

# 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

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## 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 accurately. 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.

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**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; RT, response time; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; SMD, standardized mean difference; tDCS, transcranial direct current stimulation; WM, working memory.

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## 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. 1–2 mA) [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.

## Materials 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.

### 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.

### 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 of 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.

### 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.

### 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 Supplementary material). Finally, data on perceived blinding and adverse effects were extracted.

### 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).

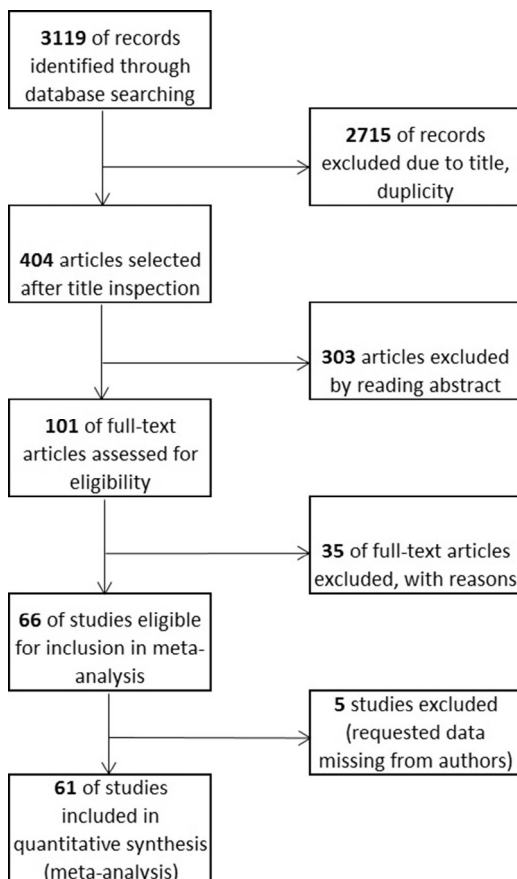
## Results

### 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 S1](#)). 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](#)).

### 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 Supplementary material).



**Figure 1.** Flow-chart of electronic database search strategy.

### Main results across all included studies

#### 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. S1](#)). 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 Supplementary material for means, standard deviations and ranges of technical stimulation parameters and clinical variables).

#### 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. S2](#); 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  $p = 0.64$ ).

#### 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.

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.

**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/cm<sup>2</sup>), 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/cm <sup>2</sup> )	Duration (min)	Outcome	Online/ offline	Condition	N (a/s)	% Fem.	Age (M)	Age (SD)
Andrews et al. (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 et al. (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 and Canavesio (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 and Vitaloni (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 et al. (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 and Jones (2012) [28]	1	F3/Contr. Check	0.04	10	Visual 2-Back	Online	HV	24/24	50	63.7	5.8
	1	F3/Contr. Check	0.04	10	Verbal 2-Back	Online	HV	24/24	50	63.7	5.8
	1	F4/Contr. Check	0.04	10	Visual 2-Back	Online	HV	24/24	50	63.7	5.8
	1	F4/Contr. Check	0.04	10	Verbal 2-Back	Online	HV	24/24	50	63.7	5.8
Boggio et al. (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 et al. (2009) [30]	1	F3/rSO	0.06	30	Visual recognition memory	Online	AD	10/10	60	79.1	8.8
Bona and Silvano (2014) [31]	1	F4/ISO	0.06	20	Visual short term memory (VSTM)	Offline	HV	15/15	53.33	25.13	3.76
Cerruti and Schlaug (2008) [32]	1	F3/rSO	0.06	20	Remote Associates test (RAT)	Offline	HV	18/18	72.22	25.5	2.6
	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/ISO	0.06	20	Remote Associates test (RAT)	Offline	HV	12/12	25	25.4	4.5
Dockery et al. (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 et al. (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 et al. (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 et al. (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/ISO	0.03	25	AX-Continuous Performance Task (CPT) – Target	Online	HV	40/40	57.5	23.4	2.58
	2	F4/ISO	0.03	25	AX-Continuous Performance Task (CPT) – Non-target	Online	HV	40/40	57.5	23.4	2.58
Fregni et al. (2005) [38]	1	F3/rSO	0.03	10	3-Back	Online	HV	15/15	73.33	20.2	–
Gill et al. (2015) [39]	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
	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

(continued on next page)



Table 1 (continued)

Author	Exp	Anode/cathode	Density (mA/cm <sup>2</sup> )	Duration (min)	Outcome	Online/offline	Condition	N (a/s)	% Fem.	Age (M)	Age (SD)
Gladwin et al. (2012) [40]	1	F3/rSO	0.03	10	Sternberg – Interference load 3	Online	HV	14/14	57.14	22	3
	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 et al. (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
Gorini et al. (2014) [42]	1	F3/F4	0.05	20	Ballloon analog risk task (BART)	Offline	Addiction	18/18	44.44	38.4	7.5
	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
	1	F3/rSO	0.03	30	Recognition memory task (word stem completion) – Errorful learning	Online	HV	18/18	72.22	23.3	3
Hammer et al. (2011) [43]	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
	2	rSO/F3	0.03	30	Recognition memory task (word stem completion) – Errorless learning	Online	HV	18/18	72.22	23	3.4
Harty et al. (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 et al. (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
Hoy et al. (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
	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
	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 et al. (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	–
	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	–
Javadi and Cheng (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 et al. (2009) [49]	1	F3/rSO	0.08	30	2-Back	Online	Stroke	10/10	30	47.9	8.9

(continued on next page)

**Table 1** (continued)

Author	Exp	Anode/cathode	Density (mA/cm <sup>2</sup> )	Duration (min)	Outcome	Online/ offline	Condition	N (a/s)	% Fem.	Age (M)	Age (SD)
Jones et al. (2015) [50]	1	F3/Contr. Check	0.04	10	WM Change Detection Task – Low WM Capacity – Active Strategy	Offline	HV	24/24	50	23.83	3.67
	1	F3/Contr. Check	0.04	10	WM Change Detection Task – Low WM – Passive Strategy	Offline	HV	24/24	50	23.83	3.67
	2	F3/Contr. Check	0.04	10	WM Change Detection Task – High WM – Active Strategy	Offline	HV	24/24	50	23.83	3.67
	2	F3/Contr. Check	0.04	10	WM Change Detection Task – High WM – Passive Strategy	Offline	HV	24/24	50	23.83	3.67
	3	F3/Contr. Check	0.04	10	WM Change Detection Task – Low WM – High Motivation	Offline	HV	20/20	60	21.95	3.28
	3	F3/Contr. Check	0.04	10	WM Change Detection Task – Low WM – Low Motivation	Offline	HV	20/20	60	21.95	3.28
	4	F3/Contr. Check	0.04	10	WM Change Detection Task – High WM – High Motivation	Offline	HV	20/20	60	21.95	3.28
	4	F3/Contr. Check	0.04	10	WM Change Detection Task – High WM – Low Motivation	Offline	HV	20/20	60	21.95	3.28
Kang et al. (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 et al. (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
Keeser et al. (2011) [53]	1	F3/rSO	0.06	20	0-Back	Offline	HV	10/10	50	28.89	2.67
	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 et al. (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 et al. (2014) [55]	1	F3/rSO	0.06	20	Auditory Go/NoGo	Offline	HV	16/16	37.5	29.9	6.1
Knechtel et al. (2014) [56]	1	F3/rSO	0.06	20	Auditory Go/NoGo	Offline	SCZ	14/14	35.71	46.7	6.4
Leite et al. (2013) [57]	1	F3/F4	0.06	30	Letter/Digit naming	Online	HV	16/16	81.25	24	7.702
	1	F4/F3	0.06	30	Letter/Digit naming	Online	HV	16/16	81.25	24	7.702
	1	F3/F4	0.06	30	Vowel/Consonant parity task	Online	HV	16/16	81.25	24	7.702
	1	F4/F3	0.06	30	Vowel/Consonant parity task	Online	HV	16/16	81.25	24	7.702
	1	F3/rSO	0.03	15	Cognitive set shifting task (no shift)	Offline	HV	15/15	80	20.3	1.99
Leite et al. (2011) [58]	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 et al. (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 et al. (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 et al. (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/ISO	0.06	20	2-Back	Online	HV	12/12	83.33	23.5	3.7
	2	ISO/F4	0.06	20	2-Back	Online	HV	12/12	83.33	23.5	3.7
Nelson et al. (2014) [61]	1	F3/F4	0.03	10	Vigilance task	Online	HV	10/10	20	27.6	7.4
	1	F4/F3	0.03	10	Vigilance task	Online	HV	10/10	20	27.6	7.4
	2	F3/F4	0.03	10	Vigilance task	Online	HV	9/9	22	28.1	6.7
	2	F4/F3	0.03	10	Vigilance task	Online	HV	9/9	22	28.1	6.7
	3	F3/F4	0.03	10	Vigilance task	Online	HV	10/10	20	27.6	7.4
	3	F4/F3	0.03	10	Vigilance task	Online	HV	10/10	20	27.6	7.4
	4	F3/F4	0.03	10	Vigilance task	Online	HV	9/9	22	28.1	6.7
	4	F4/F3	0.03	10	Vigilance task	Online	HV	9/9	22	28.1	6.7

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Table 1 (continued)

Author	Exp	Anode/cathode	Density (mA/cm <sup>2</sup> )	Duration (min)	Outcome	Online/offline	Condition	N (a/s)	% Fem.	Age (M)	Age (SD)
Nieratschker et al. (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 – response 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
Nilsson et al. (2015) [63]	1	F3/rSO	0.03	25	3-Back	Online	HV	30/30	64.67	69	7
	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 and Thompson-Schill (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
	1	F3/rSO	0.04	30	3-Back	Online	HV	15/15	66.66	26.5	3.5
Ohn et al. (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 et al. (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
	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
Powell et al. (2014) [68]	1	F3/rSO	0.06	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	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	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	Parametric Go/NoGo task – level 1/2/3 (correct response inhibition)	Online	HV	46/46	45.65	25.87	7.29
Saidmanesh et al. (2012) [69]	1	F3/rSO	0.06	20	Delayed match to sample task – verbal working memory easy	Offline	MDD	14/14	50	40.4	9.67
	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
Sela et al. (2012) [70]	1	F3/F4	0.08	20	Picture naming task	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
Smirni et al. (2015) [71]	1	F3/F4	0.04	15	Semantic decision task (unpredictable)	Offline	HV	11/11	58.33	25.23	2.65
	1	F3/F4	0.04	15	Semantic decision task (predictable)	Offline	HV	11/11	58.33	25.23	2.65
	2	F4/F3	0.04	15	Semantic decision task (unpredictable)	Offline	HV	11/11	58.33	25.23	2.65
	2	F4/F3	0.04	15	Semantic decision task (predictable)	Offline	HV	11/11	58.33	25.23	2.65
Teo et al. (2011) [72]	1	Extra-Ceph./F3	0.03	20	Recognition Memory Task	Offline	HV	20/20	80	23.56	2.25
	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
Turi et al. (2015) [73]	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
Vanderhasselt et al. (2013) [74]	1	F3/T7	0.03	15	Probabilistic reinforcement learning (RL) and choice task	Online	HV	16/16	0	22.9	2.2
	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
Vanderhasselt et al. (2013) [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
	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
	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
	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

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**Table 1** (continued)

Author	Exp	Anode/cathode	Density (mA/cm <sup>2</sup> )	Duration (min)	Outcome	Online/offline	Condition	N (a/s)	% Fem.	Age (M)	Age (SD)
Vanderhasselt et al. (2013) [75]	1	F3/rSO	0.06	20	Cued emotional conflict task (CECT) – opposite happy × sad	Offline	HV	25/25	68	22.12	3.76
	1	F3/rSO	0.06	20	Cued emotional conflict task (CECT) – actual happy × sad	Offline	HV	25/25	68	22.12	3.76
Vannorsdall et al. (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 et al. (2011) [77]	1	F3/rSO	0.06	20	Probabilistic learning task – weather prediction task	Online	SCZ	20/20	50	37.6	4.4
Wirth et al. (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 and Plewnia (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
	1	Extra-cephalic/F3	0.03	20	Delayed response working memory task (DWM) – neutral	Online	HV	28/28	71.4	30.86	10.18
Wolkenstein et al. (2014) [80]	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
Wu et al. (2014) [81]	1	F4/Contr. Check	0.06	15	Computerized corsi block tapping task (CBT) – spatial WM – forward interference	Offline	HV	20/20	60	26	–
	1	F4/Contr. Check	0.06	15	Computerized corsi block tapping task (CBT) – spatial WM – forward no interference	Offline	HV	20/20	60	26	–
	1	F4/Contr. Check	0.06	15	Computerized corsi block tapping task (CBT) – spatial WM – backward interference	Offline	HV	20/20	60	26	–
	1	F4/Contr. Check	0.06	15	Computerized corsi block tapping task (CBT) – spatial WM – backward no interference	Offline	HV	20/20	60	26	–
Zmigrod et al. (2014) [82]	1	F3/rSO	0.06	20	Event file task (EFT) – binding of features	Online	HV	13/13	65.38	20	1.698
	1	rSO/F3	0.06	20	Event file task (EFT) – binding of features	Online	HV	13/13	65.38	20	1.698
	2	F4/ISO	0.06	20	Event file task (EFT) – binding of features	Online	HV	13/13	65.38	20	1.698
	2	ISO/F4	0.06	20	Event file task (EFT) – binding of features	Online	HV	13/13	65.38	20	1.698

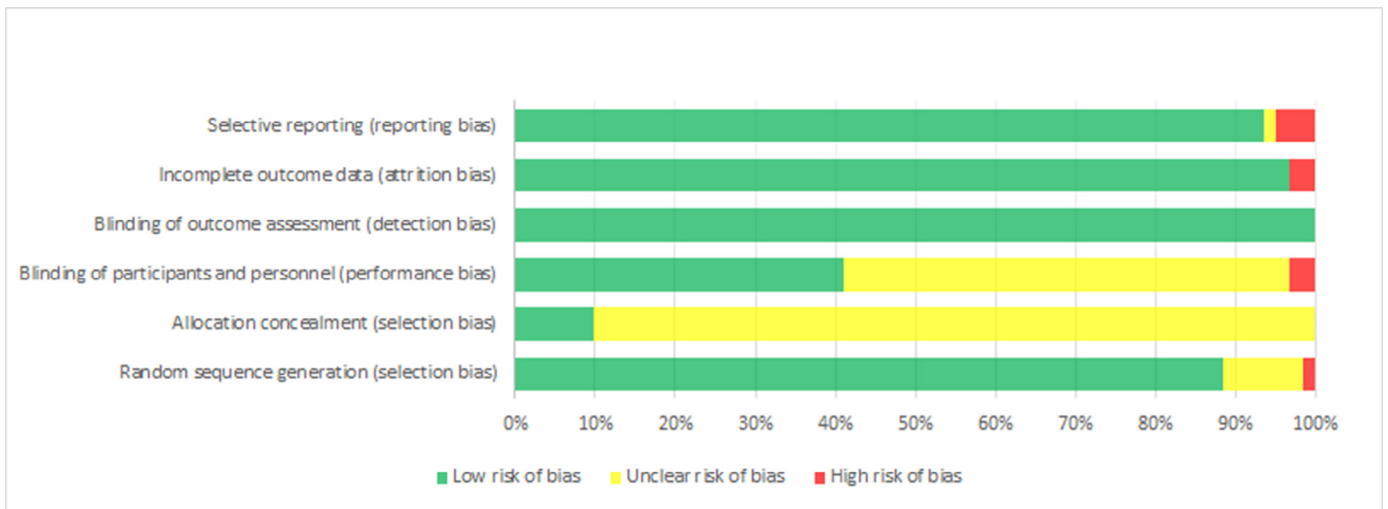
Abbrev.: Exp = Experiment number; tDCS montage: contr. = contralateral; CZ = vertex; F3 = left DLPFC; F4 = right DLPFC; ipsil. = ipsilateral; ISO = left supraorbital cortex; mA = micro-Ampère; OFC = orbitofrontal cortex; rSO = right supraorbital cortex; T7 = middle, superior temporal gyrus. Sample: AD = 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.

**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.

	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	<b>0.03</b>	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	<b>&lt;0.01</b>	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	<b>&lt;0.01</b>	<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





**Figure 2.** Risk of bias graph according to Cochrane recommendations.

**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.

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

### Main results in healthy samples

#### 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).

**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.

	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	<b>0.05</b>	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	<b>0.06</b>	<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

#### 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 toward 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).

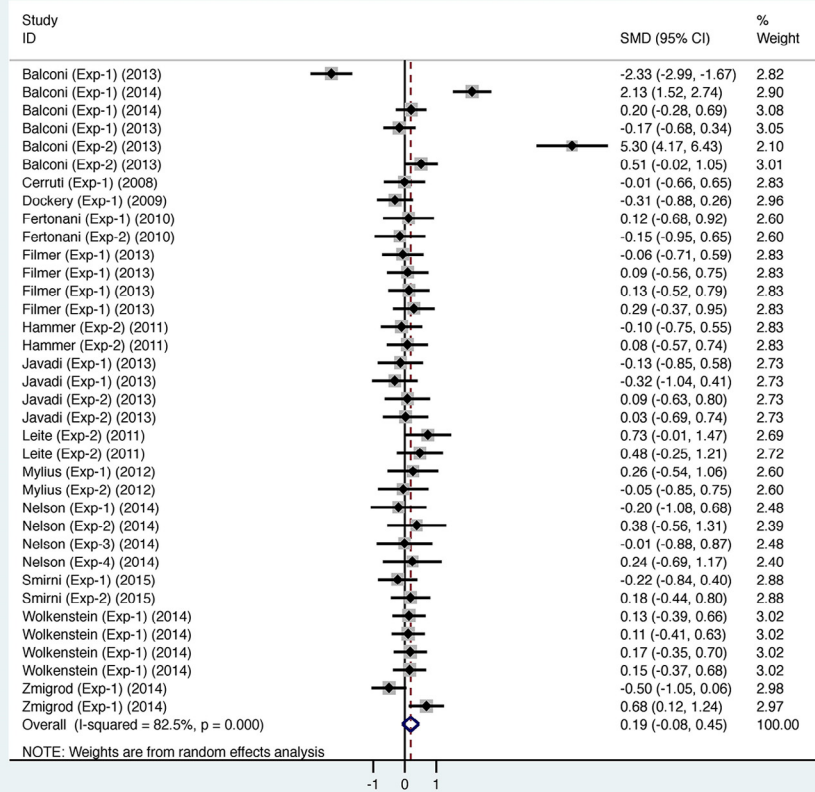
#### Main results in neuropsychiatric samples

#### Results for RT trials

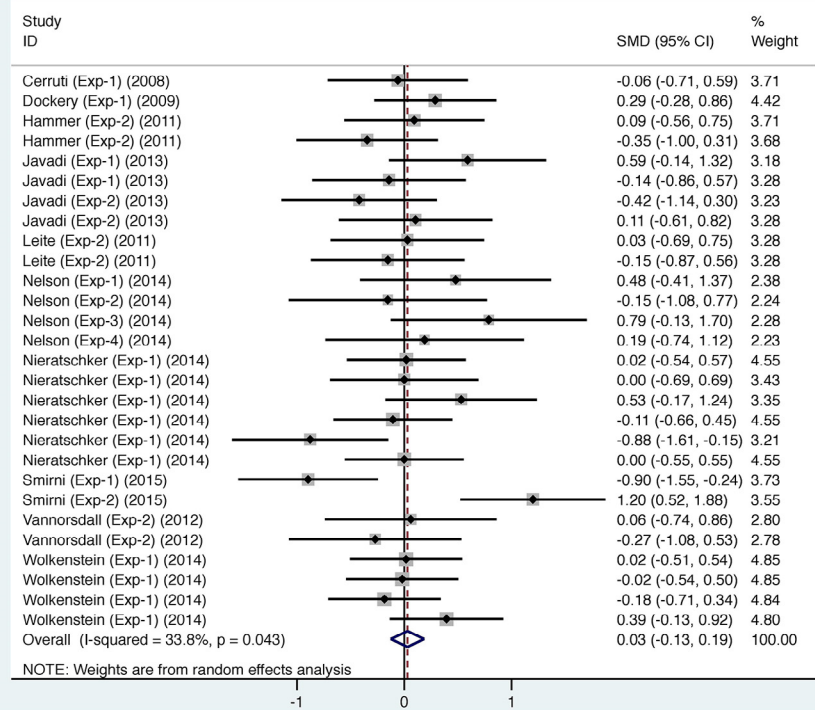
For anodal tDCS effects on RTs (N = 22), Cohen's d was −0.15 (95% CI −0.30 to 0.01,  $p = 0.065$ ; Fig. 5a). Overall, participants tended to respond faster after anodal vs. sham non-invasive brain stimulation, although this effect was non-significant. No significant heterogeneity was observed ( $I^2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

#### Results for ACC trials

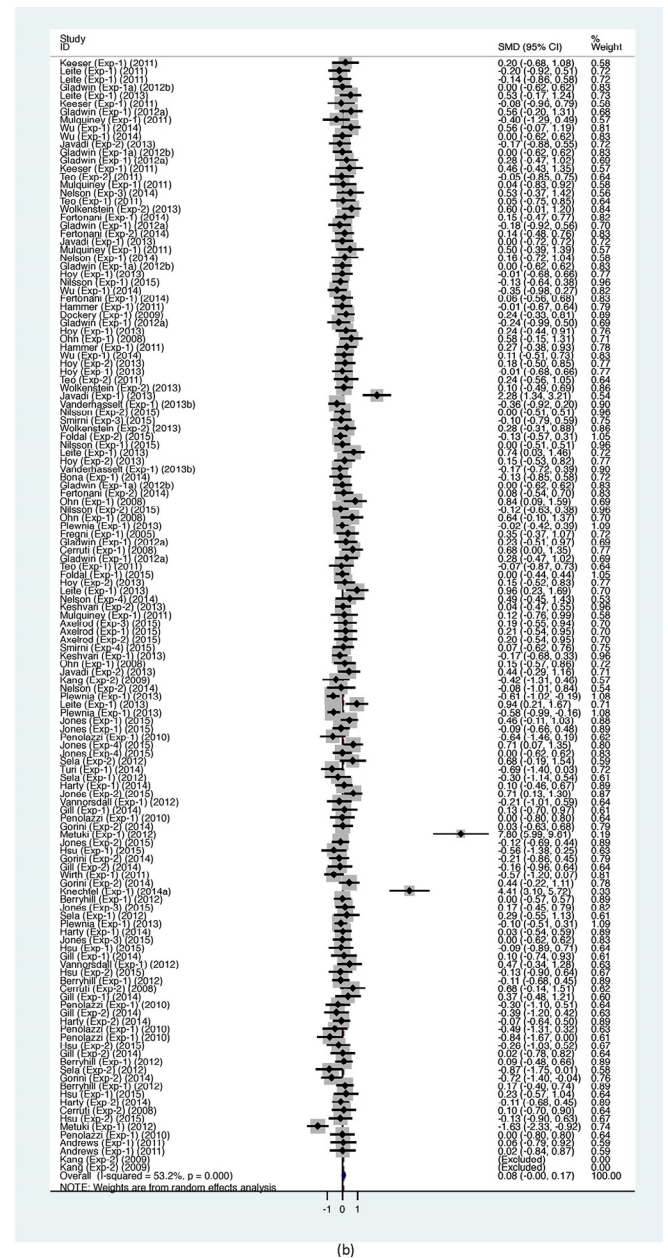
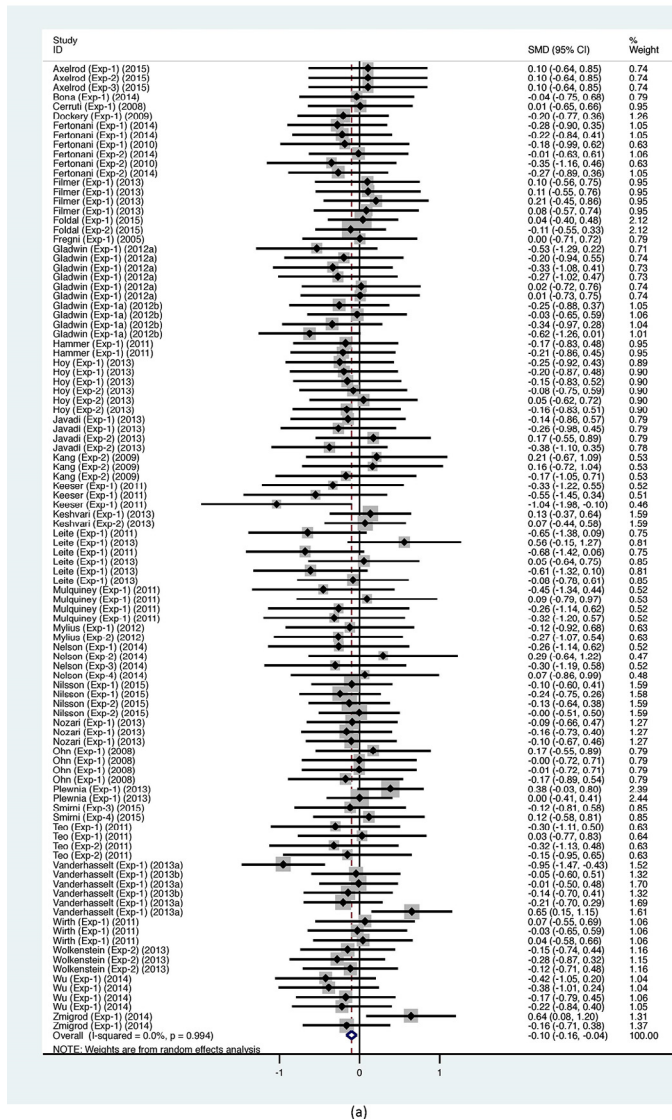
For anodal tDCS effects on ACC (N = 30) we observed a Cohen's d of 0.22 (95% CI 0.04 to 0.40,  $p < 0.05$ , Fig. 5b; significant heterogeneity,  $I^2 = 45.20\%$ ;  $\chi^2(29) = 5$ ,  $p < 0.01$ ), i.e. participants responded more accurately following active anodal tDCS compared to sham



(a)



(b)



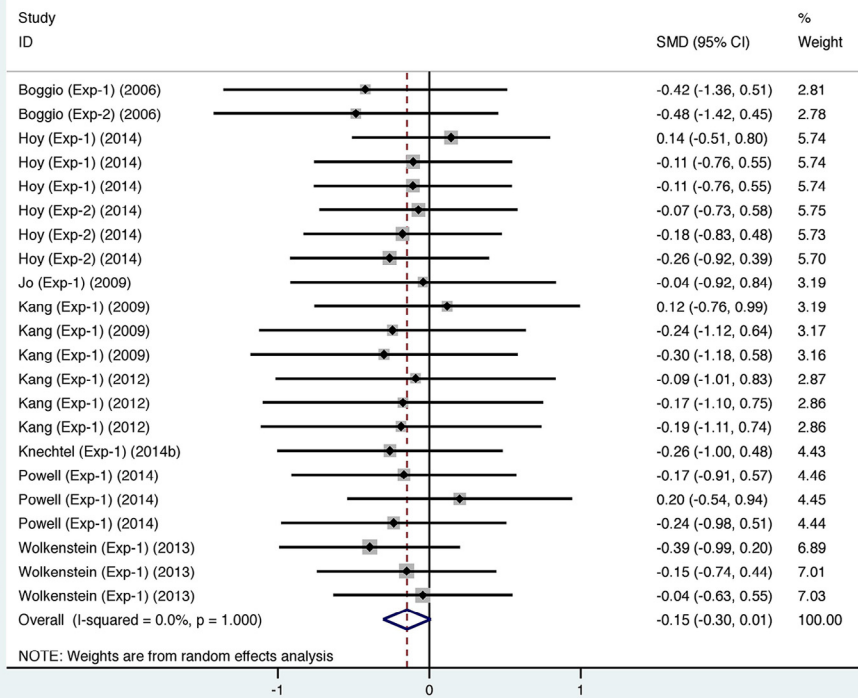
**Figure 4.** (a) Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Reaction Time (RT) from the Hedges' g random effects model in healthy participants. Positive values indicate an increase in reaction time following anodal transcranial direct current stimulation (a-tDCS). Negative values indicate a decrease in reaction time following a-tDCS. Across all included trials, a significant Hedges' g of  $-0.10$  (CI  $-0.16$  to  $-0.04$ ) was found. Error bars: 95% confidence interval. (b) 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. Across all included trials, a non-significant Hedges' g of  $0.08$  (CI  $-0.00$  to  $0.17$ ) was found. Results did not change following exclusion of outliers (cf. main text). Error bars: 95% confidence interval.

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).

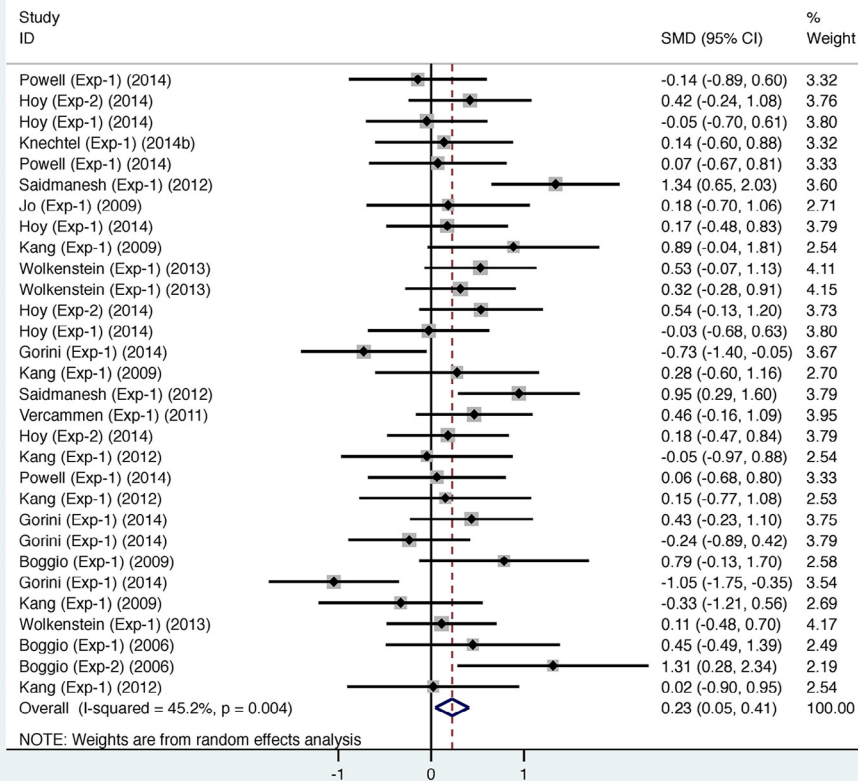
## Discussion

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

**Figure 3.** (a) 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. (b) 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.



(a)



(b)



**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.

	Coeff.	SE	T	P
Density	5.59	2.13	2.63	<b>0.01</b>
Age	<0.01	<0.01	−0.02	0.99
% Female	0.01	<0.01	3.36	<b>&lt;0.01</b>
Task type	0.01	0.04	0.26	0.79
Charge	0.16	0.08	2.01	<b>0.05</b>
Age	<0.01	<0.01	−0.39	0.70
% Female	0.01	<0.01	2.87	<b>0.01</b>
Task type	0.01	0.04	0.15	0.88

**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.

	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	<b>&lt;0.01</b>

**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.

	Coeff.	SE	t	p
Online vs. offline	0.64	0.21	3.03	<b>0.01</b>
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

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.

### 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<sup>2</sup>; M(SD) = 0.04(0.02), range 0.02–0.08) and density charge (i.e. (current density)\*(session duration); (A\*s)/cm<sup>2</sup> = C/cm<sup>2</sup>; 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

**Figure 5.** (a) Forest Plot showing the effect sizes from the comparison between anodal vs. sham tDCS for Reaction Time (RT) from the Hedges' g random effects model 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. (b) 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.



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 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 1 mA c-tDCS vs. cortical excitation following 2 mA 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.

### 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 2 mA tDCS was more effective than 1 mA 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.

### 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, possibly 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 1 mA/35 cm<sup>2</sup> is used for 20 min might not be comparable to a trial using 2 mA/35 cm<sup>2</sup> for 10 min, 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/cm<sup>2</sup>), 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/cm<sup>2</sup> [102]. In comparison, the highest density charge in our dataset was 0.15C/cm<sup>2</sup>. 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.

### 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.

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## Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2016.04.006.

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