brain areas possibly indirectly stimulating the DLPFC would be unfeasible. Thus, similarly to other meta-analyses [12,14], we decided a priori only to include studies that placed the active electrode (anode or cathode) over F3 or F4, corresponding to the DLPFC site. Lastly, data of the mean and standard deviation (SD) on cognitive outcomes had to be provided in the article or upon request. Duplicates, case studies, reviews, and unrelated studies were excluded.

2.3. Quality assessment

According to the Cochrane guidelines [19], we assessed the quality of the studies through the Cochrane risk of bias tool. Firstly, we evaluated whether randomization and/or counterbalancing was performed, and if the randomization method was properly concealed. Subsequently, we assessed if subjects and/or investigators were blind to the allocation group and if the sham method was reliable. Finally, we evaluated whether the authors obtained all relevant outcome data and reported on the results for all pre-defined primary objectives.

2.4. Data extraction

From each study, we extracted data of sample characteristics, study design, tDCS treatment characteristics and cognitive task characteristics. The cognitive tasks were categorized in: (1) memory [21], (2) attention [22], and (3) executive functioning [23]. For the cognitive outcomes, we extracted the mean and the corresponding standard deviation of the RT, and the percentage of correct responses (e.g. accuracy; ACC) post-tDCS (baseline cognitive outcome measures and error percentages were excluded from analysis, see suppl. material). Finally, data on perceived blinding and adverse effects were extracted.

2.5. Quantitative analysis

Stata software version 12 was used to perform all analyses (Statacorp, TX, USA). Anodal and cathodal trials were analyzed separately; i.e., we estimated the effect size for each trial that compared the effects of anodal and sham tDCS, and cathodal and sham tDCS on the cognitive outcomes. To this end, 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 were pooled using a random-effects model, weighted by the inverse variance method. To answer our research question, the ES was then plotted against each specific stimulation parameter of interest using meta-regression techniques. The Chi-square test was used to assess heterogeneity for each outcome. Egger's test was used to assess risk of publication bias. Regardless of whether the main effect of tDCS on cognition is significant or not, univariate meta-regression was used to assess heterogeneity and identify moderators influencing these results. The following variables were meta-regressed: stimulation intensity (continuous), density (continuous), density charge (continuous), stimulation duration (continuous), reference montage (cephalic vs. extra-cephalic), laterality (left vs. right DLPFC stimulation), and timing of tDCS (online vs. offline). Only one variable was meta-regressed at a time. Furthermore, for each of these variables in which the univariate result was significant ($p<0.05$), a multivariate meta-regression was performed including the variables age (continuous), clinical condition (healthy vs. psychiatric patients), gender (% females) and type of task (memory, attention or executive functioning).

3. RESULTS

3.1. Overview

We obtained 3119 references on Science Direct, Web of Science, Google Scholar and PubMed. However, 3018 studies were excluded after title and abstract review for reasons described earlier (cf. methods, eligibility criteria). Following a full-text evaluation, due to ineligibility, another 40 references were further excluded (for an overview, see Suppl. Table 1). In sum, 61 studies were included in the review (Fig. 1).

However, some studies reported more than one experiment (e.g. different samples), while many studies reported more than one comparison (e.g. 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; Table 1).

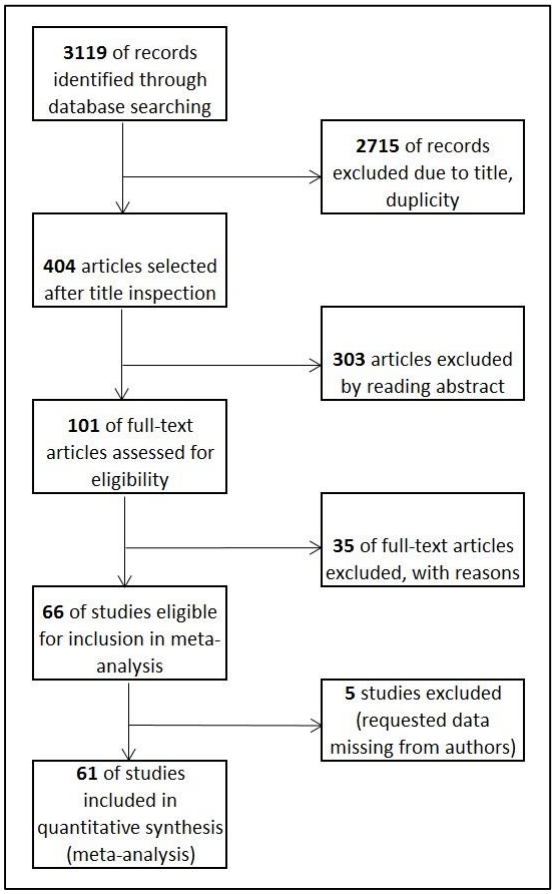

Fig. 1 Flow-chart of electronic database search strategy

Table 1. Characteristics of Studies Included in the Meta-Analysis. For each study included in the meta-analysis, the sample and the tDCS montage are described. (1) tDCS montage: electrode configuration (anode / cathode), current density (mA/cm²), duration of tDCS stimulation (in minutes, min.). (2) Sample: condition, number of participants (active / sham), proportion of females, age mean (M) and standard deviation (SD). The outcome measure is provided, as well as whether the task was administered online (during tDCS) or offline (following tDCS).

Author	Exp	Anode/cathode	Density (mA/cm²)	Duration (min)	Outcome	Online / Offline	Condition	N (a / s)	% Fem.	Age (M)	Age (SD)
Andrews (2011)[5]	1	F3 / rSO	0.03	10	Digit Span from WAIS III (forward)	Online	HV	11 / 10	60	28.1	8.72
	1	F3 / rSO	0.03	10	Digit Span from WAIS III (backward)	Online	HV	11 / 10	60	28.1	8.72
Axelrod (2015)[24]	1	F3 / rSO	0.06	20	Sustained Attention to Respond Task (SART)	Online	HV	14 / 14	42.86	24.4	3.71
	2	F3 / rSO	0.06	20	Sustained Attention to Respond Task (SART)	Online	HV	14 / 14	42.86	24.4	3.71
	3	F3 / rSO	0.06	20	Sustained Attention to Respond Task (SART)	Offline	HV	14 / 14	42.86	24.4	3.71
Balconi (2014) [25]	1	rSO / F3	0.06	13	Detection task: Picture - Congruent action	Offline	HV	33 / 33	54.55	23.44	0.88
	1	rSO / F3	0.06	13	Detection task: Picture - Incongruent action	Offline	HV	33 / 33	54.55	23.44	0.88
Balconi (2013) [26]	1	rSO / F3	0.06	15	Detection task: Picture – Congruence	Offline	HV	30 / 30	60	24.22	2.77
	1	rSO / F3	0.06	15	Detection task: Picture – Incongruence	Offline	HV	30 / 30	60	24.22	2.77
	2	rSO / F3	0.06	15	Detection task: Sentence – Congruence	Offline	HV	28 / 28	50	24.18	2.13
	2	rSO / F3	0.06	15	Detection task: Sentence – Incongruence	Offline	HV	28 / 28	50	24.18	2.13
Beeli (2008) [27]	1	F3 / Ipsil. Mastoid	0.04	5.5	Go/NoGo	Online	HV	35 / 35	48.57	24.9	3.7
	1	Ipsil. Mastoid / F3	0.04	5.5	Go/NoGo	Online	HV	35 / 35	48.57	24.9	3.7
Berryhill (2012) [28]	1	F3 / Contr. Cheeck	0.04	10	Visual 2-Back	Online	HV	24 / 24	50	63.7	5.8
	1	F3 / Contr. Cheeck	0.04	10	Verbal 2-Back	Online	HV	24 / 24	50	63.7	5.8
	1	F4 / Contr. Cheeck	0.04	10	Visual 2-Back	Online	HV	24 / 24	50	63.7	5.8
	1	F4 / Contr. Cheeck	0.04	10	Verbal 2-Back	Online	HV	24 / 24	50	63.7	5.8
Boggio (2006) [29]	1	F3 / rSO	0.03	20	3-Back	Online	PD	9 / 9	44	59.2	9.9
	2	F3 / rSO	0.06	20	3-Back	Online	PD	9 / 9	22	61	12.1

Boggio (2009) [30]	1	F3 / rSO	0.06	30	Visual recognition memory	Online	AD	10 / 10	60	79.1	8.8
Bona (2014)[31]	1	F4 / lSO	0.06	20	Visual short term memory (VSTM)	Offline	HV	15 / 15	53.33	25.13	3.76
	1	F3 / rSO	0.06	20	Remote Associates test (RAT)	Offline	HV	18 / 18	72.22	25.5	2.6
Cerruti (2008) [32]	1	rSO / F3	0.06	20	Remote Associates test (RAT)	Offline	HV	18 / 18	72.22	25.5	2.6
	2	F3 / rSO	0.06	20	Remote Associates test (RAT)	Offline	HV	12 / 12	25	25.4	4.5
	2	F4 / lSO	0.06	20	Remote Associates test (RAT)	Offline	HV	12 / 12	25	25.4	4.5
Dockery (2009) [33]	1	F3 / rSO	0.03	15	Tower of London (TOL)	Online	HV	24 / 24	79.17	24	3.16
	1	rSO / F3	0.03	15	Tower of London (TOL)	Online	HV	24 / 24	79.17	24	3.16
Fertonani (2014) [34]	1	F3 / Extra-cephalic	0.06	4	Picture naming task	Online	HV	20 / 20	50	21.2	0.9
	1	F3 / Extra-cephalic	0.06	10	Picture naming task	Offline	HV	20 / 20	50	21.2	0.9
	2	F3 / Extra-cephalic	0.06	5	Picture naming task	Online	HV	20 / 20	50	66.5	5.5
	2	F3 / Extra-cephalic	0.06	10	Picture naming task	Offline	HV	20 / 20	50	66.5	5.5
Fertonani (2010) [35]	1	F3 / Extra-cephalic	0.06	8	Picture naming task	Offline	HV	12 / 12	66.67	24.1	3.7
	1	Extra-cephalic / F3	0.06	8	Picture naming task	Offline	HV	12 / 12	66.67	24.1	3.7
	2	F3 / Extra-cephalic	0.06	10	Picture naming task	Offline	HV	12 / 12	50	21.8	1
	2	Extra-cephalic / F3	0.06	10	Picture naming task	Offline	HV	12 / 12	50	21.8	1
Filmer (2013) [36]	1	F3 / rSO	0.03	9	Auditory and visual discrimination task - single task	Offline	HV	18 / 18	83.33	22	2.55
	1	F3 / rSO	0.03	9	Auditory and visual discrimination task - single task	Offline	HV	18 / 18	83.33	22	2.55
	1	F3 / rSO	0.03	9	Auditory and visual discrimination task - dual task	Offline	HV	18 / 18	83.33	22	2.55
	1	F3 / rSO	0.03	9	Auditory and visual discrimination task - dual task	Offline	HV	18 / 18	83.33	22	2.55
	1	rSO / F3	0.03	9	Auditory and visual discrimination task - single task	Offline	HV	18 / 18	83.33	22	2.55
	1	rSO / F3	0.03	9	Auditory and visual discrimination task - single task	Offline	HV	18 / 18	83.33	22	2.55

	1	rSO / F3	0.03	9	Auditory and visual discrimination task - dual task	Offline	HV	18 / 18	83.33	22	2.55
	1	rSO / F3	0.03	9	Auditory and visual discrimination task - dual task	Offline	HV	18 / 18	83.33	22	2.55
Foldal (2015) [37]	1	F4 / lSO	0.03	25	AX-Continuous Performance Task (CPT) – Target	Online	HV	40 / 40	57.5	23.4	2.58
	2	F4 / lSO	0.03	25	AX-Continuous Performance Task (CPT) – Non-target	Online	HV	40 / 40	57.5	23.4	2.58
Fregni (2005) [38]	1	F3 / rSO	0.03	10	3-Back	Online	HV	15 / 15	73.33	20.2	.
	1	F3 / rSO	0.08	20	Training with 3-back / A-PASAT (easy) - adjusting paced auditory serial addition task	Offline	HV	11 / 11	27.27	21.8	2.7
Gill (2015)[39]	1	F3 / rSO	0.08	20	Training with 3-back / A-PASAT (hard)	Offline	HV	11 / 11	27.27	21.8	2.7
	1	F3 / rSO	0.08	20	Training with 3-back / A-PASAT (3-Back)	Online	HV	11 / 11	27.27	21.8	2.7
	2	F3 / rSO	0.08	20	Training with 1-back / A-PASAT (easy)	Offline	HV	12 / 12	41.67	19.8	1.5
	2	F3 / rSO	0.08	20	Training with 1-back / A-PASAT (hard)	Offline	HV	12 / 12	41.67	19.8	1.5
	2	F3 / rSO	0.08	20	Training with 1-back / A-PASAT (1-back)	Online	HV	12 / 12	41.67	19.8	1.5
	1	F3 / rSO	0.03	10	Sternberg - Interference load 3	Online	HV	14 / 14	57.14	22	3
Gladwin (2012) [40]	1	F3 / rSO	0.03	10	Sternberg - Interference load 5	Online	HV	14 / 14	57.14	22	3
	1	F3 / rSO	0.03	10	Sternberg - Interference load 7	Online	HV	14 / 14	57.14	22	3
	1	F3 / rSO	0.03	10	Sternberg - No Interference load 3	Online	HV	14 / 14	57.14	22	3
	1	F3 / rSO	0.03	10	Sternberg - No Interference load 5	Online	HV	14 / 14	57.14	22	3
	1	F3 / rSO	0.03	10	Sternberg - No Interference load 7	Online	HV	14 / 14	57.14	22	3
Gladwin (2012) [41]	1	F3 / rSO	0.03	10	Implicit Association Task (IAT) Congruence – target	Offline	HV	20 / 20	65	21.1	2.5
	1	F3 / rSO	0.03	10	IAT Congruence – attribute	Offline	HV	20 / 20	65	21.1	2.5
	1	F3 / rSO	0.03	10	IAT Incongruence – target	Offline	HV	20 / 20	65	21.1	2.5
	1	F3 / rSO	0.03	10	IAT Incongruence – attribute	Offline	HV	20 / 20	65	21.1	2.5
	1	F3 / F4	0.05	20	Balloon analog risk task (BART)	Offline	Addiction	18 / 18	44.44	38.4	7.5

Gorini (2014) [42]	1	F4 / F3	0.05	20	BART	Offline	Addiction	18 / 18	44.44	38.4	7.5
	1	F3 / F4	0.05	20	Game of dice task (GDT)	Offline	Addiction	18 / 18	44.44	38.4	7.5
	1	F4 / F3	0.05	20	GDT	Offline	Addiction	18 / 18	44.44	38.4	7.5
	2	F3 / F4	0.05	20	BART	Offline	HV	18 / 18	44.44	36.8	7.8
	2	F4 / F3	0.05	20	BART	Offline	HV	18 / 18	44.44	36.8	7.8
	2	F3 / F4	0.05	20	GDT	Offline	HV	18 / 18	44.44	36.8	7.8
	2	F4 / F3	0.05	20	GDT	Offline	HV	18 / 18	44.44	36.8	7.8
Hammer (2011)[43]	1	F3 / rSO	0.03	30	Recognition memory task (word stem completion) - Errorful learning	Online	HV	18 / 18	72.22	23.3	3
	1	F3 / rSO	0.03	30	Recognition memory task (word stem completion) - Errorless learning	Online	HV	18 / 18	72.22	23.3	3
	2	rSO / F3	0.03	30	Recognition memory task (word stem completion) - Errorful learning	Online	HV	18 / 18	72.22	23	3.4
	2	rSO / F3	0.03	30	Recognition memory task (word stem completion) - Errorless learning	Online	HV	18 / 18	72.22	23	3.4
Harty (2014) [44]	1	F4 / Cz	0.03	37.5	Error awareness task (EAT - Go/NoGo) – Repeat	Online	HV	24 / 24	58.33	72.13	6
	1	F4 / Cz	0.03	37.5	Error awareness task (EAT - Go/NoGo) – Stroop	Online	HV	24 / 24	58.33	72.13	6
	2	F3 / Cz	0.03	37.5	Error awareness task (EAT - Go/NoGo) – Repeat	Online	HV	24 / 24	54.17	69.41	4.3
	2	F3 / Cz	0.03	37.5	Error awareness task (EAT - Go/NoGo) – Stroop	Online	HV	24 / 24	54.17	69.41	4.3
Hoy (2014) [45]	1	F3 / rSO	0.03	20	2-Back	Offline	SCZ	18 / 18	33.33	42.17	11.04
	1	F3 / rSO	0.03	20	2-Back	Offline	SCZ	18 / 18	33.33	42.17	11.04
	1	F3 / rSO	0.03	20	2-Back	Offline	SCZ	18 / 18	33.33	42.17	11.04
	2	F3 / rSO	0.06	20	2-Back	Offline	SCZ	18 / 18	33.33	42.17	11.04
	2	F3 / rSO	0.06	20	2-Back	Offline	SCZ	18 / 18	33.33	42.17	11.04
	2	F3 / rSO	0.06	20	2-Back	Offline	SCZ	18 / 18	33.33	42.17	11.04
	1	F3 / rSO	0.03	20	N-Back	Offline	HV	17 / 17	61.11	24.71	6.97

Hoy (2013) [46]	1	F3 / rSO	0.03	20	N-Back	Offline	HV	17 / 17	61.11	24.71	6.97
	1	F3 / rSO	0.03	20	N-Back	Offline	HV	17 / 17	61.11	24.71	6.97
	2	F3 / rSO	0.06	20	N-Back	Offline	HV	17 / 17	61.11	24.71	6.97
	2	F3 / rSO	0.06	20	N-Back	Offline	HV	17 / 17	61.11	24.71	6.97
	2	F3 / rSO	0.06	20	N-Back	Offline	HV	17 / 17	61.11	24.71	6.97
Hsu (2015) [47]	1	F3 / rSO	0.02	10	NeuroRacer – Sign Only (single task)	Offline	HV	12 / 12	53.66	26.3	.
	1	F3 / rSO	0.02	10	NeuroRacer – Sign and Drive (dual task)	Offline	HV	12 / 12	53.66	26.3	.
	1	F3 / rSO	0.02	10	NeuroRacer – Sign with Road (distraction task)	Offline	HV	12 / 12	53.66	26.3	.
	2	F3 / rSO	0.02	10	NeuroRacer – Sign Only (single task)	Offline	HV	13 / 13	53.66	26.3	.
	2	F3 / rSO	0.02	10	NeuroRacer – Sign and Drive (dual task)	Offline	HV	13 / 13	53.66	26.3	.
	2	F3 / rSO	0.02	10	NeuroRacer – Sign with Road (distraction task)	Offline	HV	13 / 13	53.66	26.3	.
Javadi (2013) [48]	1	F3 / rSO	0.05	20	Long term verbal memory (reconsolidation)	Online	HV	15 / 15	63.33	22.58	1.68
	1	F3 / rSO	0.05	20	Long term verbal memory (reconsolidation)	Online	HV	15 / 15	63.33	22.58	1.68
	1	rSO / F3	0.05	20	Long term verbal memory (reconsolidation)	Online	HV	15 / 15	63.33	22.58	1.68
	1	rSO / F3	0.05	20	Long term verbal memory (reconsolidation)	Online	HV	15 / 15	63.33	22.58	1.68
	2	F3 / rSO	0.05	20	Long term verbal memory (control)	Online	HV	15 / 15	63.33	22.58	1.68
	2	F3 / rSO	0.05	20	Long term verbal memory (control)	Online	HV	15 / 15	63.33	22.58	1.68
	2	rSO / F3	0.05	20	Long term verbal memory (control)	Online	HV	15 / 15	63.33	22.58	1.68
	2	rSO / F3	0.05	20	Long term verbal memory (control)	Online	HV	15 / 15	63.33	22.58	1.68
Jo (2009) [49]	1	F3 / rSO	0.08	30	2-Back	Online	Stroke	10 / 10	30	47.9	8.9
Jones (2015) [50]	1	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – Low WM Capacity – Active Strategy	Offline	HV	24 / 24	50	23.83	3.67
	1	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – Low WM – Passive Strategy	Offline	HV	24 / 24	50	23.83	3.67

	2	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – High WM – Active Strategy	Offline	HV	24 / 24	50	23.83	3.67
	2	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – High WM – Passive Strategy	Offline	HV	24 / 24	50	23.83	3.67
	3	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – Low WM – High Motivation	Offline	HV	20 / 20	60	21.95	3.28
	3	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – Low WM – Low Motivation	Offline	HV	20 / 20	60	21.95	3.28
	4	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – High WM – High Motivation	Offline	HV	20 / 20	60	21.95	3.28
	4	F3 / Contr. Cheek	0.04	10	WM Change Detection Task – High WM – Low Motivation	Offline	HV	20 / 20	60	21.95	3.28
Kang (2009) [51]	1	F3 / rSO	0.08	20	Go/NoGo	Offline	Stroke	10 / 10	40	69.9	3
	1	F3 / rSO	0.08	20	Go/NoGo	Offline	Stroke	10 / 10	40	69.9	3
	1	F3 / rSO	0.08	20	Go/NoGo	Offline	Stroke	10 / 10	40	69.9	3
	2	F3 / rSO	0.08	20	Go/NoGo	Offline	HV	10 / 10	50	69.3	2.8
	2	F3 / rSO	0.08	20	Go/NoGo	Offline	HV	10 / 10	50	69.3	2.8
	2	F3 / rSO	0.08	20	Go/NoGo	Offline	HV	10 / 10	50	69.3	2.8
Kang (2012) [52]	1	F3 / rSO	0.08	20	Computerized contrast RT task (CCRT) - Go / NoGo	Offline	TBI	9 / 9	11.11	50.4	7.2
	1	F3 / rSO	0.08	20	Computerized contrast RT task (CCRT) - Go / NoGo	Offline	TBI	9 / 9	11.11	50.4	7.2
	1	F3 / rSO	0.08	20	Computerized contrast RT task (CCRT) - Go / NoGo	Offline	TBI	9 / 9	11.11	50.4	7.2
	1	F3 / rSO	0.06	20	0-Back	Offline	HV	10 / 10	50	28.89	2.67
Keeser (2011)[53]	1	F3 / rSO	0.06	20	1-Back	Offline	HV	10 / 10	50	28.89	2.67
	1	F3 / rSO	0.06	20	2-Back	Offline	HV	10 / 10	50	28.89	2.67
Keshvari (2013) [54]	1	F3 / F4	0.08	20	Visual 2-Back	Offline	HV	30 / 30	50	22.3	0.86
	2	F4 / F3	0.08	20	Visual 2-Back	Offline	HV	30 / 30	50	21.2	0.67
Knechtel (2014) [55]	1	F3 / rSO	0.06	20	Auditory Go / NoGo	Offline	HV	16 / 16	37.5	29.9	6.1
Knechtel (2014) [56]	1	F3 / rSO	0.06	20	Auditory Go / NoGo	Offline	SCZ	14 / 14	35.71	46.7	6.4

Leite (2013) [57]	1	F3 / F4	0.06	30	Letter / Digit namig	Online	HV	16 / 16	81.25	24	7.702
	1	F4 / F3	0.06	30	Letter / Digit namig	Online	HV	16 / 16	81.25	24	7.702
	1	F3 / F4	0.06	30	Vowel / Consonant paritytask	Online	HV	16 / 16	81.25	24	7.702
	1	F4 / F3	0.06	30	Vowel / Consonant paritytask	Online	HV	16 / 16	81.25	24	7.702
Leite (2011) [58]	1	F3 / rSO	0.03	15	Cognitive set shifting task (no shift)	Offline	HV	15 / 15	80	20.3	1.99
	1	F3 / rSO	0.03	15	Cognitive set shifting task (shift)	Offline	HV	15 / 15	80	20.3	1.99
	2	rSO / F3	0.03	15	Cognitive set shifting task (no shift)	Offline	HV	15 / 15	80	20.3	1.99
	2	rSO / F3	0.03	15	Cognitive set shifting task (shift)	Offline	HV	15 / 15	80	20.3	1.99
Metuki (2012) [7]	1	F3 / Contr. OFC	0.03	11	Compound remote associates (CRA) test – easy	Online	HV	21 / 21	52.38	23.1	2.5
	1	F3 / Contr. OFC	0.03	11	Compound remote associates (CRA) test – hard	Online	HV	21 / 21	52.38	23.1	2.5
Mulquiney (2011) [59]	1	F3 / rSO	0.03	10	Sternberg task	Online	HV	10 / 10	60	29.5	5.9
	1	F3 / rSO	0.03	10	One card learning task (OCLT)	Offline	HV	10 / 10	60	29.5	5.9
	1	F3 / rSO	0.03	10	1-Back	Offline	HV	10 / 10	60	29.5	5.9
	1	F3 / rSO	0.03	10	2-Back	Offline	HV	10 / 10	60	29.5	5.9
Mylius (2012) [60]	1	F3 / rSO	0.06	20	2-Back	Online	HV	12 / 12	50	25.1	3.4
	1	rSO / F3	0.06	20	2-Back	Online	HV	12 / 12	50	25.1	3.4
	2	F4 / lSO	0.06	20	2-Back	Online	HV	12 / 12	83.33	23.5	3.7
	2	lSO / F4	0.06	20	2-Back	Online	HV	12 / 12	83.33	23.5	3.7
Nelson (2014) [61]	1	F3 / F4	0.03	10	Vigilancetask	Online	HV	10 / 10	20	27.6	7.4
	1	F4 / F3	0.03	10	Vigilancetask	Online	HV	10 / 10	20	27.6	7.4
	2	F3 / F4	0.03	10	Vigilancetask	Online	HV	9 / 9	22	28.1	6.7
	2	F4 / F3	0.03	10	Vigilancetask	Online	HV	9 / 9	22	28.1	6.7

	3	F3 / F4	0.03	10	Vigilancetask	Online	HV	10 / 10	20	27.6	7.4
	3	F4 / F3	0.03	10	Vigilancetask	Online	HV	10 / 10	20	27.6	7.4
	4	F3 / F4	0.03	10	Vigilancetask	Online	HV	9 / 9	22	28.1	6.7
	4	F4 / F3	0.03	10	Vigilancetask	Online	HV	9 / 9	22	28.1	6.7
Nieratschker (2014) [62]	1	rSO / F3	0.03	20	Parametric Go/NoGo task (PGNG) level 1 VAL/VAL - sustained attention	Online	HV	16 / 16	78.05	24	4.2
	1	rSO / F3	0.03	20	Parametric Go/NoGo task (PGNG) level 1 MET - sustained attention	Online	HV	25 / 25	78.05	24	4.2
	1	rSO / F3	0.03	20	Parametric Go/NoGo task (PGNG) level 2 VAL/VAL - response inhibition	Online	HV	16 / 16	78.05	24	4.2
	1	rSO / F3	0.03	20	Parametric Go/NoGo task (PGNG) level 2 MET - reponse inhibition	Online	HV	25 / 25	78.05	24	4.2
	1	rSO / F3	0.03	20	Parametric Go/NoGo task (PGNG) level 3 VAL/VAL - set shifting	Online	HV	16 / 16	78.05	24	4.2
	1	rSO / F3	0.03	20	Parametric Go/NoGo task (PGNG) level 3 MET - set shifting	Online	HV	25 / 25	78.05	24	4.2
	1	F3/rSO	0.03	25	3-Back	Online	HV	30 / 30	64.67	69	7
Nilsson (2015)[63]	1	F3/rSO	0.03	25	3-Back	Offline	HV	30 / 30	64.67	69	7
	2	F3/rSO	0.06	25	3-Back	Online	HV	30 / 30	64.67	69	7
	2	F3/rSO	0.06	25	3-Back	Offline	HV	30 / 30	64.67	69	7
Nozari (2013) [64]	1	F3 / F4	0.06	20	1-Back	Online	HV	24 / 24	54.17	21.2	2.92
	1	F3 / F4	0.06	20	2-Back	Online	HV	24 / 24	54.17	21.2	2.92
	1	F3 / F4	0.06	20	3-Back	Online	HV	24 / 24	54.17	21.2	2.92
Ohn (2008) [65]	1	F3 / rSO	0.04	30	3-Back	Online	HV	15 / 15	66.66	26.5	3.5
	1	F3 / rSO	0.04	30	3-Back	Online	HV	15 / 15	66.66	26.5	3.5
	1	F3 / rSO	0.04	30	3-Back	Online	HV	15 / 15	66.66	26.5	3.5
	1	F3 / rSO	0.04	30	3-Back	Online	HV	15 / 15	66.66	26.5	3.5
Penolazzi (2010) [66]	1	F3 / F4	0.03	20	Free recall – pleasant	Online	HV	12 / 12	50	26.83	4.86

	1	F3 / F4	0.03	20	Free recall – unpleasant	Online	HV	12 / 12	50	26.83	4.86
	1	F3 / F4	0.03	20	Free recall – neutral	Online	HV	12 / 12	50	26.83	4.86
	1	F4 / F3	0.03	20	Free recall – pleasant	Online	HV	12 / 12	50	26.83	4.86
	1	F4 / F3	0.03	20	Free recall – unpleasant	Online	HV	12 / 12	50	26.83	4.86
	1	F4 / F3	0.03	20	Free recall – neutral	Online	HV	12 / 12	50	26.83	4.86
	1	F3 / rSO	0.03	20	Parametric Go/NoGo task - level 1/2/3 (set shifting)	Online	HV	46 / 46	45.65	25.87	7.29
Plewnia (2013) [67]	1	F3 / rSO	0.03	20	Parametric Go/NoGo task - level 1/2/3 (set shifting)	Online	HV	46 / 46	45.65	25.87	7.29
	1	F3 / rSO	0.03	20	Parametric Go/NoGo task - level 1/2/3 (correct response inhibition)	Online	HV	46 / 46	45.65	25.87	7.29
	1	F3 / rSO	0.03	20	Parametric Go/NoGo task - level 1/2/3 (correct response inhibition)	Online	HV	46 / 46	45.65	25.87	7.29
	1	F3 / rSO	0.06	20	Delayed match to sample task - verbal working memory easy	Offline	MDD	14 / 14	50	40.4	9.67
Powell (2014) [68]	1	F3 / rSO	0.06	20	Delayed match to sample task - verbal working memory medium	Offline	MDD	14 / 14	50	40.4	9.67
	1	F3 / rSO	0.06	20	Delayed match to sample task - verbal working memory hard	Offline	MDD	14 / 14	50	40.4	9.67
Saidmanesh (2012) [69]	1	F3 / F4	0.08	20	Picture namingtask	Online	Stroke. Aphasia	20 / 20	40	55.94	2.4
	1	F3 / F4	0.08	20	2-Back	Online	Stroke. Aphasia	20 / 20	40	55.94	2.4
	1	F3 / F4	0.04	15	Semanticdecisiontask (unpredictable)	Offline	HV	11 / 11	58.33	25.23	2.65
Sela (2012) [70]	1	F3 / F4	0.04	15	Semanticdecisiontask (predictable)	Offline	HV	11 / 11	58.33	25.23	2.65
	2	F4 / F3	0.04	15	Semanticdecisiontask (unpredictable)	Offline	HV	11 / 11	58.33	25.23	2.65
	2	F4 / F3	0.04	15	Semanticdecisiontask (predictable)	Offline	HV	11 / 11	58.33	25.23	2.65
	1	Extra-Ceph. / F3	0.03	20	Recognition Memory Task	Offline	HV	20 / 20	80	23.56	2.25
Smirni (2015)[71]	2	Extra-Ceph. / F4	0.03	20	Recognition Memory Task	Offline	HV	20 / 20	80	23.56	2.25
	3	F3 / Extra-Ceph.	0.03	20	Recognition Memory Task	Offline	HV	16 / 16	100	24.7	2.19
	4	F4 / Extra-Ceph.	0.03	20	Recognition Memory Task	Offline	HV	16 / 16	100	24.7	2.19

Teo (2011) [72]	1	F3 / rSO	0.03	20	3-Back	Online	HV	12 / 12	58.33	27.23	9.18
	1	F3 / rSO	0.03	20	Sternberg	Offline	HV	12 / 12	58.33	27.23	9.18
	2	F3 / rSO	0.06	20	3-Back	Online	HV	12 / 12	58.33	27.23	9.18
	2	F3 / rSO	0.06	20	Sternberg	Offline	HV	12 / 12	58.33	27.23	9.18
Turi (2015) [73]	1	F3 / T7	0.03	15	Probabilistic reinforcement learning (RL) and choice task	Online	HV	16 / 16	0	22.9	2.2
Vanderhasselt (2013) [74]	1	F3 / rSO	0.06	20	Internal shift task (emotional WM task) - Shift emotion	Online	HV	32 / 32	62.5	22.28	3.74
	1	F3 / rSO	0.06	20	Internal shift task (emotional WM task) - Shift non-emotion	Online	HV	32 / 32	62.5	22.28	3.74
	1	F3 / rSO	0.06	20	Internal shift task (emotional WM task) - No shift emotion	Online	HV	32 / 32	62.5	22.28	3.74
	1	F3 / rSO	0.06	20	Internal shift task (emotional WM task) - No Shift non-emotion	Online	HV	32 / 32	62.5	22.28	3.74
Vanderhasselt (2013) [75]	1	F3 / rSO	0.06	20	Cued emotional conflict task (CECT) - opposite happy x sad	Offline	HV	25 / 25	68	22.12	3.76
	1	F3 / rSO	0.06	20	Cued emotional conflict task (CECT) - actual happy x sad	Offline	HV	25 / 25	68	22.12	3.76
Vannorsdall (2012) [76]	1	F3 / Cz	0.04	30	Verbal fluency (letter)	Online	HV	12 / 12	50	37.9	11.3
	1	F3 / Cz	0.04	30	Verbal fluency (category)	Online	HV	12 / 12	50	37.9	11.3
	2	Cz / F3	0.04	30	Verbal fluency (letter)	Online	HV	12 / 12	58.33	33.5	8.7
	2	Cz / F3	0.04	30	Verbal fluency (category)	Online	HV	12 / 12	58.33	33.5	8.7
Vercammen (2011) [77]	1	F3 / rSO	0.06	20	Probabilistic learning task - weather prediction task	Online	SCZ	20 / 20	50	37.6	4.4
Wirth (2011) [78]	1	F3 / Extra-cephalic	0.04	37	Homogeneous semantic blocking	Online	HV	20 / 20	50	23.5	3.7
	1	F3 / Extra-cephalic	0.04	37	Heterogeneous semantic blocking	Online	HV	20 / 20	50	23.5	3.7
	1	F3 / Extra-cephalic	0.04	37	Semantic Interference Effect	Online	HV	20 / 20	50	23.5	3.7
	1	F3 / Extra-cephalic	0.04	37	Picture naming task (offline task)	Offline	HV	20 / 20	50	23.5	3.7
Wolkenstein (2013) [79]	1	F3 / Extra-cephalic	0.03	20	Delayed response working memory task (DWM) – emotional	Online	MDD	22 / 22	77.27	31.77	9.76
	1	F3 / Extra-cephalic	0.03	20	Delayed response working memory task (DWM) – neutral	Online	MDD	22 / 22	77.27	31.77	9.76

	1	F3 / Extra-cephalic	0.03	20	Delayed response working memory task (DWM) - no picture	Online	MDD	22 / 22	77.27	31.77	9.76
	2	F3 / Extra-cephalic	0.03	20	Delayed response working memory task (DWM) – emotional	Online	HV	22 / 22	77.27	31.91	10.51
	2	F3 / Extra-cephalic	0.03	20	Delayed response working memory task (DWM) – neutral	Online	HV	22 / 22	77.27	31.91	10.51
	2	F3 / Extra-cephalic	0.03	20	Delayed response working memory task (DWM) - no picture	Online	HV	22 / 22	77.27	31.91	10.51
	1	Extra-cephalic / F3	0.03	20	Delayed response working memory task (DWM) – emotional	Online	HV	28 / 28	71.4	30.86	10.18
Wolkenstein (2014) [80]	1	Extra-cephalic / F3	0.03	20	Delayed response working memory task (DWM) – neutral	Online	HV	28 / 28	71.4	30.86	10.18
	1	Extra-cephalic / F3	0.03	20	Arithmetic inhibition task (AIT) emotional	Offline	HV	28 / 28	71.4	30.86	10.18
	1	Extra-cephalic / F3	0.03	20	Arithmetic inhibition task (AIT) neutral	Offline	HV	28 / 28	71.4	30.86	10.18
	1	F4 / Contr. Cheeck	0.06	15	Computerized corsi block tapping task (CBT) - spatial WM - forward interference	Offline	HV	20 / 20	60	26	.
Wu (2014) [81]	1	F4 / Contr. Cheeck	0.06	15	Computerized corsi block tapping task (CBT) - spatial WM - forward no interference	Offline	HV	20 / 20	60	26	.
	1	F4 / Contr. Cheeck	0.06	15	Computerized corsi block tapping task (CBT) - spatial WM - backward interference	Offline	HV	20 / 20	60	26	.
	1	F4 / Contr. Cheeck	0.06	15	Computerized corsi block tapping task (CBT) - spatial WM - backward no interference	Offline	HV	20 / 20	60	26	.
	1	F3 / rSO	0.06	20	Event file task (EFT) - binding of features	Online	HV	13 / 13	65.38	20	1.698
Zmigrod (2014) [82]	1	rSO / F3	0.06	20	Event file task (EFT) - binding of features	Online	HV	13 / 13	65.38	20	1.698
	2	F4 / lSO	0.06	20	Event file task (EFT) - binding of features	Online	HV	13 / 13	65.38	20	1.698
	2	lSO / F4	0.06	20	Event file task (EFT) - binding of features	Online	HV	13 / 13	65.38	20	1.698

Abbrev.: Exp = Experiment number. tDCS montage: contr. = contralateral; CZ = vertex; F3 = left DLPFC; F4 = right DLPFC; ipsil. = ipsilateral; lSO = left supraorbital cortex; mA = micro-Ampère; OFC = orbitofrontal cortex; rSO = right supraorbital cortex; T7 = middle, superior temporal gyrus. Sample: AD = patients with Alzheimer's disease; HV = healthy volunteers; MDD = patients with Major Depressive Disorder; N (a/s) = number of participants (active/sham); PD = patients with Parkinson's Disease; SCZ = patients with Schizophrenia; TBI = patients with Traumatic Brain Injury.

3.2. Quality assessment

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 (For a Risk of bias graph according to Cochrane recommendations, see Fig. 2, for a detailed quality assessment description, see suppl. material).

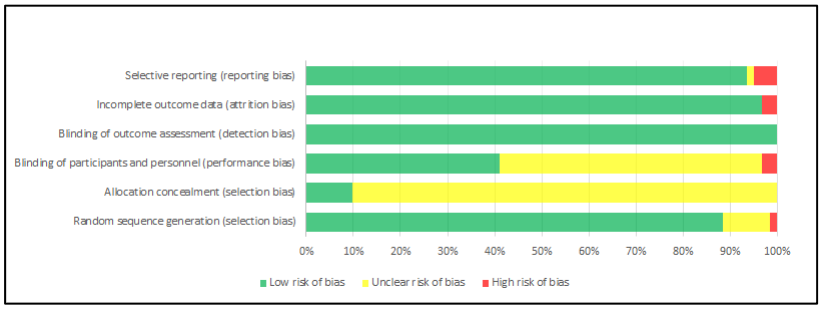

Fig. 2 Risk of Bias Graph according to Cochrane Recommendations

3.3. Main results across all included studies.

3.3.1. Main results for RT trials

For anodal tDCS effects on RTs (N of trials = 124), Cohen's d was -0.107 (95% CI -0.17 to -0.05, p<0.01; Suppl. Fig. 1). Overall, participants were faster in responding after anodal vs. sham non-invasive brain stimulation. No significant heterogeneity was observed (I^2=0%; $\chi^2(123)=73.24$, p=1) and Egger's test was non-significant (p=0.36). In contrast, cathodal tDCS vs. sham had no overall significant effect on RTs (N=36; Cohen's d 0.18, 95% CI -0.07 to 0.44, p=0.16, Fig. 3a; significant heterogeneity, I^2=82.50%; $\chi^2(35)=199$, p<0.01; Egger's test p=0.40). Nonetheless, further analyses focused on the possible influence of technical tDCS parameters in a-tDCS trials, as well as c-tDCS trials.

Univariate meta-regression analyses showed no significant effect of the technical stimulation parameters on the effects of a-tDCS and c-tDCS on response times (Table 2). Therefore, no additional multivariate meta-regressions were performed (see suppl. material for means, standard deviations and ranges of technical stimulation parameters and clinical variables).

3.3.2. Main results for ACC trials

Two important significant outliers were excluded as they presented large, positive effect sizes (Knechtel (Exp-1) and Metuki (Exp-1)) – these studies presented Cohen's d three SDs above 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 effects on ACC (N=165) we observed a Cohen's d of 0.18 (95% CI 0.03 to 0.18, $p<0.01$, Suppl. Fig. 2; significant heterogeneity, $I^2=52.50\%$; $\chi^2(164)=344.9$, $p<0.01$), i.e. participants responded more accurately following active anodal tDCS compared to sham stimulation. In contrast, cathodal tDCS vs. sham had no overall significant effect on ACC (N=28; Cohen's d 0.03, 95% CI -0.13 to 0.19, $p=0.70$, Fig. 3b; significant heterogeneity, $I^2=33.8\%$; $\chi^2(27)=40.79$, $p<0.05$; Egger's test $p=0.64$).

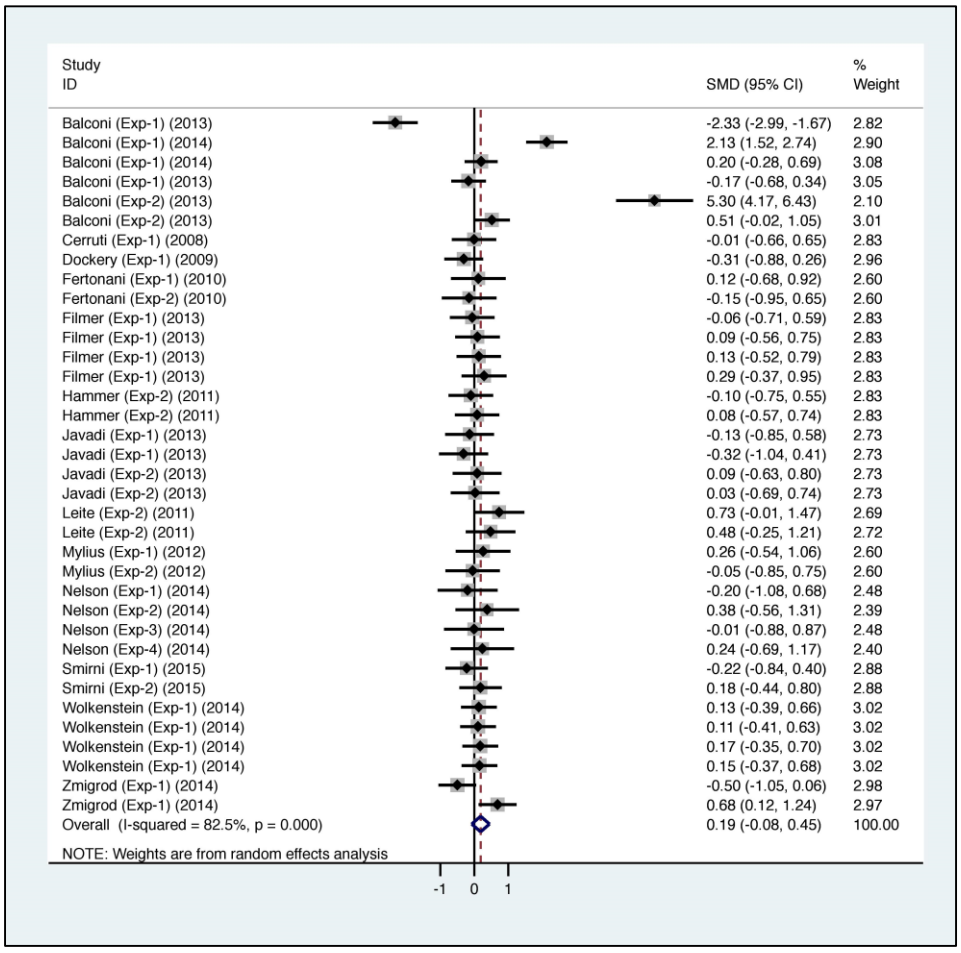

Fig. 3a Forest Plot showing the effect sizes from the comparison between cathodal vs. sham tDCS for Reaction Time (RT) from the Hedges g' random effects model. Positive values indicate an increase in reaction time following cathodal transcranial direct current stimulation (c-tDCS). Negative values indicate a decrease in reaction time following c-tDCS. Error bars: 95% confidence interval

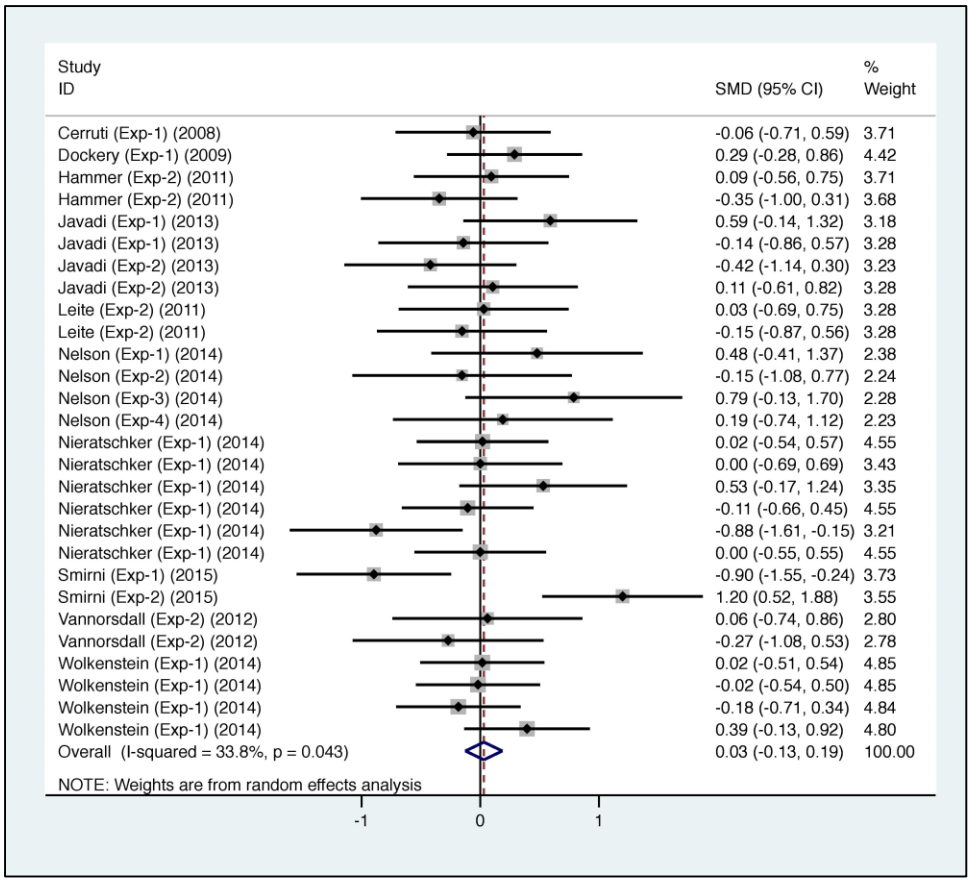

Fig. 3b Forest Plot showing the effect sizes from the comparison between cathodal vs. sham tDCS for Accuracy (ACC) from the Hedges g' random effects model. Positive values indicate an increase in accuracy following cathodal transcranial direct current stimulation (c-tDCS). Negative values indicate a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

3.3.3. Univariate and multivariate meta-regressions for ACC trials

Univariate meta-regression analyses showed a direct association of stimulation current ($p<0.05$), current density ($p<0.01$), and density charge ($p<0.01$) on the effects of a-tDCS on accuracy (Table 2). However, univariate meta-regression analyses suggested no important influence of the technical stimulation parameters on c-tDCS results (Table 2).

Additional multivariate meta-regressions revealed, only, a direct influence of gender (% female) and study sample (neuropsychiatric vs. healthy) on the effects of stimulation current, density, and density charge on post-tDCS accuracy rates (Table 3). Because univariate meta-regressions showed no significant effect of the other stimulation parameters (Table 2), no multivariate meta-regressions were performed for these variables.

	RT - Anodal tDCS				ACC - Anodal tDCS				RT - Cathodal tDCS				ACC - Cathodal tDCS			
	Coeff.	**SE**	**t**	**P**	**Coeff.**	**SE**	**t**	**p**	**Coeff.**	**SE**	**t**	**P**	**Coeff.**	**SE**	**t**	**p**
Current	-0.08	0.06	-0.13	0.89	0.17	0.07	2.24	**0.03**	0.28	0.38	0.75	0.46	0.26	0.34	0.78	0.44
Density	0.88	1.81	0.48	0.62	5.47	1.91	2.85	**<0.01**	6.82	12.8	0.53	0.59	7.23	12.09	0.60	0.55
Duration	<0.01	<0.01	1.57	0.14	<0.01	<0.01	0.95	0.34	-0.01	0.03	-0.43	0.67	-0.01	0.03	-0.49	0.63
Charge	0.09	0.06	1.36	0.17	0.20	0.07	2.83	**<0.01**	<0.01	0.56	-0.01	0.99	<0.01	0.55	0.01	0.99
Laterality	0.05	0.04	1.14	0.25	-0.01	0.04	-0.25	0.80	-0.03	0.27	-0.14	0.89	-0.03	0.26	-0.11	0.92
Reference montage	-0.03	0.08	-0.41	0.68	0.07	0.11	0.66	0.51	-0.16	0.39	-0.42	0.67	0.05	0.18	0.30	0.76
Online vs. Offline	0.04	0.06	0.64	0.52	0.08	0.06	1.21	0.22	-0.31	0.34	-1.03	0.34	-0.32	0.33	-0.95	0.34

Table 2. Results of additional univariate meta-regressions for anodal tDCS and cathodal tDCS trials. Coefficient (SE), t-values and p-values are provided. The coefficient represents the regression coefficient of each regression. Significant results are marked in bold

	Coeff.	**SE**	**T**	**p**
Current	0.17	0.08	2.20	**0.03**
Age	<0.01	<0.01	0.45	0.65
% Female	<0.01	<0.01	2.95	**<0.01**
Condition	-0.20	0.09	-2.12	**<0.01**
Task Type	-0.02	0.04	-0.58	0.56
Density	6.60	1.98	3.34	**<0.01**
Age	<0.01	<0.01	0.65	0.51
% Female	<0.01	<0.01	3.53	**<0.01**
Condition	-0.19	0.09	-2.07	**0.04**
Task Type	-0.02	0.04	-0.50	0.60
Charge	0.20	0.07	2.69	**<0.01**
Age	<0.01	<0.01	0.29	0.77
% Female	<0.01	<0.01	2.92	**<0.01**
Condition	-0.19	0.09	-2.07	**0.04**
Task Type	-0.02	0.04	-0.68	0.50

Table 3. Results of additional multivariate meta-regressions for accuracy trials in anodal tDCS research. Coefficient (SE), t-values and p-values are provided. The coefficient represents the regression coefficient of each regression. Significant results are marked in bold

As the analyses showed that the influence of stimulation parameters (i.e. stimulation current, density, and density charge) on a-tDCS effects on accuracy was significantly moderated by the 'condition' (i.e. healthy vs. neuropsychiatric patients) to which participants belong, two new meta-analyses were performed for healthy participants and neuropsychiatric patients separately. Because the studies in neuropsychiatric patients only investigated the effects of a-tDCS on cognition, and not c-tDCS, the separate group analyses reported on a-tDCS trials only. The results for c-tDCS trials in healthy participants were equal to those of the main analyses.

3.4. Main results in healthy samples

3.4.1. Results for RT trials

For anodal tDCS effects on RTs (N=102), Cohen's d was -0.10 (95% CI -0.16 to -0.04, p<0.01; Fig. 4a). Overall, healthy participants were faster in responding after anodal vs. sham non-invasive brain stimulation. No significant heterogeneity was observed (I^2=0%; $\chi^2(101)$=6, p=0.98). Univariate meta-regression analyses showed no significant effect of the technical stimulation parameters on the effects of a-tDCS on response times (Table 4).

3.4.2. Main results for ACC trials

For anodal tDCS effects on ACC (N=131) we observed a Cohen's d of 0.04 (95% CI -0.02 to 0.11, p=0.19, Fig. 4b; significant heterogeneity, I^2=24%; $\chi^2(130)$=1, p<0.01), i.e. a-tDCS did not significantly influence accuracy rates in healthy volunteers. However, univariate analyses showed a trend towards a significant influence of current density (p=0.054), and density charge (p=0.059) on the effects of a-tDCS on accuracy (Table 4). Additional multivariate meta-regressions showed that there was indeed a significant influence of current density (p<0.05) and density charge (p<0.01) on accuracy rates following a-tDCS, which was moderated by gender (i.e. % Female) (Table 5).

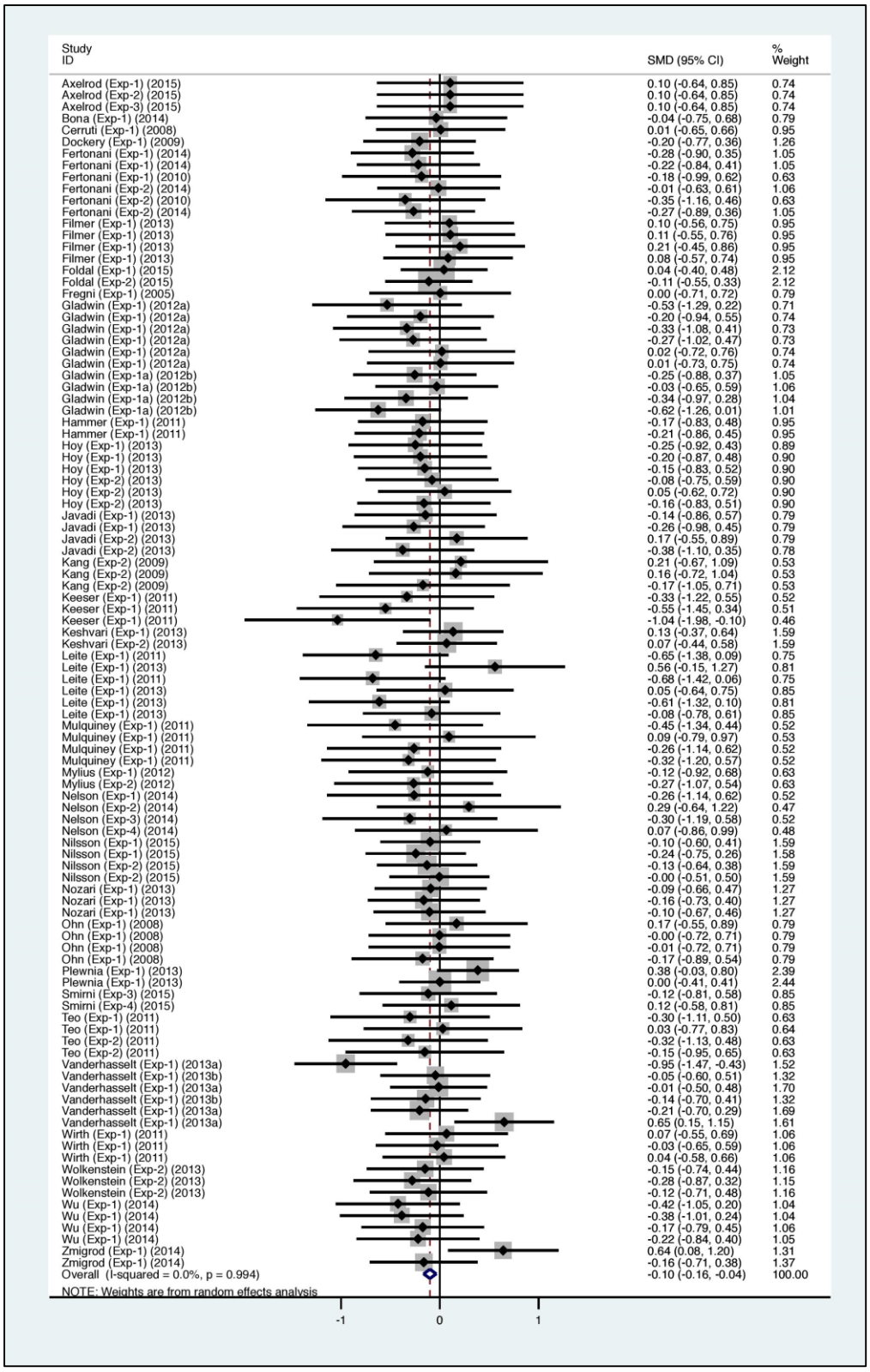

Fig. 4a Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Reaction Time (RT) from the Hedges g' random effects model in healthy participants. Positive values indicate an increase in reaction time following anodal transcranial direct current stimulation (a-tDCS). Negative values indicate a decrease in reaction time following a-tDCS. Error bars: 95% confidence interval

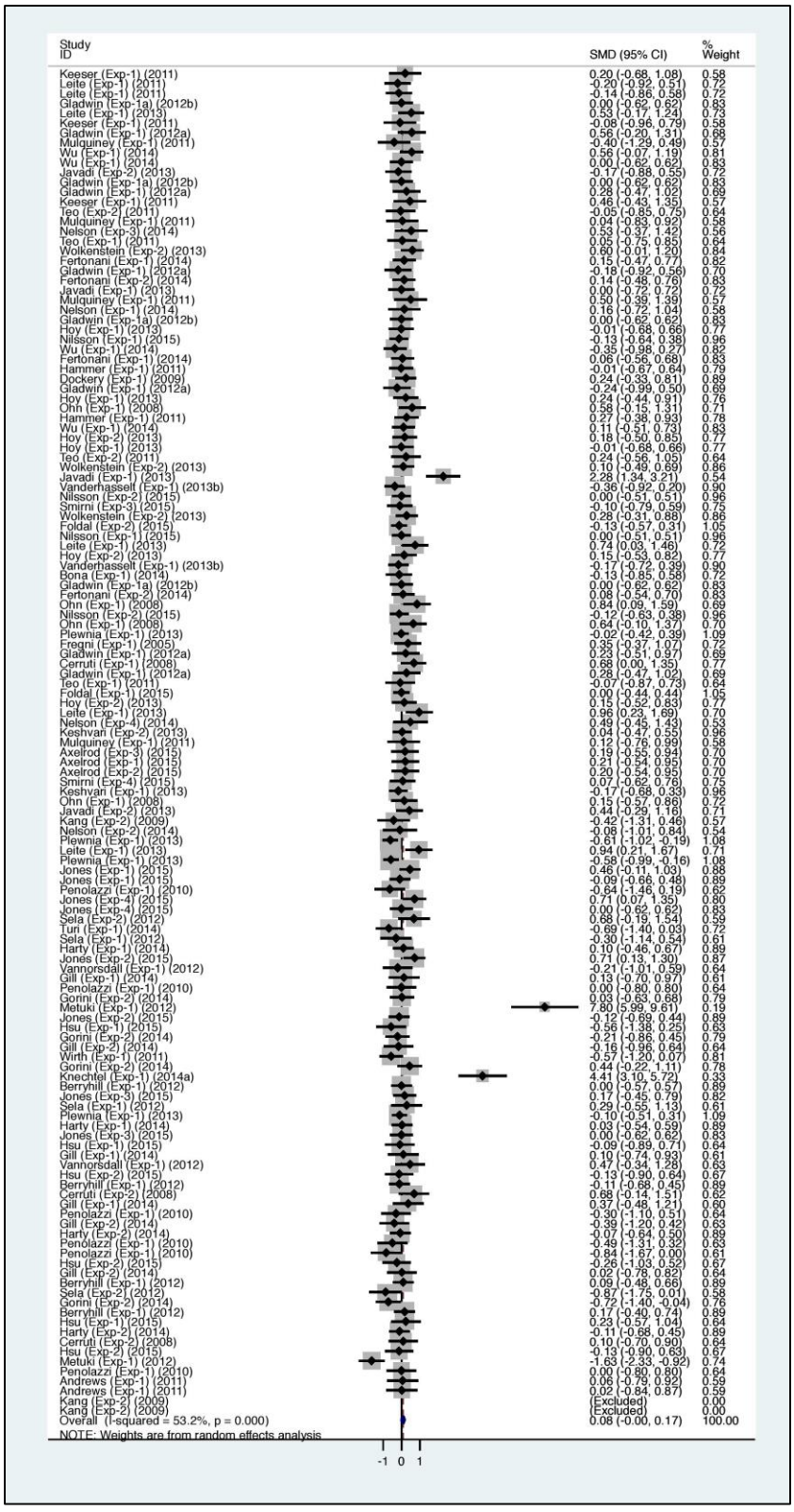

Fig. 4b Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Accuracy (ACC) from the Hedges g' random effects model in healthy participants. Positive values indicate an increase in accuracy following anodal transcranial direct current stimulation (a-tDCS). Negative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

	RT - Anodal tDCS				ACC - Anodal tDCS				RT - Cathodal tDCS				ACC - Cathodal tDCS			
	Coeff.	**SE**	**t**	**P**	**Coeff.**	**SE**	**t**	**p**	**Coeff.**	**SE**	**t**	**p**	**Coeff.**	**SE**	**t**	**p**
Current	<0.01	0.07	-0.02	0.98	0.11	0.08	1.31	0.19	0.28	0.38	0.75	0.46	0.26	0.34	0.78	0.44
Density	1.28	2.06	0.62	0.53	4.20	2.16	1.94	**0.05**	6.82	12.8	0.53	0.59	7.23	12.09	0.60	0.55
Duration	0.01	<0.01	1.51	0.13	<0.01	<0.01	0.60	0.55	-0.01	0.03	-0.43	0.67	-0.01	0.03	-0.49	0.63
Charge	0.11	0.07	1.54	0.13	0.15	0.08	1.91	**0.06**	<0.01	0.56	-0.01	0.99	<0.01	0.55	0.01	0.99
Laterality	0.05	0.05	1.05	0.30	<0.01	0.05	0.06	0.95	-0.03	0.27	-0.14	0.89	-0.03	0.26	-0.11	0.92
Reference montage	-0.02	0.09	-0.27	0.78	0.05	0.12	0.40	0.68	-0.16	0.39	-0.42	0.67	0.05	0.18	0.30	0.76
Online vs. Offline	0.06	0.07	0.84	0.40	0.01	0.07	0.10	0.92	-0.31	0.34	-1.03	0.34	-0.32	0.33	-0.95	0.34

Table 4. Results of additional univariate meta-regressions for anodal tDCS and cathodal tDCS trials in healthy samples. Coefficient (SE), t-values and p-values are provided. The coefficient represents the regression coefficient of each regression. Significant results are marked in bold

	Coeff.	**SE**	**T**	**P**
Density	5.59	2.13	2.63	**0.01**
Age	<0.01	<0.01	-0.02	0.99
% Female	0.01	<0.01	3.36	**<0.01**
Task Type	0.01	0.04	0.26	0.79
Charge	0.16	0.08	2.01	**0.05**
Age	<0.01	<0.01	-0.39	0.70
% Female	0.01	<0.01	2.87	**0.01**
Task Type	0.01	0.04	0.15	0.88

Table 5. Results of additional multivariate meta-regressions for accuracy trials in anodal tDCS research in healthy samples. Coefficient (SE), t-values and p-values are provided. The coefficient represents the regression coefficient of each regression. Significant results are marked in bold

3.5. Main results in neuropsychiatric samples

3.5.1. Results for RT trials

For anodal tDCS effects on RTs (N=22), Cohen's d was -0.15 (95% CI -0.30 to 0.01, p=0.065; Fig. 5a). Overall, participants tended to respond faster after anodal vs. sham non-invasive brain stimulation, although this effect was non-significant. No significant heterogeneity was observed (I^2=0%; $\chi^2(21)=4$, p>0.05). Univariate meta-regression analyses showed no significant effect of the technical stimulation parameters on the effects of a-tDCS on response times (Table 6).

3.5.2. Results for ACC trials

For anodal tDCS effects on ACC (N=30) we observed a Cohen's d of 0.22 (95% CI 0.04 to 0.40, $p<0.05$, Fig. 5b; significant heterogeneity, $I^2=45.20\%$; $\chi^2(29)=5$, $p<0.01$), i.e. participants responded more accurately following active anodal tDCS compared to sham stimulation. Univariate meta-regressions showed a significant influence of whether the cognitive task was performed during (online) or following (offline) stimulation ($p<0.01$) on the effects of a-tDCS on accuracy (Table 6). Additional multivariate meta-regressions demonstrated that the clinical variables age, % female, and task type did not influence the outcome (Table 7).

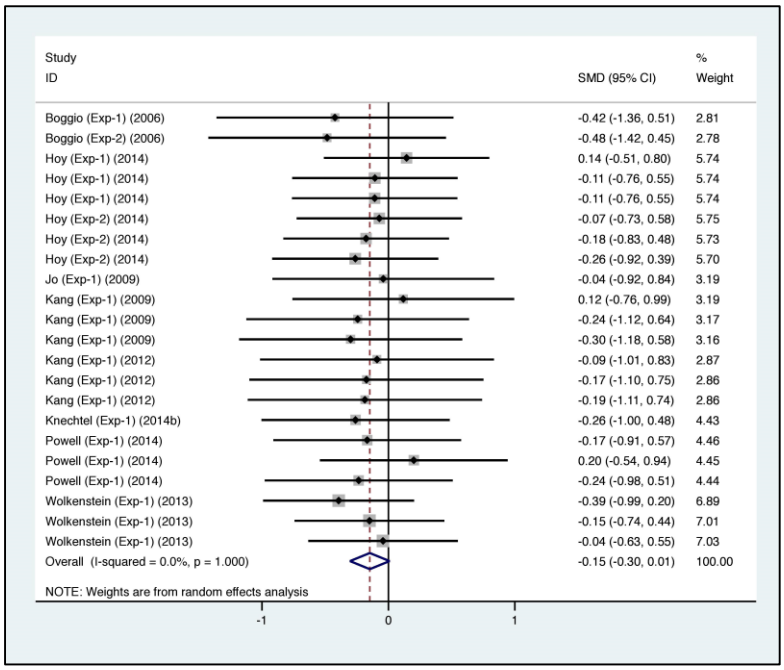

Fig. 5a Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Reaction Time (RT) from the Hedges g' random effects model in neuropsychiatric patients. Positive values indicate an increase in reaction time following anodal transcranial direct current stimulation (a-tDCS). Negative values indicate a decrease in reaction time following a-tDCS. Error bars: 95% confidence interval

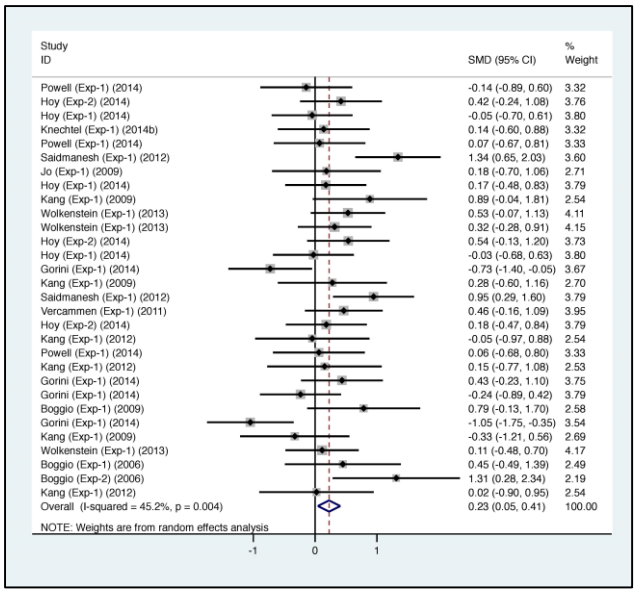

Fig. 5b Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Accuracy (ACC) from the Hedges g' random effects model in neuropsychiatric patients. Positive values indicate an increase in accuracy following anodal transcranial direct current stimulation (a-tDCS). Negative values indicate a decrease in accuracy following a-tDCS. Error bars: 95% confidence interval

	RT - Anodal tDCS				ACC - Anodal tDCS			
	Coeff.	**SE**	**t**	**p**	**Coeff.**	**SE**	**t**	**p**
Current	-0.02	0.16	-0.10	0.92	0.27	0.21	1.26	0.22
Density	-0.05	4.00	-0.01	0.99	6.60	4.82	1.37	0.18
Duration	0.01	0.05	0.24	0.81	0.03	0.04	0.64	0.53
Charge	0.01	0.17	0.06	0.95	0.28	0.21	1.36	0.18
Laterality	-	-	-	-	-0.07	0.11	-0.58	0.57
Reference montage	-0.05	0.19	-0.30	0.76	0.10	0.28	0.37	0.71
Online vs. Offline	-0.11	0.17	-0.64	0.53	0.58	0.17	3.46	**<0.01**

Table 6. Results of additional univariate meta-regressions for anodal tDCS trials in neuropsychiatric patients. Coefficient (SE), t-values and p-values are provided. The coefficient represents the regression coefficient of each regression. Results for "Laterality" influences on anodal tDCS effects on RT are not provided due to collinearity. Significant results are marked in bold

	Coeff.	**SE**	**t**	**p**
Online vs. Offline	0.64	0.21	3.03	**0.01**
Age	0.01	0.01	1.45	0.16
% Female	-0.01	0.01	-1.05	0.30
Task Type	-0.08	0.14	-0.58	0.57

Table 7. Results of additional multivariate meta-regressions for accuracy trials in anodal tDCS research in neuropsychiatric patients. Coefficient (SE), t-values and p-values are provided. The coefficient represents the regression coefficient of each regression. Significant results are marked in bold

4. DISCUSSION

In this meta-analysis, 61 single-session, sham-controlled, cross-over DLPFC tDCS studies were included. Quality assessment revealed that studies were of acceptable quality and publication bias, according to the Egger's test was low. Over all participants across all trials, analyses revealed a small, significant effect of a-tDCS (but not c-tDCS) on improving RTs and accuracy in cognitive tasks: in general, participants responded faster and more accurate after active stimulation. Stimulation parameters (stimulation current, density and density charge) were only predictive of task accuracy, but not RTs after a-tDCS. Importantly however, meta-regression analyses showed that these parameter effects were dependent on the condition (i.e. healthy vs. neuropsychiatric sample) and on gender (i.e. stronger increase in accuracy following a-tDCS in females). Therefore, subsequent meta-analyses were performed separately for healthy participants and neuropsychiatric patients, and revealed sample-specific influences of stimulation parameters on a-tDCS modulated cognition. These sample-specific findings will be discussed in more detail.

4.1. Healthy participants

In line with previous meta-analyses, we found that healthy participants responded significantly faster [12] on cognitive tasks following single-session DLPFC a-tDCS, but not more accurately. However, other meta-analyses showed a trend for increased accuracy [14], or showed no effect of a-tDCS on cognition [15]. Some methodological differences might explain these discrepant findings. For instance, different study inclusion criteria were used: data from healthy participants and neuropsychiatric patients were either analyzed together [12,14], or for healthy participants separately [15]; some included single-session tDCS studies only [12,15], while others also included repeated-session tDCS studies [14]; some included within-subject tDCS studies only [15], while others also included between-subject tDCS studies [12,14]; and some only included working memory (WM) tasks [12,13], while others evaluated tDCS effects on various cognitive outcomes [15]. Lastly, these DLPFC tDCS meta-analyses predominantly evaluated studies using highly heterogeneous stimulation parameters, without making distinctions between them.

Univariate meta-regressions showed that current density (i.e. current/electrode surface area; mA/cm^2; M(SD)=0.04(0.02), range 0.02-0.08) and density charge (i.e. (current density)*(session duration); $(A*s)/Cm^2 = C/cm^2$; M(SD)=0.05(0.03), range 0.01-0.15; see [83]), influenced a-tDCS effects on cognition: higher current densities/charges lead to stronger a-tDCS effects on accuracy, which is partly in line with Hill et al. [14]. However, Hill et al. investigated the possible effects of only two stimulation parameters (density and duration) in

a pooled sample of studies including healthy volunteers and psychiatric patients. In this pooled sample, the a-tDCS effect on accuracy was indeed modulated by current density although sample characteristics (healthy vs. neuropsychiatric) may have influenced these results. Moreover, the investigators only evaluated tDCS effects on WM tasks (i.e. n-back, Sternberg, digit-span), thereby limiting the number of included studies (N=16). Lastly, Hill et al. did not control for participants' characteristics (e.g. age, gender), which might limit interpretation of their findings [14]. In general, studies in healthy participants have shown mixed findings regarding the effects of current intensity [72], which can be explained by our results.

Additional multivariate meta-regressions revealed that gender moderated the effects of stimulation dose (i.e. current density and density charge) on post-a-tDCS accuracy. More specifically, the higher the percentage of females included in the trials, the stronger the effect sizes. This finding could be explained by sex differences in the anatomical location of the DLPFC [84] and in cognitive task performance and associated brain activation patterns (e.g. women take a more 'top-down' cognitive strategy than men, relying more heavily on higher-order frontal regions, which is enhanced by DLPFC tDCS) [85]; or, most plausibly, hormonal differences affecting brain stimulation induced changes in cortical excitability between women and men [86–88], as demonstrated previously in studies investigating the effects of rTMS on cortical excitability [89,90]. However, the finding that gender influences the effects of stimulation dose on a-tDCS efficacy for accuracy rates should be interpreted with caution, as our meta-analysis is based on aggregate, and not individual patient data [91,92].

For c-tDCS, no effects on cognition were observed in healthy samples, which is in line with previous meta-analyses [12,93]. Moreover, stimulation parameters did not influence c-tDCS effects on cognition. However, only a small number of trials investigated the effect of c-tDCS on accuracy and/or RT. As no main effects of c-tDCS on cognition were found, it could be suggested that although the polarity-dependent effects of tDCS (i.e. a-tDCS increases vs. c-tDCS decreases cortical excitability) might occur in motor cortical studies, it might not occur in prefrontal cortex studies. Indeed, the "inhibitory" cathodal tDCS effects over a tertiary associative cortical area (DLPFC) might be different than a the effects over a primary cortical region (M1) [93]. Alternatively, the effects of c-tDCS on cognition are suggested to be non-linear with possible reversed effects of c-tDCS on motor cortical excitability when applying more intense stimulation currents (e.g. motor cortical inhibition following 1mA c-tDCS vs. cortical excitation following 2mA c-tDCS) [94], which can lead to heterogeneous results. Thus, increasing stimulation dose in c-tDCS studies might not exert the expected effects of increasing cortical inhibition.

4.2. Neuropsychiatric patients

Compared to healthy participants, neuropsychiatric patients showed a different pattern of cognitive improvement following single-session tDCS, namely increased accuracy and only a trend for faster responding following a-tDCS. Although previous meta-analyses show contrasting findings – i.e. faster responding [12] and a trend for increased accuracy following a-tDCS [14], the results of our meta-analysis and these studies cannot be entirely compared as these studies evaluated the effects of tDCS on cognition in a combined sample of healthy participants and neuropsychiatric patients.

Univariate meta-regressions showed that stimulation dose (i.e. current, density, density charge) did not affect post-a-tDCS accuracy or response time. This result contradicts previous findings where 2mA tDCS was more effective than 1mA tDCS in improving cognition in patients with Parkinson´s disease [29] or schizophrenia [45] and suggests that other stimulation parameters play a role. Indeed, in line with Hill et al., we found a small effect of the timing of task performance (i.e. online vs. offline; 10 trials vs. 20 trials respectively) [14]: patients responded more accurate on cognitive tasks performed during a-tDCS (online), than on tasks performed following a-tDCS (offline). This effect was not moderated by age, gender or task type, as shown by additional multivariate meta-regressions. Conceivably, modulating neural membrane excitability in specific neural regions through tDCS, simultaneous with performance of a cognitive task engaging equal neural networks, might lead to a synergistic effect in comparison to a task performance following the stimulation.

The effects of cathodal tDCS on cognition in neuropsychiatric samples were not investigated as no such study was included in our review. Therefore, the possible influence of stimulation parameters on c-tDCS effects on accuracy and response time in neuropsychiatric patients could not be evaluated.

Other tDCS technical parameters could theoretically, also impact the prefrontal tDCS effects on cognition. For instance, an extra-cephalic reference electrode (vs. cephalic) can theoretically alter current flow and thus possibly the efficacy of the active electrode [95]. However, this variable did not influence our results in either of the populations; possibly because this effect might be counter-balanced due to an increased distance between the scalp electrode and the reference electrode [96,97]. We also examined whether laterality of the stimulation target (i.e. left vs. right DLPFC) influenced tDCS effects on cognition, considering lateralization of some cognitive functions to the left or the right hemisphere [98]. However, this variable did not influence our results in either healthy participants or neuropsychiatric patients.

4.3 Limitations and implications for future research

A study limitation is the significant heterogeneity that was observed in the trials. For meta-analytic purposes, we had to collapse "neuropsychiatric disorders" in one category and, although classified in three distinct categories (i.e. memory, attention, executive functioning), highly variable cognitive tasks were analyzed simultaneously. However, this was handled by performing a random-effects model analysis that takes into account this heterogeneity. Furthermore, multivariate meta-regressions revealed no significant influence of task type on the a-tDCS effects on accuracy. Also, the studies included in this meta-analysis had small sample sizes, possible reducing the power of the analysis. Finally, parameters such as current density and density charge should be investigated further, since a trial in which a density of 1mA/35cm² is used for 20min might not be comparable to a trial using 2mA/35cm² for 10min, even though both trials used the same density charge. However, it is presumable that both the current density and duration are interactively determining the effects of prefrontal tDCS on cognition as the current density charge influenced tDCS effects.

In spite of these limitations, we demonstrated that increasing the administered stimulation dose (i.e. density or density charge) modestly enhances the accuracy rate following a-tDCS in healthy participants, especially for women. Notably, we did not find a significant main effect of a-tDCS on accuracy in these participants. In contrast, task performance during tDCS (online) leads to stronger effects in post-a-tDCS accuracy in neuropsychiatric patients, compared to task completion following a-tDCS (offline). Interestingly, in neuropsychiatric patients, increasing the stimulation dose did not affect post-a-tDCS cognitive outcomes. Lastly, c-tDCS does not seem to impact cognition in prefrontal tDCS studies in healthy participants, and stimulation parameters do not seem to affect these c-tDCS effects on cognition.

Future research should therefore assess how an increased stimulation dose can be reached, without increasing discomfort and/or adverse effects. With increased stimulation doses, a-tDCS could then possibly influence accuracy significantly in healthy participants, and more specifically in females. Given our results, it seems more plausible to increase the density charge (C/cm²), rather than merely increasing the current density (i.e. higher current intensity, smaller electrodes), by increasing stimulation duration as well. Importantly, higher current intensities are associated more with discomfort, adverse effects and study blinding breaking [99]. Some methods could be used to mitigate these issues, such as topical anesthetics [100] and ketoprofen [101] as well as customized electrode sponges and gear. Furthermore, present studies apply current charges well below the safety threshold. Liebetanz et al. showed, in rats, that the dose responsible for inducing lesions was 5.24C/cm² [102]. In

comparison, the highest density charge in our dataset was 0.15C/cm². Moreover, in the study by Liebetanz et al., the investigators had to remove the skin of the rats' scalp in order to fix the electrode directly to the skull. Therefore, safe doses in humans may be even higher [102]. Lastly, our results suggest that changing stimulation parameter settings will not influence the effects of cathodal tDCS on cognition. Therefore, further exploration of the neurophysiological mechanisms underlying this lack of c-tDCS effects on neurocognitive plasticity is recommended.

5. CONCLUSIONS

The importance of this meta-analytic review lies in the demonstration that for anodal tDCS, the administration of higher current doses (density and density charge) results in higher accuracy percentages on cognitive tasks in healthy participants, although these effects are modest and more pronounced in women. Therefore, we advise future research in healthy samples to focus on evaluating the effects of tDCS administered at higher doses, preferably higher density charges. In contrast, completing the cognitive task during tDCS (online), compared to following tDCS (offline) is suggested to lead to increased accuracy percentages on cognitive tasks following anodal tDCS in neuropsychiatric patients. Thus, in clinical single-session tDCS settings, an online task protocol might be preferred over an offline task protocol.

6. REFERENCES

[1] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2015;127:1031-48. doi:10.1016/j.clinph.2015.11.012.

[2] Nitsche MA, Nitsche MS, Klein CC, Tergau F, Rothwell JC, Paulus W. Level of action of cathodal dc polarisation induced inhibition of the human motor cortex. Clin Neurophysiol 2003;114:600–4. doi:10.1016/S1388-2457(02)00412-1.

[3] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9. doi:10.1111/j.1469-7793.2000.t01-1-00633.x.

[4] Tortella G, Casati R, Aparicio LVM, Mantovani A, Senço N, D'Urso G, et al. Transcranial direct current stimulation in psychiatric disorders. World J Psychiatry 2015;5:88–102. doi:10.5498/wjp.v5.i1.88.

[5] Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 2011;4:84–9. doi: 10.1016/j.brs.2010.06.004.

[6] Boggio P, Campanha C, Valasek CA, Fecteau S, Pascual-Leone A, Fregni F. Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. Eur J Neurosci 2010;31:593-7. doi: 10.1111/j.1460-9568.2010.07080.x.

[7] Metuki N, Sela T, Lavidor M. Enhancing cognitive control components of insight problems solving by anodal tDCS of the left dorsolateral prefrontal cortex. Brain Stimul 2012;5:110–5. doi: 10.1016/j.brs.2012.03.002.

[8] Balconi M. Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques. Neurosci Bull 2013;29:381-9. doi: 10.1007/s12264-013-1309-z.

[9] Vanderhasselt MA, De Raedt R, Leyman L, Baeken C. Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. J Psychiatry Neurosci 2009;34:119-26.

[10] Shin Y, Foerster Á, Nitsche MA. Transcranial direct current stimulation (tDCS)–Application in neuropsychology. Neuropsychologia 2015;74:74-95. doi: 10.1016/j.neuropsychologia.2015.06.021.

[11] Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 2014;85:948-60. doi: 10.1016/j.neuroimage.2013.05.117.

[12] Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cognition 2014;86:1–9. doi:10.1016/j.bandc.2014.01.008.

[13] Jaeggi SM, Buschkuehl M, Perrig WJ, Meier B. The concurrent validity of the N-back task as a working memory measure. Memory 2010;18:394–412. doi:10.1080/09658211003702171.

[14] Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric

populations. Brain Stimul 2015;9:197-208. doi:10.1016/j.brs.2015.10.006.

[15] Horvath JC, Forte JD, Carter O. Quantitative review finds no evidence of cognitive effects in healthy populations from single-session transcranial direct current stimulation (tDCS). Brain Stimul 2015;8:535-50. doi:10.1016/j.brs.2015.01.400.

[16] Horvath JC, Carter O, Forte JD. Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). Front Syst Neurosci 2014;8:2. doi:10.3389/fnsys.2014.00002.

[17] Nitsche MA, Bikson M, Bestmann S. On the use of meta-analysis in neuromodulatory non-invasive brain stimulation. Brain Stimul 2015;8:666-7. doi: 10.1016/j.brs.2015.03.008.

[18] Elbourne DR. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol 2002;31:140–9. doi:10.1093/ije/31.1.140.

[19] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. Vol. 5. Chichester: Wiley-Blackwell; 2008.

[20] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis, JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W-65-W-94. doi: 10.7326/0003-4819-151-4-200908180-00136.

[21] Norman D. Models of human memory. Elsevier; 2013.

[22] Cohen RA, Sparling-Cohen YA, O'Donnell BF. The neuropsychology of attention. New York: Plenum Press; 1993.

[23] Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 2000;41:49–100. doi:10.1006/cogp.1999.0734.

[24] Axelrod V, Rees G, Lavidor M, Bar M. Increasing propensity to mind-wander with transcranial direct current stimulation. PNAS 2015;112:3314-9. doi: 10.1073/pnas.1421435112.

[25] Balconi M, Canavesio Y. The contribution of dorsolateral prefrontal cortex and temporoparietal areas in processing instrumental versus functional semantic violations in action representation. J Clin Exp Neuropsychol 2014;36:701-15. doi: 10.1080/13803395.2014.929093.

[26] Balconi M, Vitaloni S. 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 2014;26:305-18. doi: 10.1162/jocn_a_00500.

[27] Beeli G, Casutt G, Baumgartner T, Jäncke L. Modulating presence and impulsiveness by external stimulation of the brain. Behav Brain Funct 2008;4:33. doi: 10.1186/1744-9081-4-33.

[28] Berryhill ME, Jones KT. tDCS selectively improves working memory in older adults with more education. Neurosci Lett 2012;521:148–51. doi:10.1016/j.neulet.2012.05.074.

[29] Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 2006;249:31–8. doi: 10.1016/j.jns.2006.05.062.

[30] Boggio PS, Khoury LP, Martins DC, Martins OE, de Macedo EC, Fregni F. Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J Neurol Neurosurg Psychiatry 2009;80:444-7. doi: 10.1136/jnnp.2007.141853.

[31] Bona S, Silvanto J. Accuracy and confidence of visual short-term memory do not go hand-in-hand: behavioral and neural dissociations. PLoS One 2014;9:e90808. doi: 10.1371/journal.pone.0090808.

[32] Cerruti C, Schlaug G. Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. J Cogn Neurosci 2009;21:1980-7. doi: 10.1162/jocn.2008.21143.

[33] Dockery CA, Hueckel-Weng R, Birbaumer N, Plewnia C. Enhancement of planning ability by transcranial direct current stimulation. J Neurosci 2009;29:7271–7. doi. 10.1523/JNEUROSCI.0065-09.2009.

[34] Fertonani A, Brambilla M, Cotelli M, Miniussi C. The timing of cognitive plasticity in physiological aging: a tDCS study of naming. Front Aging Neurosci 2014;6:131. doi: 10.3389/fnagi.2014.00131.

[35] Fertonani A, Rosini S, Cotelli M, Rossini PM, Miniussi C. Naming facilitation induced by transcranial direct current stimulation. Behav Brain Res 2010;208:311–8. doi:10.1016/j.bbr.2009.10.030.

[36] Filmer HL, Mattingley JB, Dux PE. Improved multitasking following prefrontal tDCS. Cortex 2013;49:2845–52. doi: 10.1016/j.cortex.2013.08.015.

[37] Foldal MD. Manipulating intra-individual variation in cognitive control with transcranial direct current

stimulation: proactive vs. reactive control. 2015.

[38] Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166(1):23–30. doi: 10.1007/s00221-005-2334-6.

[39] Gill J, Shah-Basak PP, Hamilton R. It's the thought that counts: examining the task-dependent effects of transcranial direct current stimulation on executive function. Brain Stimul 2014;8:253-9. doi: 10.1016/j.brs.2014.10.018.

[40] Gladwin TE, den Uyl TE, Fregni FF, Wiers RW. Enhancement of selective attention by tDCS: interaction with interference in a sternberg task. Neurosci Lett 2012;512:33–7. doi: 10.1016/j.neulet.2012.01.056.

[41] Gladwin TE, den Uyl TE, Wiers RW. Anodal tDCS of dorsolateral prefontal cortex during an Implicit Association Test. Neurosci Lett 2012;517:82-6. doi: 10.1016/j.neulet.2012.04.025.

[42] Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front Hum Neurosci 2014;8:661. doi: 10.3389/fnhum.2014.00661.

[43] Hammer A, Mohammadi B, Schmicker M, Saliger S, Münte TF. Errorless and errorful learning modulated by transcranial direct current stimulation. BMC Neurosci 2011;12:72. doi: 10.1186/1471-2202-12-72.

[44] Harty S, Robertson IH, Miniussi C, Sheehy OC, Devine CA, McCreery S, et al. Transcranial direct current stimulation over right dorsolateral prefrontal cortex enhances error awareness in older age. J Neurosci 2014;34:3646-52. doi: 10.1523/JNEUROSCI.5308-13.2014.

[45] Hoy KE, Arnold SL, Emonson MRL, Daskalakis ZJ, Fitzgerald PB. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr Res 2014;155:96–100. doi: 10.1016/j.schres.2014.03.006.

[46] Hoy KE, Emonson MRL, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia 2013;51:1777-84. doi: 10.1016/j.neuropsychologia.2013.05.018.

[47] Hsu WY, Ku Y, Zanto TP, Gazzaley A. Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. Neurobiol Aging 2015;36:2348-59. doi: 10.1016/j.neurobiolaging.2015.04.016.

[48] Javadi AH, Cheng P. Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. Brain Stimul 2013;6:668-74. doi:10.1016/j.brs.2012.10.007.

[49] Jo JM, Kim YH, Ko MH, Ohn SH, Joen B, Lee KH. Enhancing the working memory of stroke patients using tDCS. Am J Phys Med Rehab 2009;88:404-9. doi: 10.1097/PHM.0b013e33181a0e4cb.

[50] Jones KT, Gözenman F, Berryhill ME. The strategy and motivational influences on the beneficial effect of neurostimulation: a tDCS and fNIRS study. Neuroimage 2015;105:238-47. doi: 10.1016/j.neuroimage.2014.11.012.

[51] Kang EK, Baek MJ, Kim SY, Paik NJ. Non-invasive cortical stimulation improves post-stroke attention decline. Restor Neurol Neurosci 2009;27:647–50. doi: 10.3233/RNN-2009-0514.

[52] Kang EK, Kim DY, Paik NJ. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. J Rehabil Med 2012;44:346–50. doi: 10.2340/16501977-0947.

[53] Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, et al. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA). Neuroimage 2011;55:644-57. doi: 10.1016/j.neuroimage.2010.12.004.

[54] Keshvari F, Pouretemad H, Ekhtiari H. The polarity-dependent effects of the bilateral brain stimulation on working memory. Basic Clin Neurosci 2013;4:224-31. doi:

[55] Knechtel L, Schall U, Cooper G, Ramadan S, Stanwell P, Jolly T, et al. Transcranial direct current stimulation of prefrontal cortex: An auditory event-related potential and proton magnetic resonance spectroscopy study. Neurol Psychiatry Brain Res 2014;20:96-101. doi:10.1016/j.npbr.2014.06.001.

[56] Knechtel L, Thienel R, Cooper G, Case V, Schall U. Transcranial direct current stimulation of prefrontal cortex: An auditory event-related potential study in schizophrenia. Neurol Psychiatry Brain Res 2014;20:102–6. doi: 10.1016/j.npbr.2014.10.002

[57] Leite J, Carvalho S, Fregni F, Boggio PS, Gonçalves OF. The effects of cross-hemispheric dorsolateral prefrontal cortex transcranial direct current stimulation (tDCS) on task switching. Brain Stimul 2013;6:660–7. doi: 10.1016/j.brs.2012.10.006.

[58] Leite J, Carvalho S, Fregni F, Gonçalves OF. Task-specific effects of tDCS-induced cortical excitability changes on cognitive and motor sequence set shifting performance. PLoS One 2011;6:e24140. doi: 10.1371/journal.pone.0024140.

[59] Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clin Neurophysiol 2011;122:2384-9. doi: 10.1016/j.clinph.2011.05.009.

[60] Mylius V, Jung M, Menzler K, Haag A, Khader PH, Oertel WH, et al. Effects of transcranial direct current stimulation on pain perception and working memory. Eur J Pain 2012;16:974–82. doi: 10/1002/j.1532-2149.2011.00105.x.

[61] Nelson JT, McKinley RA, Golob EJ, Warm JS, Parasuraman R. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage 2014;85:909–17. doi: 10.1016/j.neuroimage.2012.11.061.

[62] Nieratschker V, Kiefer C, Giel K, Krüger R, Plewnia C. The COMT Val/Met polymorphism modulates effects of tDCS on response inhibition. Brain Stimul 2014;8:283-8. doi: 10.1016/j.brs.2014.11.009.

[63] Nilsson J, Lebedev AV, Lövdén M. No significant effect of prefrontal tDCS on working memory performance in older adults. Front Aging Neurosci 2015;7:230. doi:10.3389/fnagi.2015.00230.

[64] Nozari N, Thompson-Schill SL. More attention when speaking: does it help or does it hurt? Neuropsychologia 2013;51:2770–80. doi:10.1016/j.neuropsychologia.2013.08.019.

[65] Ohn SH, Park CI, Yoo WK, Ko MH, Choi KP, Kim GM, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Cogn Neurosci Neuropsychol 2008;19:43-7. doi:10.1097/WNR.0b013e3282f2adfd.

[66] Penolazzi B, Di Domenico A , Marzoli D, Mammarella N, Fairfield B, Franciotti R, et al. Effects of transcranial direct current stimulation on episodic memory related to emotional visual stimuli. PLoS One 2010;5:e10623. doi: 10.1371/journal.pone.0010623.

[67] Plewnia C, Zwissler B, Längst I, Maurer B, Giel K, Krüger R. Effects of transcranial direct current stimulation (tDCS) on executive functions: influence of COMT Val/Met polymorphism. Cortex 2013;49:1801–7. doi: 10.1016/j.cortex.2012.11.002.

[68] Powell TY, Boonstra TW, Martin DM, Loo CK, Breakspear M. Modulation of cortical activity by transcranial direct current stimulation in patients with affective disorder. PLoS One 2014;9:e98503. doi: 10.1371/journal.pone.0098503.

[69] Saidmanesh M, Pouretemad HR, Amini A, et al. Effects of transcranial direct current stimulation on working memory in patients with non-fluent aphasia disorder. Res J Biol Sci 2012;7:290-6. doi: 10.3923/rjbsci.2012.290.296.

[70] Sela T, Ivry R, Lavidor M. Prefrontal control during a semantic decision task that involves idiom comprehension: a transcranial direct current stimulation study. Neuropsychologia 2012;50:2271–80. doi: 10.1016/j.neuropsychologia.2012.05.031.

[71] Smirni D, Turriziani P, Mangano G, Cipolotti L, Oliveri M. Modulating memory performance in healthy subjects with transcranial direct current stimulation over the right dorsolateral prefrontal cortex. PLoS One 2015;10:e0144838. doi: 10.1371/journal.pone.0144838.

[72] Teo F, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Investigating the role of current strength in tDCS modulation of working memory performance in healthy controls. Front Psychiatry 2011;2:45. doi: 10.3389/fpsyt.2011.00045.

[73] Turi Z, Mittner M, Opitz A, Popkes M, Paulus W, Antal A. Transcranial direct current stimulation over the left prefrontal cortex increases randomness of choice in instrumental learning. Cortex 2015;63:145-54. doi: 10.1016/j.cortex.2014.08.026.

[74] Vanderhasselt MA, Brunoni AR, Loeys T, Boggio PS, De Raedt R. Nosce te ipsum–Socrates revisited? Controlling momentary ruminative self-referent thoughts by neuromodulation of emotional working memory. Neuropsychologia 2013;51:2581-9. doi: 10.1016/j.neuropsychologia.2013.08.011.

[75] Vanderhasselt MA, De Raedt R, Brunoni AR, Campanhã C, Baeken C, Remue J, et al. tDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. PLoS One 2013;8:e62219. doi: 10.1371/journal.pone.0062219.

[76] Vannorsdall TD, Schretlen DJ, Andrejczuk M, Ledoux K, Bosley LV, Weaver JR, et al. Altering automatic verbal processes with transcranial direct current stimulation. Front Psychiatry 2012;3:73. doi: 10.3389/fpsyt.2012.00073.

[77] Vercammen A, Rushby JA, Loo C, Short B, Weickert CS, Weickert TW. Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr Res 2011;131:198-205. doi: 10.1016/j.schres.2011.06.021.

[78] Wirth M, Rahman RA, Kuenecke J, Koenig T, Horn H, Sommer W, et al. Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production. Neuropsychologia 2011;49:3989–98. doi: 10.1016/j.neuropsychologia.2011.10.015.

[79] Wolkenstein L, Plewnia C. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol Psychiatry 2013;73:646-51. doi: 10.1016/j.biopsych.2012.10.010.

[80] Wolkenstein L, Zeiller M, Kanske P, Plewnia C. Induction of a depression-like negativity bias by cathodal transcranial direct current stimulation. Cortex 2014;59:103-12. doi: 10.1016/j.cortex.2014.07.011.

[81] Wu YJ, Tseng P, Chang CF, Pai MC, Hsu KS, Lin CC, et al. Modulating the interference effect on spatial working memory by applying transcranial direct current stimulation over the right dorsolateral prefrontal cortex. Brain Cogn 2014;91:87-94. doi: 10.1016/j.bandc.2014.09.002.

[82] Zmigrod S, Colzato L, Hommel B. Evidence for a role of the right dorsolateral prefrontal cortex in controlling stimulus-response integration: a transcranial direct current stimulation (tDCS) study. Brain Stimul 2014;7:516-20. doi: 10.1016/j.brs.2014.03.004.

[83] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17:37–53. doi:10.1177/1073858410386614.

[84] Mylius V, Ayache SS, Ahdab R, Farhat WH, Zouari HG, Belke M, et al. Definition of DLPFC and M1 according to anatomical landmarks for navigated brain stimulation: inter-rater reliability, accuracy, and influence of gender and age. Neuroimage 2013;78:224–32. doi:10.1016/j.neuroimage.2013.03.061.

[85] Butler T, Pan H, Imperato-McGinley J, Voyer D, Cunningham-Bussel AC, Cordero JJ, et al. A network approach to fMRI condition-dependent cognitive activation studies as applied to understanding sex

differences. Clin Neurosci Res 2007;6:391–8. doi:10.1016/j.cnr.2007.05.005.

[86] Kuo MF, Nitsche MA, Paulus W. Gender differences of cortical neuroplasticity in humans, as revealed by transcranial direct current stimulation. Klin Neurophysiol 2006;37:A131. doi:10.1055/s-2006-939214.

[87] Chaieb L, Antal A, Paulus W. Gender-specific modulation of short-term neuroplasticity in the visual cortex induced by transcranial direct current stimulation. Vis Neurosci 2008;25:77-81. doi: 10.1017/S0952523808080097.

[88] Boggio PS, Rocha RR, da Silva MT, Fregni F. Differential modulatory effects of transcranial direct current stimulation on a facial expression go-no-go task in males and females. Neurosci Lett 2008;447:101-5. doi: 10.1016/j.neulet.2008.10.009.

[89] Smith MJ, Keel JC, Greenberg BD, Adams LF, Schmidt PJ, Rubinow DA, et al. Menstrual cycle effects on cortical excitability. Neurology 1999;53:2069–72. doi:10.1212/WNL.53.9.2069.

[90] Inghilleri M, Conte A, Currà A, Frasca V, Lorenzano C, Berardelli A. Ovarian hormones and cortical excitability. An rTMS study in humans. Clin Neurophysiol 2004;115:1063–8. doi:10.1016/j.clinph.2003.12.003.

[91] Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. BMJ 2010;340:c221. doi:10.1136/bmj.c221.

[92] Kaiser A, Haller S, Schmitz S, Nitsch C. On sex/gender related similarities and differences in fMRI language research. Brain Res Rev 2009;61:49–59. doi:10.1016/j.brainresrev.2009.03.005.

[93] Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2012;216:1-10. doi: 10.1007/s00221-011-2891-9.

[94] Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. J Physiol 2013;591:1987–2000. doi:10.1113/jphysiol.2012.249730.

[95] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul 2008;1:206–23. doi:10.1016/j.brs.2008.06.004.

[96] Moliadze V, Antal A, Paulus W. Electrode-distance dependent after-effects of transcranial direct and

random noise stimulation with extracephalic reference electrodes. Clin Neurophysiol 2010;121:2165-71. doi: 10.1016/j.clinph.2010.04.033.

[97] Bikson M, Datta A, Rahman A, Scaturro J. Electrode montages for tDCS and weak transcranial electrical stimulation: role of "return" electrode's position and size. Clin Neurophysiol 2010;121:1976–8. doi:10.1016/j.clinph.2010.05.020.

[98] Kaller CP, Rahm B, Spreer J, Weiller C, Unterrainer JM. Dissociable contributions of left and right dorsolateral prefrontal cortex in planning. Cereb Cortex 2011;21:307–17. doi:10.1093/cercor/bhq096.

[99] O'Connell NE, Cossar J, Marston L, Wand BM, Bunce D, Moseley GL, et al. Rethinking clinical trials of transcranial direct current stimulation: participant and assessor blinding is inadequate at intensities of 2mA. PLoS One 2012;7:e47514. doi:10.1371/journal.pone.0047514.

[100] McFadden JL, Borckardt JJ, George MS, Beam W. Reducing procedural pain and discomfort associated with transcranial direct current stimulation. Brain Stimul 2011;4:38–42. doi:10.1016/j.brs.2010.05.002.

[101] Guarienti F, Caumo W, Shiozawa P, Cordeiro Q, Boggio PS, Benseñor IM, et al. Reducing transcranial direct current stimulation-induced erythema with skin pretreatment: considerations for sham-controlled clinical trials. Neuromodulation 2015;18:261–5. doi:10.1111/ner.12230.

[102] Liebetanz D, Koch R, Mayenfels S, König F, Paulus W, Nitssche MA. Safety limits of cathodal transcranial direct current stimulation in rats. Clin Neurophysiol 2009;120:1161-7. doi: 10.1016/j.clinph.2009.01.022.

HIGHLIGHTS

- We meta-analyzed 233 within-subject experiments investigating the effect of single-session DLPFC tDCS on cognitive outcomes.
- No main effects of cathodal tDCS on reaction time, nor response accuracy were found.
- No effects of stimulation parameters on cathodal tDCS effects on cognition were found.
- Anodal tDCS significantly decreased response time in healthy participants, and increased response accuracy in neuropsychiatric patients.
- In healthy participants, increased current densities/charges are associated to increased a-tDCS effects on response accuracy.
- In neuropsychiatric patients, online task performance is associated to increased a-tDCS effects on accuracy, compared to offline task performance.

SUPPLEMENTARY MATERIAL

Data Extraction

However, not many trials measure error percentages (N = 44; 18.88% of the trials). Therefore, we did not perform a meta-analysis on this data. Furthermore, we analyzed post-tDCS data, as most studies did not evaluate cognitive data at baseline (i.e. before the tDCS session; N = 16/61 studies; N = 65/233 trials; 27.89% of the trials reported baseline data).

Quality Assessment

Quality assessment showed that 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. In only 6/61 studies there was a low risk of allocation concealment bias as 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 [1,2] up to 2 minutes and 45 seconds [3–5]. However, in 3 studies tDCS was given with a placebo stimulator [6–8], while in 1 study, the stimulator was turned off for the entire session [9]. Regarding blinding, 47 out of the 61 studies were single-blinded. The other 14 studies used a double-blind design. The time period in between the active stimulation session and the sham stimulation session ranged from 3.5 minutes [9] to two weeks [10]. The risk of incomplete outcome data and selective outcome reporting were generally low across studies. To date, researchers investigating the effects of tDCS are advised to evaluate the occurrence of adverse effects as well [11,12]. However, only 35 of the 61 studies included in this review (i.e. 57.38%) 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 [5,13–17] or did not take psychiatric medication [18,19]. Psychiatric interviews and/or questionnaires were used to screen patients.

Technical Stimulation Parameters and Clinical Variables

The following variables were meta-regressed: stimulation intensity (in mA; M=1.40, SD=0.45; range 0.70-2.00), density (in mA/Cm²; M=0.04, SD=0.02; range 0.02-0.08), density charge (i.e. A*s/Cm²; in C/Cm²; M=0.05, SD=0.03; range 0.01-0.15), stimulation duration (in minutes; M=18.19, SD=6.92; range 4.00-37.50, reference montage (cephalic vs. extra-cephalic), laterality (left vs. right DLPFC stimulation), and timing of tDCS (online vs. offline). Furthermore, for each of these variables in which the univariate result was significant ($p<0.05$), a multivariate meta-regression was performed including the variables age (in years; M=30.94, SD=13.97; range 19.80-79.10), clinical condition (healthy vs. psychiatric patients), gender (in % females; M=55.87, SD=16.68; range 0-100) and type of task (memory, attention or executive functioning)

References

[1] Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res 2005;166(1):23–30. doi: 10.1007/s00221-005-2334-6.

[2] Mylius V, Jung M, Menzler K, Haag A, Khader PH, Oertel WH, et al. Effects of transcranial direct current stimulation on pain perception and working memory. Eur J Pain 2012;16:974–82. doi: 10/1002/j.1532-2149.2011.00105.x.

[3] Andrews SC, Hoy KE, Enticott PG, Daskalakis ZJ, Fitzgerald PB. Improving working memory: the effect of combining cognitive activity and anodal transcranial direct current stimulation to the left dorsolateral prefrontal cortex. Brain Stimul 2011;4:84–9. doi: 10.1016/j.brs.2010.06.004.

[4] Hoy KE, Emonson MRL, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: investigating the effect of tDCS dose on working memory enhancement in healthy controls. Neuropsychologia 2013;51:1777-84. doi: 10.1016/j.neuropsychologia.2013.05.018.

[5] Hoy KE, Arnold SL, Emonson MRL, Daskalakis ZJ, Fitzgerald PB. An investigation into the effects of tDCS dose on cognitive performance over time in patients with schizophrenia. Schizophr Res 2014;155:96–100. doi: 10.1016/j.schres.2014.03.006.

[6] Balconi M, Canavesio Y. The contribution of dorsolateral prefrontal cortex and temporoparietal areas in processing instrumental versus functional semantic violations in action representation. J Clin Exp Neuropsychol 2014;36:701-15. doi: 10.1080/13803395.2014.929093.

[7] Balconi M, Vitaloni S. 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 2014;26:305-18. doi: 10.1162/jocn_a_00500.

[8] Keeser D, Padberg F, Reisinger E, Pogarell O, Kirsch V, Palm U, et al. Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: a standardized low resolution tomography (sLORETA). Neuroimage 2011;55:644-57. doi: 10.1016/j.neuroimage.2010.12.004.

[9] Beeli G, Casutt G, Baumgartner T, Jäncke L. Modulating presence and impulsiveness by external stimulation of the brain. Behav Brain Funct 2008;4:33. doi: 10.1186/1744-9081-4-33.

[10] Ohn SH, Park CI, Yoo WK, Ko MH, Choi KP, Kim GM, et al. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Cogn Neurosci Neuropsychol 2008;19:43-7. doi:10.1097/WNR.0b013e3282f2adfd.

[11] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimul 2008;1:206–23. doi:10.1016/j.brs.2008.06.004.

[12] Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int J Neuropsychoph 2011;14:1133-45. doi: 10.1017/S1461145710001690.

[13] Kang EK, Kim DY, Paik NJ. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. J Rehabil Med 2012;44:346–50. doi: 10.2340/16501977-0947.

[14] Powell TY, Boonstra TW, Martin DM, Loo CK, Breakspear M. Modulation of cortical activity by transcranial direct current stimulation in patients with affective disorder. PLoS One 2014;9:e98503. doi: 10.1371/journal.pone.0098503.

[15] Vercammen A, Rushby JA, Loo C, Short B, Weickert CS, Weickert TW. Transcranial direct current stimulation influences probabilistic association learning in schizophrenia. Schizophr Res 2011;131:198-205. doi: 10.1016/j.schres.2011.06.021.

[16] Wolkenstein L, Plewnia C. Amelioration of cognitive control in depression by transcranial direct current stimulation. Biol Psychiatry 2013;73:646-51. doi: 10.1016/j.biopsych.2012.10.010.

[17] Knechtel L, Schall U, Cooper G, Ramadan S, Stanwell P, Jolly T, et al. Transcranial direct current stimulation of prefrontal cortex: An auditory event-related potential and proton magnetic resonance spectroscopy study. Neurol Psychiatry Brain Res 2014;20:96-101. doi:10.1016/j.npbr.2014.06.001.

[18] Boggio PS, Ferrucci R, Rigonatti SP, Covre P, Nitsche M, Pascual-Leone A, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci 2006;249:31–8. doi: 10.1016/j.jns.2006.05.062.

[19] Gorini A, Lucchiari C, Russell-Edu W, Pravettoni G. Modulation of risky choices in recently abstinent dependent cocaine users: a transcranial direct-current stimulation study. Front Hum Neurosci 2014;8:661. doi: 10.3389/fnhum.2014.00661.

SUPPLEMENTARY FIGURE 1

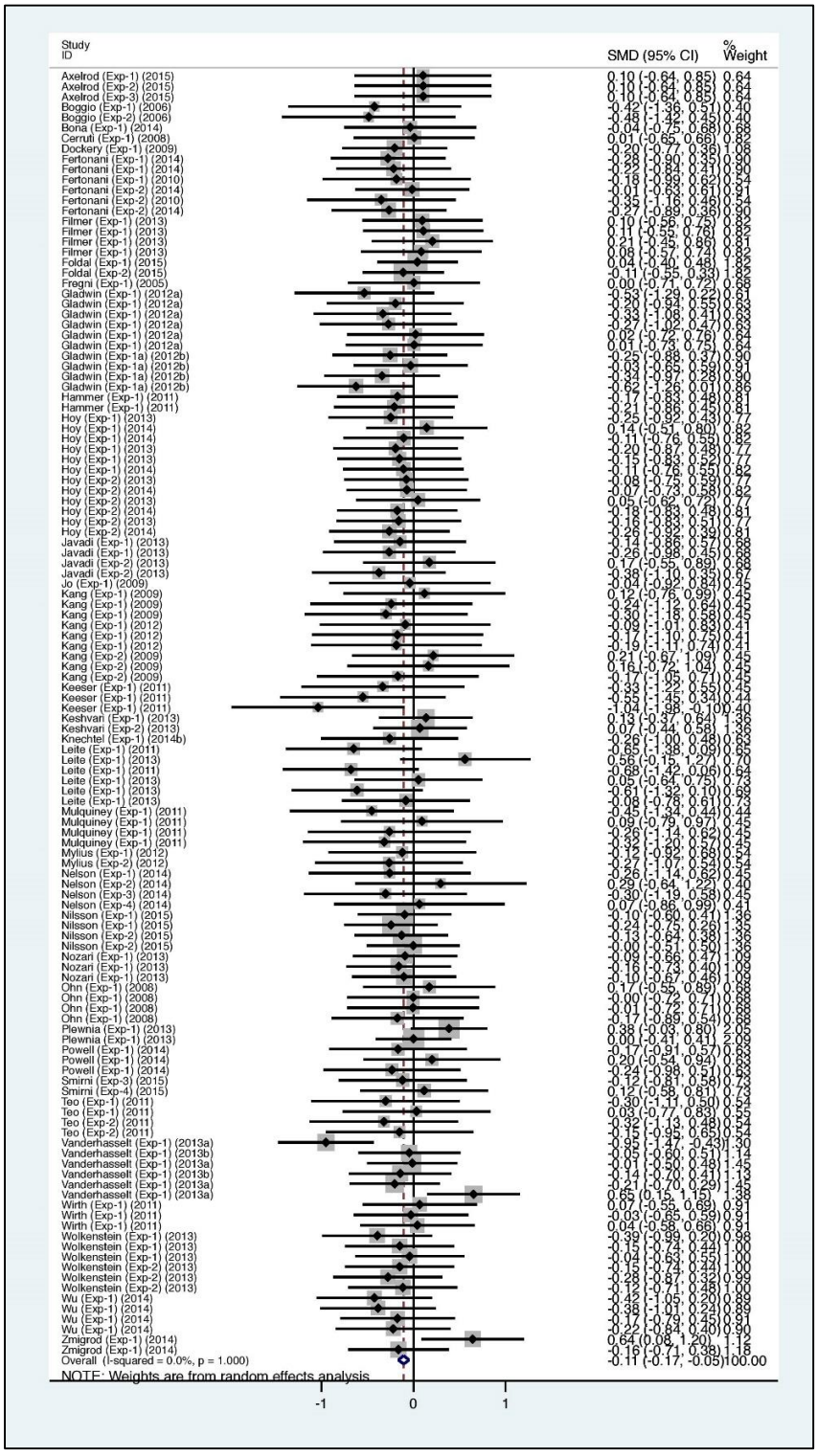

Fig. 1 Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Reaction Time (RT) from the Hedges g' random effects model. Positive values indicate an increase in reaction time following anodal transcranial direct current stimulation (a-tDCS). Negative values indicate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

SUPPLEMENTARY FIGURE 2

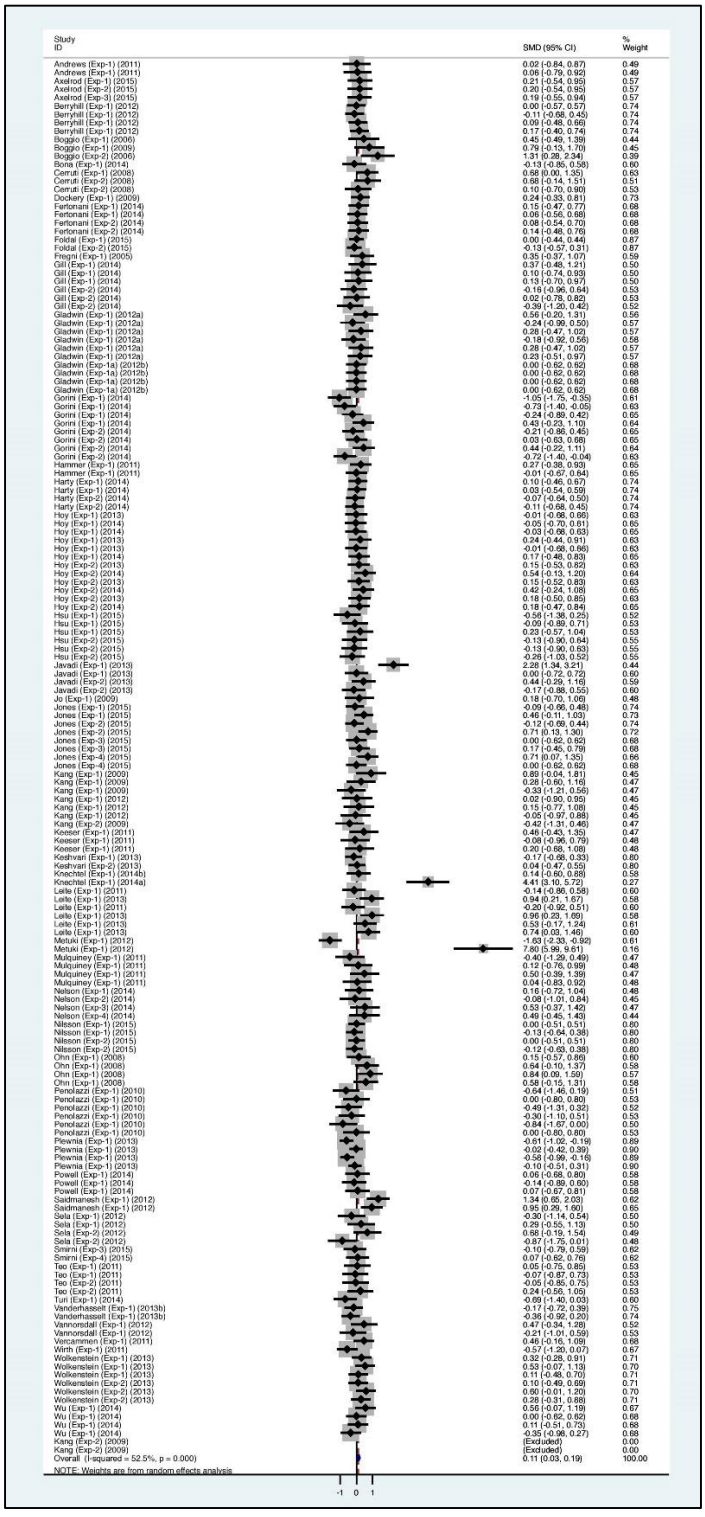

Fig. 2 Forest Plot showing effect sizes from the comparison between anodal vs. sham tDCS for Accuracy (ACC) from the Hedges g' random effects model. Positive values indicate an increase in accuracy rates following anodal transcranial direct current stimulation (a-tDCS). Negative values indicate a decrease in accuracy rates following a-tDCS. Error bars: 95% confidence interval

SUPPLEMENTARY TABLE 1

Excluded studies – studies excluded from the review and associated reason for exclusion.

Authors	**Reason for Exclusion**
Brunoni (2013)	Only valence data, and neuroendocrine results
Capone (2014)	No overall accuracy rates, error outcomes, or RT reported
Conson (2015)	No clear cognitive outcome measure
Elder (2015)	No sham-controlled design
Fecteau (2014)	No single sessions
Giglia (2014)	No outcome data available (via e-mail correspondence)
Göder (2013)	Slow oscillatory tDCS
Gray (2015)	Between subject design
Hoy (2015)	Data subset of a previously included study
Kekic (2014)	Primary outcome is food craving
Kongthong (2013)	Subliminal face paradigm
Lafontaine (2013)	No outcome data available (via e-mail correspondence)
Lapenta (2014)	No outcome data available (via e-mail correspondence)
Loo (2010)	No single sessions
Maeoka (2012)	Only valence data, and EEG data
Mameli (2010)	Different tDCS electrode montage (4 electrodes)
Manenti (2013)	Between subject DLPFC-PARC Factor; No analysis for DLPFC separately
Marshall (2004)	Intermittent tDCS
Marshall (2005)	Intermittent tDCS
Martin (2014)	No sham-controlled design
Mengarelli (2015)	Between subject design
Moreno (2015)	Between subject design
Motohashi (2013)	No single sessions
Nihonsugi (2015)	No clear cognitive outcome measure
Nitsche (2012)	No outcome data available (via e-mail correspondence)
Palm (2009)	No single sessions
Peña-Gomez (2011)	Only valence data
Priori (2008)	Different tDCS electrode montage (3 electrodes)
Pripfl (2013)	Different tDCS electrode montage (4 electrodes)
Roy (2015)	Parietal sham design
Sakai, H (2014)	No clear cognitive outcome measure
Schmidt (2015)	Conference abstract - not published
Schroeder (2015)	No clear cognitive outcome measure
Sellers (2015)	Between subject design
Smittenaar (2014)	No clear cognitive outcome measure
Woods (2014)	No clear cognitive outcome measure
Ye (2015)	Between subject design
Zaehle (2011)	No outcome data available (via e-mail correspondence)
Zhou (2014)	No cognitive outcome measure
Zmigrod (2015)	Sham without tDCS

Abbrev.: PARC = Parietal Cortex; RT = Reaction Time.