Brain Stimulation 9 (2016) 197–208

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations

Aron T. Hill *, Paul B. Fitzgerald, Kate E. Hoy

Monash Alfred Psychiatry Research Centre, Central Clinical School, The Alfred and Monash University, Melbourne, Victoria, Australia

A R T I C L E I N F O

Article history:
Received 25 April 2015
Received in revised form 25 September 2015
Accepted 13 October 2015
Available online 23 October 2015

Keywords:
Transcranial direct current stimulation (tDCS)
Cognition
Working memory
Dorsolateral prefrontal cortex
Psychiatry

A B S T R A C T

Background: Several studies have trialled anodal transcranial direct current stimulation (a-tDCS) for the enhancement of working memory (WM) in both healthy and neuropsychiatric populations. However, the efficacy of this technique remains to be clearly established.
Objective: This review provides a quantitative synthesis of the published literature investigating the effects of a-tDCS, compared to sham, on WM, as assessed using the n-back, Sternberg and digit-span tasks. We also separated results from tasks performed 'online' (during stimulation) and 'offline' (following stimulation). The secondary aim was to assess for any additional effects of current density and stimulation duration.
Methods: Comprehensive literature searches were performed using MEDLINE, Embase, PsychINFO, CENTRAL and Scopus from July 1998 to June 2014.
Results: In healthy cohorts, a-tDCS produced a trend towards improvement for offline WM accuracy ($p = 0.05$) and a small, but significant improvement in reaction time ($p = 0.04$); however, no significant effects were observed for online tasks (accuracy [$p = 0.29$], reaction time [$p = 0.42$]). In the neuropsychiatric cohort, a-tDCS significantly improved accuracy for online ($p = 0.003$), but not offline ($p = 0.87$) tasks, and no effect was seen for either online ($p = 0.20$) or offline ($p = 0.49$) reaction times. Secondary analyses controlling for current density and stimulation duration provided limited support for the role of these factors in influencing a-tDCS efficacy.
Conclusions: This review provides some evidence of a beneficial effect of a-tDCS on WM performance. However, the small effect sizes obtained, coupled with non-significant effects on several analyses require cautious interpretation and highlight the need for future research aimed at investigating more optimised stimulation approaches.

Introduction

Cognitive deficits, including working memory (WM) impairment, are core features of a number of neuropsychiatric disorders, contributing substantially to burden of disease and remaining largely refractory to conventional drug-based therapies [1–3]. Transcranial direct current stimulation (tDCS) is emerging as a safe and relatively inexpensive means of modulating both psychological and physiological processes through the non-invasive application of low-voltage currents to the brain [4]. Indeed, a number of studies have now reported beneficial effects of tDCS on memory function in neuropsychiatric populations [5–12] as well as in healthy individuals [13–24]. However, despite these promising findings, the level of efficacy with which this nascent technology can modulate cognition, as well as the optimal parameters required for achieving these outcomes, remain to be fully elucidated.

Administration of tDCS typically involves applying two large (25–35 cm^2) saline-soaked sponge electrodes, consisting of an anode and a cathode, to the scalp. A weak constant current in the range of 1–2 mA is then passed through the electrodes for several minutes resulting in either facilitation or inhibition of spontaneous neuronal activity within the underlying cortex [25–27]. Specifically, anodal tDCS (a-tDCS) is able to enhance cortical excitability, while cathodal stimulation typically leads to a reduction in excitability [4,26,28,29]. Importantly, the effects of tDCS have been shown to persist for over an hour beyond the period of stimulation [28,30]. Such ongoing effects are likely the result of N-methyl-D-aspartate

* Corresponding author. Tel.: +61 3 9076 6564; fax: +61 3 9076 5075.
E-mail address: aron.hill@monash.edu (A.T. Hill).

1935-861X/© 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.brs.2015.10.006

(NMDA) receptor mediated neuroplasticity-based mechanisms [31,32] and are, to some extent, contingent on stimulation parameters including the current density (i.e., the ratio of injected current divided by the electrode surface area) and stimulation duration [27,28,33].

To date, the ability of a-tDCS to modulate WM has been explored in a number of studies, albeit with mixed results. WM provides the ability to hold and manipulate information over a short period of time, with WM capacity linked to a variety of higher order cognitive abilities including selective attention, reading comprehension, reasoning and complex decision making [34–38]. Moreover, dysfunctional WM has been reported in a range of neuropsychiatric conditions including depression [39], schizophrenia [40] and Parkinson's disease [41]. The dorsolateral prefrontal cortex (DLPFC; Brodmann area 9/46), with its robust neuroanatomical connections to numerous cortical and subcortical structures, is strongly implicated in WM [42–44], and consequently, the majority of research investigating the effects of a-tDCS on WM function has chosen the DLPFC as the target region for stimulation, which can be accurately stimulated by positioning the anode over either the F3 (left DLPFC) or F4 (right DLPFC) regions on the scalp in accordance with the international 10–20 system for electrode placement [45].

Although a number of studies have demonstrated improvements in WM in both healthy and clinical cohorts, either during ('online') or shortly after ('offline') a-tDCS delivery, heterogeneous outcomes between individual studies, coupled with differences in experimental methodology, make accurate judgements regarding efficacy incredibly challenging. Small sample sizes, which are present in many such studies, are one potential limiting factor, and pooling the results from these experiments in a meta-analysis can help curtail this problem. Furthermore, inter-study variability in stimulation parameters such as current density and stimulation duration, both of which are known moderators of tDCS dose [46,47], also likely contributes to the disparity in results observed thus far. Available neurophysiological data from studies of the motor cortex show some support for a dose–response relationship between cortico-spinal excitability and either current density or stimulation duration, whereby, within specific limits, larger current densities or longer stimulation durations lead to more pronounced excitability changes [26,48,49]. However, these results are certainly not without exception [33,50,51] and whether any such relationship can be extended to stimulation of other brain regions, or to cognitive/behavioural outcome measures, remains to be established, with inconsistent findings having been reported thus far [11,16,52,53]. As such, carefully constructed quantitative reviews which employ rigorous and transparent inclusion/exclusion criteria and attempt to account for methodological variables which are known to influence the outcome measures are vital for gaining a better understanding of tDCS-related effects [54,55].

The goals of the present systematic review and meta-analysis were twofold. Our primary aim was to evaluate the efficacy with which a-tDCS, compared to sham, could improve WM in both healthy and neuropsychiatric cohorts. In order to achieve this aim, we analysed results from n-back, Sternberg and digit-span WM tasks, taking into account both online and offline effects, where possible. Additionally, as the optimal stimulation parameters required to enhance WM function remain unclear; our secondary aim was to investigate whether differences in two important a-tDCS parameters, namely current density and stimulation duration, might impact WM performance. We anticipated that such analyses could help to better identify important variables for consideration in future trials. We specifically hypothesised that, compared to sham, a-tDCS would lead to significant improvements in WM in both healthy and neuropsychiatric cohorts. Furthermore, we also anticipated that higher current densities and longer stimulation durations would produce more robust improvements in WM function.

Methods

Protocol registration

The protocol for this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42014013464).

Literature search

An extensive literature search was conducted using the following databases: MEDLINE (PubMed), Embase (Ovid), PsycINFO (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid) and SCOPUS from 1 July 1998 (i.e., first published evidence of the effects of a contemporary tDCS paradigm on cortical excitability by Priori et al. [56]) to 17 June 2014 (see Supplementary Material for detailed search strategy). Once all relevant studies were retrieved, their title and abstract were screened against the inclusion/exclusion criteria (Table 1). In cases where the title and abstract alone provided insufficient information to determine whether the study could be included, the full-text version of the article was screened (see Fig. 1 for a flow-chart depicting relevant stages of the literature search and selection process).

Selection criteria

Included studies were required to meet the selection criteria outlined in Table 1. Specifically, studies were included if: (1) they were performed on either healthy volunteers or individuals suffering from a neuropsychiatric illness, (2) participants were over the age of 18 years, (3) either 'online' or 'offline' data were available for at least

Table 1
Inclusion and exclusion criteria.

	Inclusion	Exclusion
Participants	≥18 years of age	Non-human subjects
	Either healthy or suffering from a neuropsychiatric illness	Neuropsychiatric illness secondary to another illness
Intervention	tDCS, anode applied over either the left or right DLPFC	Anode applied over brain region other than DLPFC
Comparison	Sham stimulation	Any other control group
Outcomes	WM as measured by n-back, Sternberg, or digit-span tasks	Other type of WM assessment
	WM measured either 'online' or 'offline'	Distinction not made between 'online' and 'offline' WM assessment
Trial design	Randomised controlled trials	Review articles
	Controlled trials	Case reports
	Single or double-blind	
Publication type	Published in a peer-reviewed journal	Unpublished data, grey literature
	Written in English	Non-English language articles

DLPFC, dorsolateral prefrontal cortex; WM, working memory.

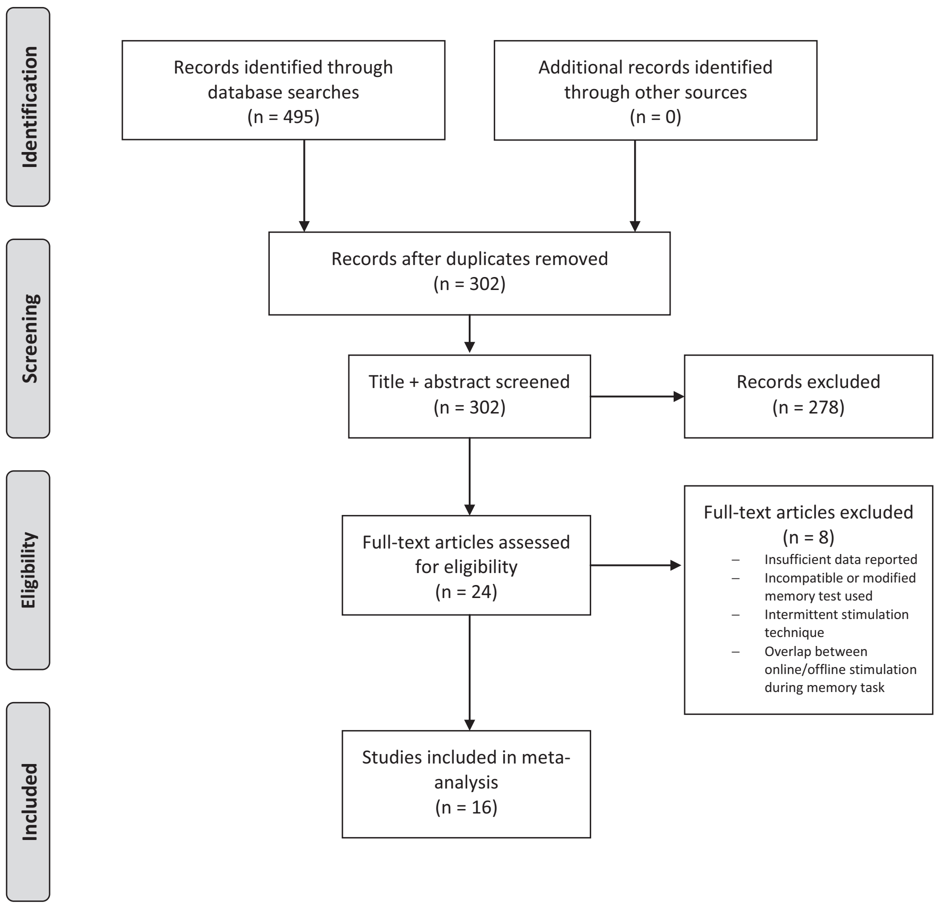

Figure 1. PRISMA flow chart depicting the flow of information through different phases of the review.

one of the specified WM tasks, (4) studies were published in a peer-reviewed scientific journal, (5) sham stimulation was used as a comparator, (6) articles were written in English and (7) studies employed, at a minimum, a single-blind technique (i.e., participants blinded to the type of stimulation they received). Both parallel and crossover study designs were included, and studies employing repeated stimulation sessions were also included, provided that they met all other inclusion criteria. Furthermore, studies were limited to those which applied stimulation to the DLPFC. The DLPFC was included as the stimulation site for WM studies for two main reasons: firstly, due to its direct involvement in this type of memory [57,58] and, secondly, to help maintain consistency between the different individual studies, the vast majority of which selected the DLPFC as the target for stimulation.

Working memory tasks

n-Back and Sternberg tasks

The n-back and Sternberg tasks are frequently employed as indexes of WM function in tDCS research. The n-back task involves the presentation of a consecutive series of stimuli (letters or numbers) to the participant who is required to respond when a match is obtained between the present stimulus and that presented 'n' trials earlier (e.g., 2 trials earlier for the 2-back task). In the present review, we included experiments utilising either 1-back, 2-back or 3-back tasks; 0-back tasks were excluded as they do not require the manipulation of information within WM [57]. The Sternberg task [59] involves the presentation of a memory set of several letters, which after a retention period of several seconds is followed by a probe stimulus containing a single letter. The participant is required to determine whether this probe stimulus also appeared in the previous memory set. In the current meta-analysis, WM performance on both tasks was segmented into data for accuracy and reaction time. Accuracy measures how well a participant can respond to a correct target stimulus, while reaction-time measures how quickly they are able to do so. In addition, we chose to separate tasks based on whether they were performed 'online' (i.e., during a-tDCS delivery) or 'offline' (i.e., after a-tDCS had been administered). This decision was made based on the different neurobiological processes known to occur during and directly after stimulation, whereby the online effects of a-tDCS have been attributed to resting membrane potential alterations, while the offline effects of a-tDCS appear to result from modulation of synaptic plasticity [60,61].

Digit-span task

Several published studies [8–10,18] have utilised the digit-span task to assess WM. This task requires participants to repeat back a series of digits read-out by an examiner, either in the same order in which they were presented (digits forward) or in reverse order (digits backward), and is included as a subset for the assessment of WM in the Wechsler Adult Intelligence Scale [62]. In the current analysis, both digits-forward and digits-backward results were included as measures of WM accuracy.

Risk of bias

We utilised the risk of bias assessment tool provided as part of the RevMan software package [63]. Fig. 2 depicts the methodological

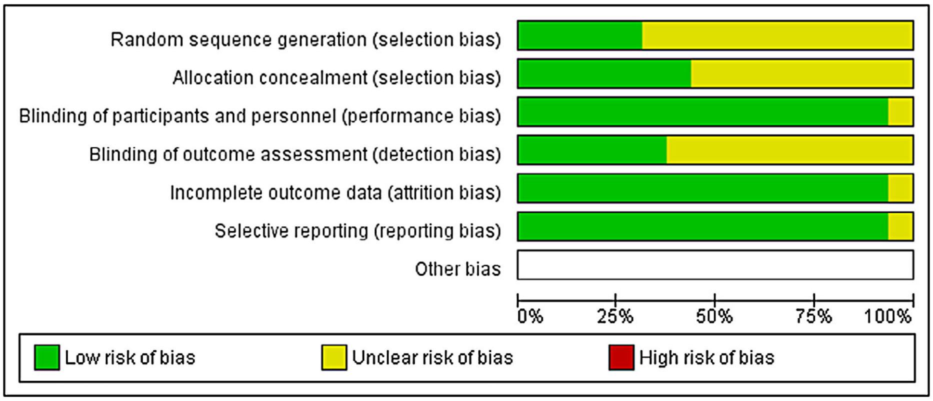

Figure 2. Risk of bias graph indicating the review authors' judgements about each risk of bias item presented as percentages across all included studies.

quality graph obtained, indicating the authors' judgements regarding risk of bias for various aspects of each included study. In addition, funnel plots were generated to assess for any potential publication bias (Fig. 3).

Data extraction

Means and standard deviations of the outcome measures of interest were collected, as were sample sizes for each included study.

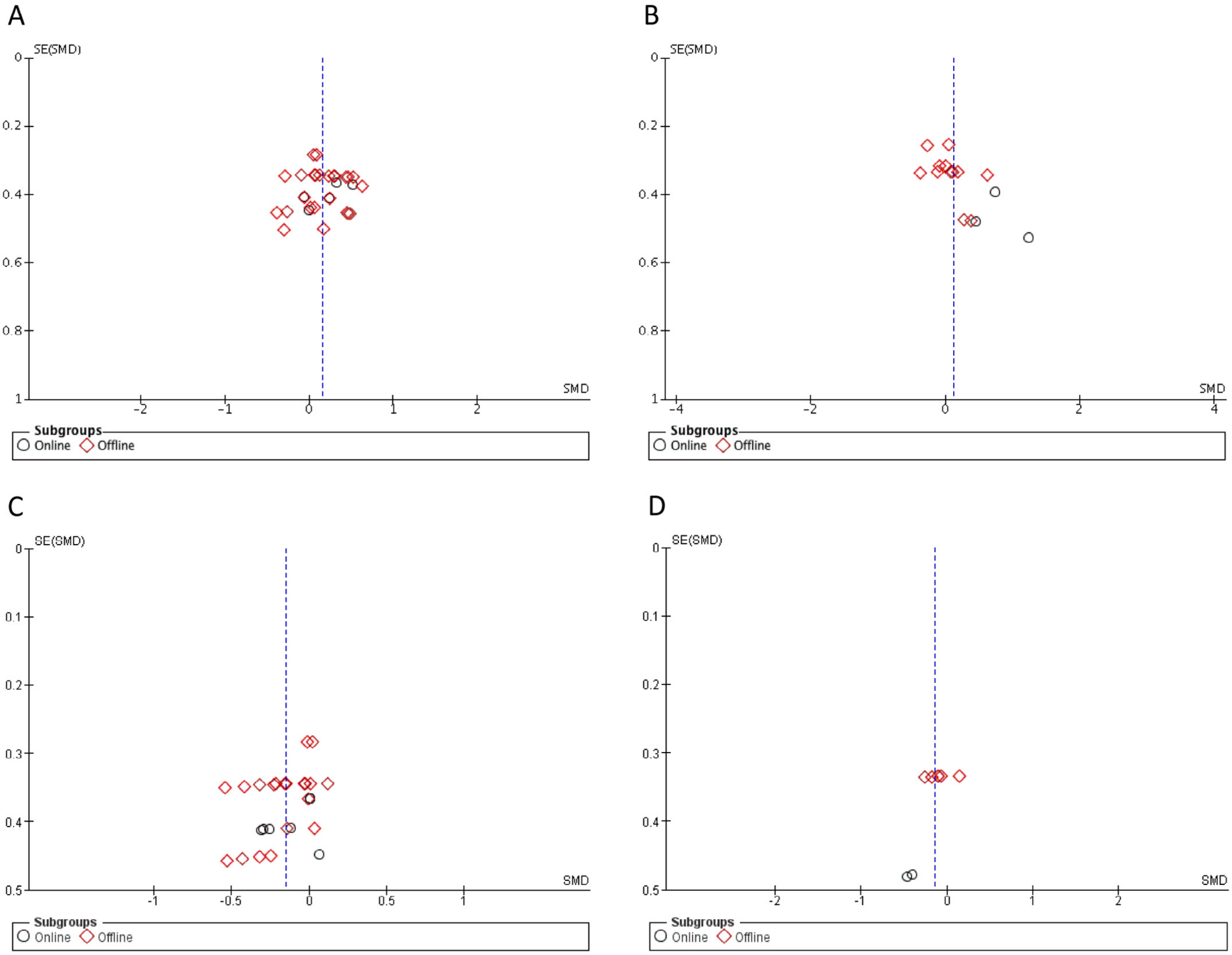

Figure 3. Funnel plots exploring publication bias: Accuracy in healthy (A) and clinical (B) cohorts and reaction time in healthy (C) and clinical (D) cohorts. Circles denote WM tasks performed online, while diamonds denote WM tasks performed offline. The horizontal axis represents the effect size (SMD), while the vertical axis indicates the standard error (SE) of the SMD. In all instances, the studies appear roughly symmetrical around the SMD, suggesting a lack of publication bias.

In cases where standard error values were reported, standard deviation values were calculated using the formula: SD = SE √n [64]. If studies contained data in a graphical rather than a numerical format, the Plot Digitizer software package [65] was used to extract the plotted values. This Java-based software allows plotted values to be accurately converted into a numerical format and has been previously employed in a number of other meta-analytical reviews (e.g., references 48,66,67). In instances where insufficient data were available, or where there was any ambiguity regarding the data presented, an attempt was made to contact the corresponding author(s) via email to obtain further information/clarification. Many of the studies included in the current review also reported results for more than one experimental condition. For example, several studies performed separate experiments investigating different stimulation intensities (e.g., [16,53]), post-stimulation time-points (e.g., [11,16]), or memory load (e.g., [15,20]). In these instances, each experimental condition was treated as a unique dataset. Table 2 provides a summary of the characteristics of the studies included in this review.

Meta-analysis

All studies included in the analyses used continuous outcome measures. The RevMan software package, version 5.3 [63], was used to calculate effect size. The standard mean difference (SMD) was chosen to measure effect size as it allows for direct comparisons to be made between studies utilising different memory scales [64]. The particular formulation of the SMD implemented by the RevMan package is Hedge's adjusted *g*, which is similar to Cohen's *d*, but includes an adjustment for small sample bias [69]. Using the convention proposed by Cohen [70], effect sizes can be interpreted as either small (0.2), medium (0.5) or large (0.8).

Tests of heterogeneity and selection of statistical model

We tested for heterogeneity using the chi-squared test [64]. Heterogeneity was also further quantified using the I^2 statistic, which can range from 0% to 100%, where 0% indicates no heterogeneity, values between 30% and 60% represent moderate heterogeneity, while values between 75% and 100% are indicative of high levels of heterogeneity [64]. Statistical heterogeneity was low for all included datasets. Nevertheless, although overall low heterogeneity was observed, a random-effects model was chosen for all statistical analyses. The random-effects model, as opposed to a fixed-effects model, is generally considered to be more appropriate for analysing data which have been accumulated from a series of independent studies and is able to better account for differences in effect sizes across studies [71].

Results

Study selection

Online database searches identified a total of 495 records matching the specific search terms. After removal of duplicate records, 302 studies remained. Screening of the title and abstract of these studies excluded a further 278 records which failed to meet inclusion criteria. Full-text versions of the remaining 24 articles were then screened for eligibility, which excluded a further eight studies. The remaining 16 studies met all inclusion criteria and were included in the current review. Overall, sample sizes were relatively small, and considerable inter-study variability was present, with sample sizes ranging from 10 to 60 participants (median = 18). Crossover experimental designs were also favoured by the majority of studies, with only four [8–10,12] utilising parallel designs. In addition, most studies employed single a-tDCS sessions, with three of the 16 studies [8–10] using repeated stimulation sessions. Both current density and duration of stimulation varied considerably between studies, with current densities ranging from 0.029 to 0.08 mA/cm^2 and stimulation durations ranging from 10 to 30 minutes. In terms of electrode placement, the left DLPFC was chosen as the target site for anodal stimulation in all but two experiments (i.e., Berryhill and Jones, experiment 2; Mylius et al., experiment 2) [17,68], which chose the right DLPFC as the stimulation target; while the cathode was placed over the contralateral supraorbital region in all experiments except for Berryhill and Jones (experiments 1 and 2 – cathode placed over contralateral cheek) [17] and Oliveira et al. (cathode placed over F4) [12].

Participants in included studies

A total of 352 participants were included from all combined trials, comprising of 170 healthy individuals and 182 individuals with a neuropsychiatric diagnosis. These numbers could be further partitioned into 146 with a diagnosis of depression, 18 with Parkinson's disease and 18 with schizophrenia.

Risk of bias

A risk of bias graph summarising the authors' judgements about the likelihood of any systematic error being present in the included studies is presented in Fig. 2. Overall, risk of bias was low; nevertheless, all six domains of bias covered by the risk of bias assessment tool contained some level of unclear risk. This was most pronounced for the 'selection bias' and 'detection bias' domains. Specifically, although some blinding information was available from all of the studies (e.g., single, or double blind), detail was often lacking about blinding of outcome assessors. In addition, although many of the included studies stated that stimulation session orders were randomised (crossover designs) or that participants were randomly allocated to either active or sham stimulation groups (parallel designs), information pertaining to exactly how randomisation was achieved was often lacking. Funnel plots exploring potential publication bias are presented in Fig. 3. These plot the effect size (horizontal axis) against the standard error of the SMD (vertical axis). Typically, studies with larger sample sizes cluster closer to the top of the graph, with smaller studies scattered more widely at the bottom [72]. In the absence of bias, the plot should roughly resemble an inverted funnel, symmetrical around the mean effect size [73]. In the present review, no evidence of obvious asymmetry was seen in any of the funnel plots, suggesting an absence of publication bias.

Change in reaction time on n-back/Sternberg tasks with a-tDCS compared to sham stimulation

Fig. 4A provides a summary of the reaction time results for the healthy cohort. The combined results from online and offline studies demonstrate that a-tDCS, compared to sham, produced a small but significant reduction in reaction times on the WM tasks (SMD = –0.15, 95% CI = –0.29, –0.01, p = 0.03). These results failed to reach significance at the subgroup level for online WM tasks (SMD = –0.12, 95% CI = –0.42, 0.17, p = 0.42); however, a small but significant reduction in reaction time was observed for offline tasks (SMD = –0.16, 95% CI = –0.31, –0.00, p = 0.04). Fig. 4B summarises the reaction time results for the clinical cohort. The combined results demonstrate no significant change in reaction time with a-tDCS (SMD = –0.14, 95% CI = –0.39, 0.11, p = 0.26), with subgroup analyses also showing no significant change in reaction time for either the online (SMD = –0.43, 95% CI = –1.10, 0.23, p = 0.20) or offline (SMD = –0.09, 95% CI = –0.36, 0.17, p = 0.49) tasks.

Table 2
Characteristics of included working memory studies.

Study	Trial design	Cohort	Experiment	Sample size	Intervention	Anode location	Cathode location	Stimulation duration (min)	Stimulation strength (mA)	Anode size (cm^2)	Current density (mA/cm^2)	Online/offline memory task	Memory task
Andrews et al. [18]	Crossover	HS	1	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	
			2	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits backward
			3	11	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits-forward
			4	11	a-tDCS	F3	RSO	10	1	35	0.029	Offline	Digits-backward
Berryhill and Jones [17]	Crossover	HS	1	25	a-tDCS	F3	CC	10	1.5	35	0.043	Offline	2-back
			2	25	a-tDCS	F4	CC	10	1.5	35	0.043	Offline	2-back
Boggio et al. [52]	Crossover	PD	1	9	a-tDCS	F3	RSO	20	1	35	0.029	Online	3-back
			2	9	a-tDCS	F3	RSO	20	2	35	0.057	Online	3-back
Fregni et al. [13]	Crossover	HS	–	15	a-tDCS	F3	RSO	10	1	35	0.029	Online	3-back
Fregni et al. [10]	Parallel	Depression	1	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits forward
			2	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits backward
Hoy et al. [16]	Crossover	HS	1	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T0)	2-back
			2	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T0)	2-back
			3	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T0)	3-back
			4	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T0)	3-back
			5	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T20)	2-back
			6	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T20)	2-back
			7	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T20)	3-back
			8	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T20)	3-back
			9	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T40)	2-back
			10	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T40)	2-back
			11	17	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T40)	3-back
			12	17	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T40)	3-back
Hoy et al. [11]	Crossover	SCZ	1	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T0)	2-back
			2	18	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T0)	2-back
			3	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T20)	2-back
			4	18	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T20)	2-back
			5	18	a-tDCS	F3	RSO	20	1	35	0.029	Offline (T40)	2-back
			6	18	a-tDCS	F3	RSO	20	2	35	0.057	Offline (T40)	2-back
Jeon and Han [19]	Parallel	HS	1	32	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits forward
			2	32	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Digits backward
Keeser et al. [20]	Crossover	HS	1	10	a-tDCS	F3	RSO	20	2	35	0.057	Offline	1-back
			2	10	a-tDCS	F3	RSO	20	2	35	0.057	Offline	2-back
Loo et al. [9]	Parallel	Depression	1	40	a-tDCS	F3	RSO†	20	1	35	0.029	Offline	Digits forward
			2	40	a-tDCS	F3	RSO†	20	1	35	0.029	Offline	Digits backward
Loo et al. [8]	Parallel	Depression	1	60	a-tDCS	F3	RSO†	20	2	35	0.057	Offline	Digits forward
			2	60	a-tDCS	F3	RSO†	20	2	35	0.057	Offline	Digits backward
Mulquiney et al. [15]	Crossover	HS	1	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	1-back
			2	10	a-tDCS	F3	RSO	10	1	35	0.029	Offline	2-back
			3	10	a-tDCS	F3	RSO	10	1	35	0.029	Online	Sternberg
Mylius et al. [68]	Crossover	HS	1	12	a-tDCS	F3	RSO	20	2	35	0.057	Online	2-back
			2	12	a-tDCS	F4	LSO	20	2	35	0.057	Online	2-back
Ohn et al. [21]	Crossover	HS	1	15	a-tDCS	F3	RSO	30	1	25	0.04	Online	3-back
			2	15	a-tDCS	F3	RSO	30	1	25	0.04	Offline	3-back
Oliveira et al. [12]	Parallel	Depression	–	28	tDCS	F3	F4	30	2	25	0.08	Online	2-back
Teo et al. [53]	Crossover	HS	1	12	a-tDCS	F3	RSO	20	1	35	0.029	Online	3-back
			2	12	a-tDCS	F3	RSO	20	2	35	0.057	Online	3-back
			3	12	a-tDCS	F3	RSO	20	1	35	0.029	Offline	Sternberg
			4	12	a-tDCS	F3	RSO	20	2	35	0.057	Offline	Sternberg

CC, contralateral cheek, HS, healthy sample, LSO, left supraorbital area, PD, Parkinson's disease, RSO, right supraorbital area († denotes lateral aspect), SCZ, schizophrenia, T0, 0 minutes post-stimulation, T20, 20 minutes post-stimulation, T40, 40 minutes post-stimulation.

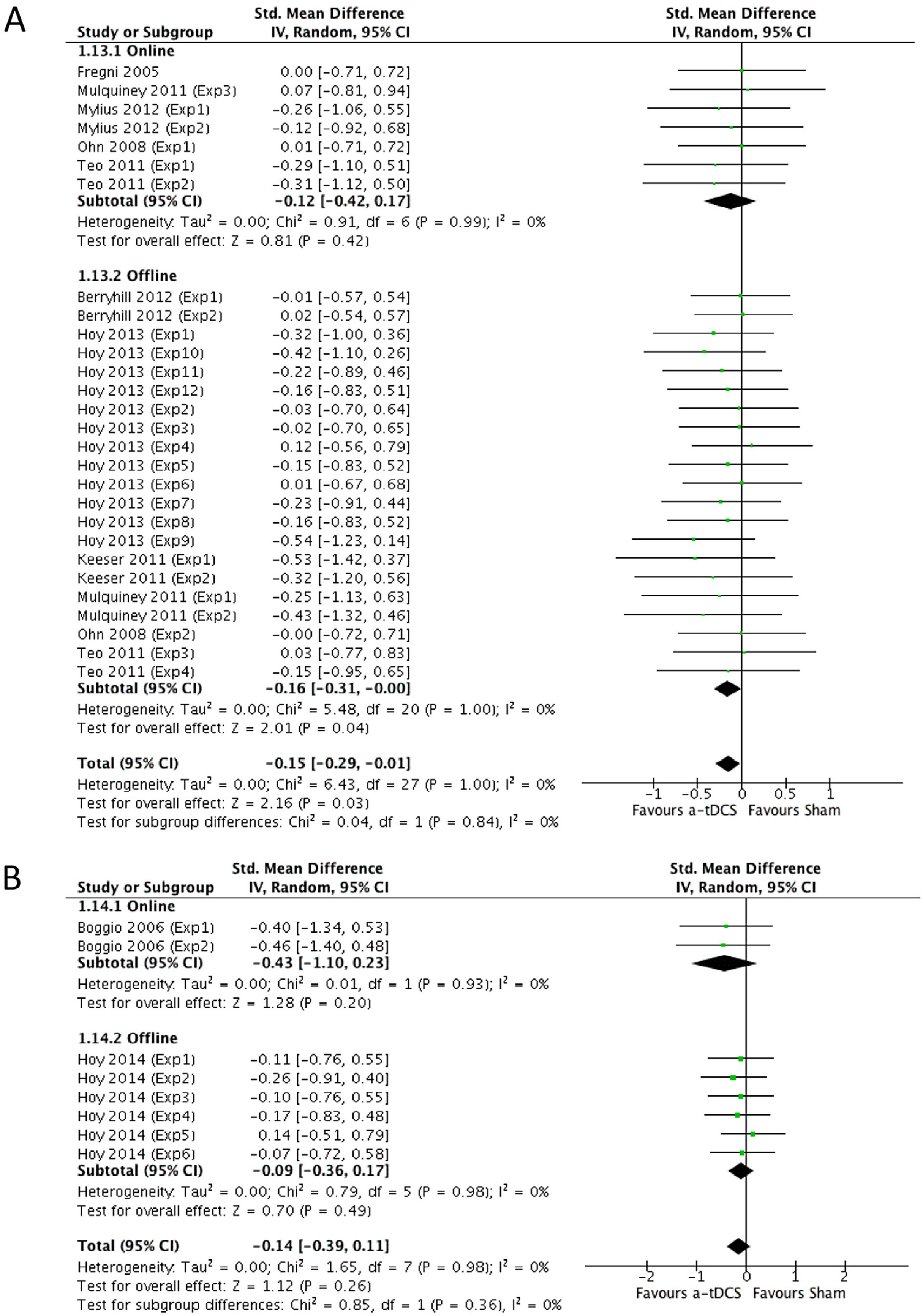

Figure 4. Forest plot depicting the effect of a-tDCS compared to sham stimulation on reaction times for the working memory tasks in healthy (A) and neuropsychiatric (B) cohorts.

Change in accuracy on n-back/Sternberg/digit-span working memory tasks with a-tDCS compared to sham stimulation

Fig. 5A provides a summary of the accuracy results for the healthy cohort. Overall, greater response accuracy was achieved by participants who received a-tDCS compared to sham stimulation (SMD = 0.15, 95% CI = 0.02, 0.28, $p = 0.02$). This finding did not reach significance for online assessments (SMD = 0.19, 95% CI = –0.16, 0.54, $p = 0.29$); however, a trend towards significance at the subgroup level for tasks performed offline was observed (SMD = 0.14, 95% CI = 0.00, 0.29, $p = 0.05$). The forest plot for the clinical cohort is shown in Fig. 5B. In this group, no overall effect of a-tDCS on WM accuracy was observed (SMD = 0.11, 95% CI = –0.07, 0.29, $p = 0.24$); however, subgroup analyses revealed a significant and moderate improvement in accuracy for tasks performed online (SMD = 0.77, 95% CI = 0.26, 1.29, $p = 0.003$), while no significant change in accuracy was observed for offline tasks (SMD = 0.02, 95% CI = –0.17, 0.20, $p = 0.87$).

Effect of current density and stimulation duration

Current density and stimulation duration are both known to influence tDCS dose. As there was considerable variation between studies with regard to these two parameters, separate analyses were performed in an attempt to better elucidate any moderating effects on WM performance. In all analyses, we pooled results from healthy and neuropsychiatric cohorts in order to maintain suitable statistical power. Furthermore, when investigating the effect of current density on WM performance, data were pooled from online and offline experiments. However, only offline data were analysed for comparisons based on stimulation duration, as online task performance should not be affected by this parameter.

Separate forest plots were generated comparing a-tDCS to sham stimulation on accuracy and reaction time for WM experiments using either lower (≤ 0.029 mA/cm^2) or higher (>0.029 mA/cm^2) stimulation current densities as well as for offline experiments using shorter (≤ 10 minutes) compared to longer (>10 minutes) stimulation durations. The results of these subsequent analyses are summarised in Table 3 (see Supplementary Figs. S1–S9 for accompanying forest plots and flow-diagram indicating how individual data-sets were dichotomised with regard to current density and stimulation duration). In all instances, the effect sizes for both reaction time and accuracy in the a-tDCS compared to sham conditions on WM tasks remained modest. However, there was some indication that higher current densities and longer stimulation durations have a greater impact on WM performance. Specifically, the pooled data demonstrate significantly improved WM accuracy scores compared to sham in the higher current density group ($p = 0.005$), but not in the lower current density group ($p = 0.48$). Similarly, compared to sham, reaction times were also significantly improved with longer stimulation durations ($p = 0.04$), but not with shorter stimulation durations ($p = 0.58$). Additionally, effect sizes were also larger for these significant analyses.

Discussion

The present systematic review and meta-analysis aimed to provide a comprehensive assessment of the effects of a-tDCS, compared to sham, on WM in both healthy and neuropsychiatric populations, examining both online and offline task performance. Our secondary aim was to assess if a-tDCS efficacy was influenced by either current density or stimulation duration. Given the expanding use of a-tDCS, both as a means of modulating cognitive processes in healthy populations, as well as an emerging therapeutic device for the treatment of memory dysfunction in clinical cohorts, we felt that such a review was necessary to better delineate the effects achieved thus far with this technology.

Overall, with respect to the primary aim of the study, we found only partial support for our hypothesis of an enhancing effect of a-tDCS on WM performance. Specifically, in healthy cohorts, reaction times were shown to be significantly improved with stimulation on the offline WM tasks, while a strong trend towards significance for response accuracy was obtained. In the neuropsychiatric cohort, online response accuracy, but not reaction times, was improved with stimulation. No significant results were obtained for WM tasks performed online in the healthy cohort, whereas the neuropsychiatric cohort showed no significant improvement in offline WM performance. To date, two previous quantitative reviews have explored the effects of a-tDCS on WM. Brunoni and Vanderhasselt [74] pooled results from studies investigating the effects of either repetitive transcranial magnetic stimulation (rTMS) or a-tDCS applied over the DLPFC on n-back task performance in healthy and neuropsychiatric cohorts, ultimately finding an overall improvement in both reaction time and accuracy scores. However, meta-regression analyses performed by these authors indicated that WM accuracy was only improved in participants receiving rTMS and not a-tDCS. Our findings are largely consistent with this previous review; however, our results indicate that a-tDCS applied to the DLPFC does appear to have some capacity for enhancing WM accuracy, with significant online improvements seen in the clinical group and a strong trend towards significance for the offline healthy group ($p = 0.05$). Nevertheless, our results demonstrated only very modest effect sizes. It is quite likely that these subtle differences are due to the broader inclusion criteria used in the present review, which combined results from a larger number of studies and did not restrict WM assessment to the n-back task alone.

In a more recent quantitative review, Horvath et al. [75] explored the effects of single-session tDCS on a wide range of cognitive processes in healthy adults. These authors ultimately reported a null effect of stimulation on all analysed cognitive outcome measures, including WM. These findings differ from our results with respect to the significant improvements we observed in offline reaction time in healthy controls. It is possible that this discrepancy is due to a greater level of statistical power in the current study, which pooled data from a larger number of experiments. However, there are also a number of reported statistical and methodological issues with Horvath et al. which limit the validity of directly comparing these two studies [76,77].

Our finding of significant offline reaction time effects, with a strong trend towards significance for accuracy in healthy cohorts and a significant online effect for accuracy in the neuropsychiatric cohort, is interesting. Although the basis for these differences remains uncertain, the different neurobiological processes, which occur during, compared to following stimulation, might provide one potential explanation. Specifically, the online effects of a-tDCS appear to be solely dependent on membrane potential changes [60,78], whereas offline effects are driven by changes in synaptic strength involving the modulation of GABAergic and glutamatergic activity [32,60,78]. While speculative, in patient populations, where there is abnormal excitation/inhibition (E/I) balance and impaired plasticity [30,79,80], the initial membrane potential changes might alter the cortical environment sufficiently to modulate this balance, leading to subsequent detectable changes in behaviour. While in healthy controls, who presumably have more optimal homeostatic control of cortical excitability and inhibition [80], any online changes in neuronal firing rates may not be robust enough to lead to a demonstrable behavioural change. However, it is possible that the later occurring (i.e., offline) synaptically driven changes might more strongly influence behavioural responses in this group. Clearly,

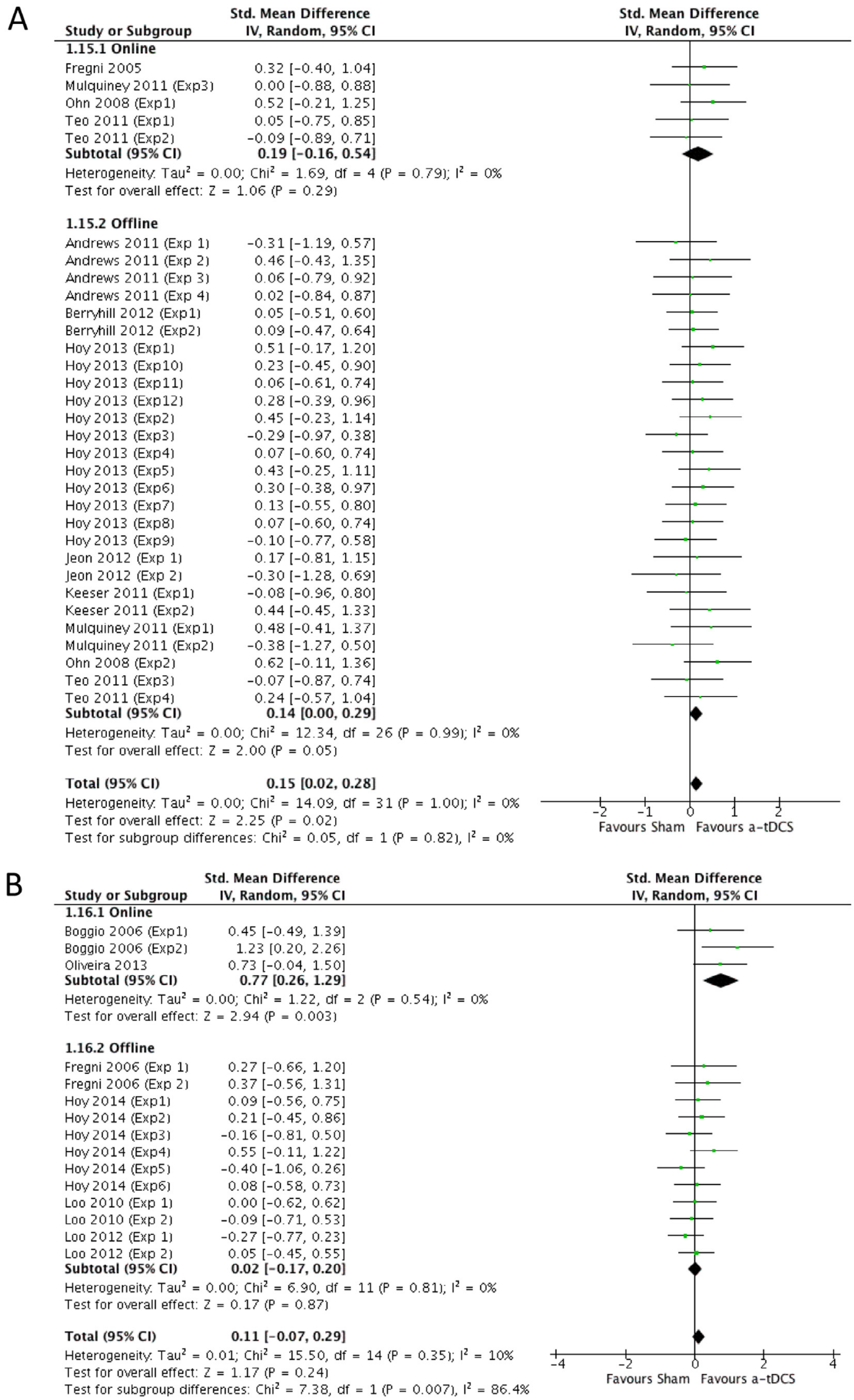

Figure 5. Forest plot depicting the effect of a-tDCS compared to sham stimulation on accuracy for the working memory tasks in healthy (A) and neuropsychiatric (B) cohorts.

Table 3
Summary of the effects of a-tDCS compared to sham on working memory (reaction time and accuracy) controlling for current density and stimulation duration.

Stimulation parameter	Value	Outcome measure	N of experiments	SMD (95% CI)	p Value
Current density	≤0.029 mA/cm^2	Reaction time	16	−0.17 (−0.35, 0.02)	0.07
Current density	>0.029 mA/cm^2	Reaction time	20	−0.13 (−0.29,−0.02)	0.10
Current density	≤0.029 mA/cm^2	Accuracy	26	0.05 (−0.10, 0.20)	0.48
Current density	>0.029 mA/cm^2	Accuracy	21	0.21 (0.06, 0.36)	0.005
Stimulation duration	≤10 minutes	Reaction time	4	−0.09 (−0.43, 0.24)	0.58
Stimulation duration	>10 minutes	Reaction time	23	−0.15 (−0.30,−0.01)	0.04
Stimulation duration	≤10 minutes	Accuracy	8	0.06 (−0.21, 0.32)	0.66
Stimulation duration	>10 minutes	Accuracy	31	0.10 (−0.02, 0.23)	0.10

however, further research conducted in healthy and clinical cohorts is required to better contextualise these findings.

The secondary aim of this review was to investigate whether differences in current density and stimulation duration could affect the efficacy of a-tDCS mediated WM enhancement. Previous research applying a-tDCS over the motor cortex has found that increases to either of these parameters, within specific limits, can lead to subsequent increases in cortico-motor excitability [26,28,49]; however, whether similar effects might also be observed for behavioural outcome measures and in other brain regions remain uncertain. In the present review, we pooled results from experiments conducted in both healthy and neuropsychiatric populations based on: (1) anodal current density either greater than or less than/equal to 0.029 mA/cm^2 (i.e., equivalent to 1 mA applied using a 35 cm^2 electrode) and (2) stimulation durations either greater than or less than/equal to 10 minutes. Although the SMD effect sizes failed to reach significance in the majority of analyses (see Table 3), accuracy scores were shown to be significantly improved in the higher current density group ($p = 0.005$), but not the lower current density group ($p = 0.48$); while longer ($p = 0.04$), but not shorter ($p = 0.58$), stimulation durations also led to significantly faster reaction times. In both of these instances, effect sizes were also larger for the higher current density and longer stimulation duration groups.

These results, therefore, provide some limited support for a potential dose–response relationship involving current density and duration of stimulation. Nevertheless, the precise implications of these findings remain unclear, as effect sizes remained modest and several analyses failed to reach significance. Interestingly, these findings are largely consistent with two recent meta-analyses exploring the effects of tDCS over motor regions. Specifically, Bastani and Jaberzadeh [48] found that, in healthy populations, a-tDCS applied using greater current densities and longer stimulation durations resulted in larger changes in cortico-spinal excitability as measured using TMS evoked potentials [48], while Chhatbar et al. [81] also recently described a positive dose–response relationship involving current density in studies utilising tDCS for the treatment of post-stroke motor recovery. Our current results build on these interesting findings by providing some initial support for a dose-dependent effect of a-tDCS for WM enhancement, when applied over the DLPFC. However, it is important to note that the dose analysis combined patients with healthy controls, and there is some evidence that tDCS dose-effects may differ between these two populations [11,16]. Future studies, which attempt to further explore this potential association, are therefore warranted. Such studies would also benefit from the collection of both behavioural and neurophysiological data, which could provide important information regarding the neurophysiological mechanisms underlying any cognitive modulation. Functional imaging techniques such as EEG and fMRI, as well as the more recently developed combined TMS and EEG (TMS-EEG), provide powerful ways of exploring these brain-behaviour relationships [82–84].

Limitations

The current findings should be discussed in light of a number of important limitations. First, as we restricted our literature search to peer-reviewed English language articles, this would have excluded any unpublished articles, or articles published in the grey literature (i.e., literature that has not been published in peer-reviewed scientific journals). It is possible that this may have led to a degree of publication bias; however, this was not reflected in our funnel plots, which were symmetrical and did not show any evidence of small study effects. Second, although several different neuropsychiatric populations were included in the current meta-analysis, including participants with depression, schizophrenia and Parkinson's disease, the efficacy of a-tDCS in enhancing WM function in other disorders remains to be established, which somewhat limits the generalisability of the results. Furthermore, it is possible that underlying neurobiological differences between participants with different neuropsychiatric diagnoses could have potentially affected the pooled results, as some disorders might respond better to a-tDCS than others. Sample sizes in many of the studies included in the current review were also modest, and given that participants in a number of studies were receiving medication, there remains a possibility of medication-related interaction effects. Finally, in all the included studies, WM was assessed either during or shortly after treatment with a-tDCS; therefore, no comment can be made as to the duration of post-stimulation treatment effects.

Future directions

The results from this review highlight the need for further well-powered randomised controlled trials to more thoroughly assess the efficacy of a-tDCS for improving WM function in both healthy and clinical populations. In particular, systematic evaluation of any moderating effects of current density and stimulation duration would be of particular interest, given our current findings. In addition, it would be useful to more comprehensively explore differences between online versus offline WM changes. There is also a growing need for research examining the effects of stimulation over multiple brain regions, either independently or simultaneously. Results from neuroimaging studies highlight a number of widely distributed cortical networks implicated in WM function, incorporating frontal, parietal and cerebellar brain regions [85–89]. Hence, research into the differential effects of stimulation over these locations might help further delineate the neural mechanisms underlying WM processes and might also help uncover additional therapeutic targets. Recently developed multichannel stimulation devices, which allow for stimulation over multiple cortical sites using small 'high definition' electrodes, provide a novel way of potentially achieving this aim [90]. Finally, if a-tDCS is to become an effective neurorehabilitative device, it is imperative that it induces behavioural changes that last well beyond the period of stimulation. Currently, little research has been conducted into the long-term effects of a-tDCS; however, there is emerging evidence that repeated same-day stimulation sessions can substantially prolong changes in cortical excitability [91,92]; however, whether these changes also translate into lasting behavioural improvements remain to be established.

Conclusions

Overall, this systematic review and meta-analysis indicate that a-tDCS has some limited capacity to enhance WM in both healthy and neuropsychiatric populations. Specifically, offline WM reaction times were improved in the healthy cohort, with a trend towards significance for accuracy also, while online accuracy scores were improved in the neuropsychiatric cohort. However, the modest effect sizes obtained, coupled with non-significant effects on a number of analyses, make firm conclusions regarding the overall efficacy of a-tDCS for either enhancing WM in healthy populations, or treating its dysfunction in neuropsychiatric cohorts, difficult. Nevertheless, given the very limited options currently available for the amelioration cognitive dysfunction in neuropsychiatric disorders, there is clearly a need for further investigation of refined tDCS protocols targeted towards restoration of WM function. Our finding that higher current densities and longer stimulation durations might be more effective at modulating WM provides one potential avenue for future research and is also consistent with previous behavioural and neurophysiological analyses performed in motor brain regions [48,81]. Future research is needed to more thoroughly explore and refine the optimal stimulation parameters required for a-tDCS-based cognitive enhancement, implementing well-powered experimental designs and using both healthy and clinical populations.

Acknowledgements

ATH was supported by an Australian Postgraduate Award. KEH (1082894) and PBF (1078567) were supported by National Health and Medical Research Council (NHMRC) fellowships.

Appendix. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2015.10.006.

References

[1] Minzenberg MJ, Carter CS. Developing treatments for impaired cognition in schizophrenia. Trends Cogn Sci 2012;16(1):35–42.
[2] Marazziti D, Consoli G, Picchetti M, Carlini M, Faravelli L. Cognitive impairment in major depression. Eur J Pharmacol 2010;626(1):83–6.
[3] Insel TR. Rethinking schizophrenia. Nature 2010;468(7321):187–93.
[4] Kuo MF, Nitsche MA. Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. Neurosci Bull 2015;31(2):198–206.
[5] Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, et al. Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease. Brain Stimul 2012;5(3):223–30.
[6] 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(4):444–7.
[7] Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology 2008;71(7):493–8.
[8] Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry 2012;200(1):52–9.
[9] Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol 2010;13(1):61–9.
[10] Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety 2006;23(8):482–4.
[11] Hoy KE, Arnold SL, Emonson MR, 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(1–3):96–100.
[12] Oliveira JF, Zanão TA, Valiengo L, Lotufo PA, Benseñor IM, Fregni F, et al. Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neurosci Lett 2013;537:60–4.
[13] 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.
[14] Zaehle T, Sandmann P, Thorne JD, Jäncke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci 2011;12:2.
[15] 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(12):2384–9.
[16] Hoy KE, Emonson MR, 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(9):1777–84.
[17] Berryhill ME, Jones KT. tDCS selectively improves working memory in older adults with more education. Neurosci Lett 2012;521(2):148–51.
[18] 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(2):84–9.
[19] Jeon SY, Han SJ. Improvement of the working memory and naming by transcranial direct current stimulation. Ann Rehabil Med 2012;36(5):585–95.
[20] 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) study. Neuroimage 2011;55(2):644–57.
[21] 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. Neuroreport 2008;19(1):43–7.
[22] Javadi AH, Cheng P. Transcranial direct current stimulation (tDCS) enhances reconsolidation of long-term memory. Brain Stimul 2013;6(4):668–74.
[23] Javadi AH, Cheng P, Walsh V. Short duration transcranial direct current stimulation (tDCS) modulates verbal memory. Brain Stimul 2012;5(4):468–74.
[24] Javadi AH, Walsh V. Transcranial direct current stimulation (tDCS) of the left dorsolateral prefrontal cortex modulates declarative memory. Brain Stimul 2012;5(3):231–41.
[25] Kuo HI, Bikson M, Datta A, Minhas P, Paulus W, Kuo MF, et al. Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: a neurophysiological study. Brain Stimul 2013;6(4):644–8.
[26] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527(Pt 3):633–9.
[27] Zaghi S, Acar M, Hultgren B, Boggio PS, Fregni F. Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation. Neuroscientist 2010;16(3):285–307.
[28] Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology 2001;57(10):1899–901.
[29] 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(4):600–4.
[30] Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. Neuroimage 2014;85(Pt 3):948–60.
[31] Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. Neuron 2010;66(2):198–204.
[32] Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 2002;125(Pt 10):2238–47.
[33] Bastani A, Jaberzadeh S. Differential modulation of corticospinal excitability by different current densities of anodal transcranial direct current stimulation. PLoS ONE 2013;8(8):e72254.
[34] Klingberg T. Training and plasticity of working memory. Trends Cogn Sci 2010;14(7):317–24.
[35] Jausovec N, Jausovec K. Working memory training: improving intelligence – changing brain activity. Brain Cogn 2012;79(2):96–106.
[36] Baddeley A. Working memory. New York: Oxford University Press; 1986.
[37] Johnson MK, McMahon RP, Robinson BM, Harvey AN, Hahn B, Leonard CJ, et al. The relationship between working memory capacity and broad measures of cognitive ability in healthy adults and people with schizophrenia. Neuropsychology 2013;27(2):220–9.
[38] Daneman M, Carpenter PA. Individual differences in working memory and reading. J Verbal Learning Verbal Behav 1980;19(4):450–66.
[39] Rose EJ, Ebmeier KP. Pattern of impaired working memory during major depression. J Affect Disord 2006;90(2–3):149–61.
[40] Potkin SG, Turner JA, Brown GG, McCarthy G, Greve DN, Glover GH, et al. Working memory and DLPFC inefficiency in schizophrenia: the FBIRN study. Schizophr Bull 2009;35(1):19–31.
[41] Gilbert B, Belleville S, Bherer L, Chouinard S. Study of verbal working memory in patients with Parkinson's disease. Neuropsychology 2005;19(1):106–14.

[42] Levy R, Goldman-Rakic PS. Segregation of working memory functions within the dorsolateral prefrontal cortex. Exp Brain Res 2000;133(1):23–32.
[43] Courtney SM. Attention and cognitive control as emergent properties of information representation in working memory. Cogn Affect Behav Neurosci 2004;4(4):501–16.
[44] Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Pascual-Leone A. Can noninvasive brain stimulation enhance cognition in neuropsychiatric disorders? Neuropharmacology 2013;64:566–78.
[45] Herwig U, Satrapi P, Schonfeldt-Lecuona C. Using the international 10–20 EEG system for positioning of transcranial magnetic stimulation. Brain Topogr 2003;16(2):95–9.
[46] Peterchev AV, Wagner TA, Miranda PC, Nitsche MA, Paulus W, Lisanby SH, et al. Fundamentals of transcranial electric and magnetic stimulation dose: definition, selection, and reporting practices. Brain Stimul 2012;5(4):435–53.
[47] Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. Front Psychiatry 2012;3:91.
[48] Bastani A, Jaberzadeh S. Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. Clin Neurophysiol 2012;123(4):644–57.
[49] Jaberzadeh S, Bastani A, Kidgell D. Does the longer application of anodal-transcranial direct current stimulation increase corticomotor excitability further? A pilot study. Basic Clin Neurosci 2012;3(4):28–35.
[50] 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(Pt 7):1987–2000.
[51] Ho KA, Taylor JL, Chew T, Gálvez V, Alonzo A, Bai S, et al. The effect of Transcranial Direct Current Stimulation (tDCS) electrode size and current intensity on motor cortical excitability: evidence from single and repeated sessions. Brain Stimul 2015;doi:10.1016/j.brs.2015.08.003.
[52] 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(1):31–8.
[53] 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.
[54] Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533–7.
[55] Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Systematic reviews in health care. BMJ Publishing Group; 2008. p. 285–312.
[56] Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport 1998;9(10):2257–60.
[57] Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005;25(1):46–59.
[58] Curtis CE, D'Esposito M. Persistent activity in the prefrontal cortex during working memory. Trends Cogn Sci 2003;7(9):415–23.
[59] Sternberg S. High-speed scanning in human memory. Science 1966; 153(3736):652–4.
[60] Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. Neuroscientist 2011;17(1):37–53.
[61] Medeiros LF, de Souza IC, Vidor LP, de Souza A, Deitos A, Volz MS, et al. Neurobiological effects of transcranial direct current stimulation: a review. Front Psychiatry 2012;3:110.
[62] Wechsler D. Wechsler adult intelligence scale. 4th ed. San Antonio: Pearson; 2008.
[63] Cochrane Collaboration, RevMan, The Nordic Cochrane Centre. The RevMan software package, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2013.
[64] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions: the Cochrane Collaboration. Wiley; 2008.
[65] Joseph AH. Plot Digitizer. <http://www.softpedia.com/get/Multimedia/Graphic/Graphic-Others/Plot-Digitizer.shtml>; 2010.
[66] Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clin Neurophysiol 2014;125(9):1847–58.
[67] Butler AJ, Shuster M, O'Hara E, Hurley K, Middlebrooks D, Guilkey K. A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. J Hand Ther 2013;26(2):162–71.
[68] 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(7):974–82.
[69] Deeks J, Higgins J. Statistical algorithms in review manager 5, cochrane collaboration [internet]. <http://ims.cochrane.org/revman/documentation/statistical-methods-in-revman-5.pdf>; 2010 [accessed 08.14].
[70] Cohen J, editor. Statistical power analysis for the behavioral sciences. 2nd ed. New Jersey: Lawrence Erlbaum Publishers; 1988.
[71] Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Fixed-effect versus random-effects models. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, editors. Introduction to meta-analysis. John Wiley & Sons, Ltd.; 2009. p. 77–86.
[72] Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
[73] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[74] Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn 2014;86C:1–9.
[75] 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(3):535–50.
[76] Nitsche MA, Bikson M, Bestmann S. On the use of meta-analysis in neuromodulatory non-invasive brain stimulation. Brain Stimul 2015;8(3):666–7.
[77] Price AR, Hamilton RH. A re-evaluation of the cognitive effects from single-session transcranial direct current stimulation. Brain Stimul 2015;8(3):663–5.
[78] Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol 2003;553(Pt 1):293–301.
[79] Nitsche MA. The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS activ, The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs. J Physiol 2012;590(Pt 19):4641–62.
[80] Krause B, Marquez-Ruiz J, Kadosh RC. The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Front Hum Neurosci 2013;7:602.
[81] Chhatbar PY, Ramakrishnan V, Kautz S, George MS, Adams RJ, Feng W. Transcranial Direct current stimulation post-stroke upper extremity motor recovery studies exhibit a dose-response relationship. Brain Stimul 2015;doi:10.1016/j.brs.2015.09.002.
[82] Fitzgerald PB. TMS-EEG: a technique that has come of age? Clin Neurophysiol 2010;121(3):265–7.
[83] Rogasch NC, Fitzgerald PB. Assessing cortical network properties using TMS-EEG. Hum Brain Mapp 2013;34(7):1652–69.
[84] Daskalakis ZJ, Farzan F, Radhu N, Fitzgerald PB. Combined transcranial magnetic stimulation and electroencephalography: its past, present and future. Brain Res 2012;1463:93–107.
[85] Ravizza SM, McCormick CA, Schlerf JE, Justus T, Ivry RB, Fiez JA. Cerebellar damage produces selective deficits in verbal working memory. Brain 2006;129(Pt 2):306–20.
[86] Durisko C, Fiez JA. Functional activation in the cerebellum during working memory and simple speech tasks. Cortex 2010;46(7):896–906.
[87] Chein JM, Fiez JA. Evaluating models of working memory through the effects of concurrent irrelevant information. J Exp Psychol Gen 2010;139(1):117–37.
[88] Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. Nat Neurosci 2004;7(1):75–9.
[89] Collette F, Hogge M, Salmon E, Van der Linden M. Exploration of the neural substrates of executive functioning by functional neuroimaging. Neuroscience 2006;139(1):209–21.
[90] Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. Neuroimage 2014;89:216–25.
[91] Bastani A, Jaberzadeh S. Within-session repeated a-tDCS: the effects of repetition rate and inter-stimulus interval on corticospinal excitability and motor performance. Clin Neurophysiol 2014;125(9):1809–18.
[92] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimul 2013;6(3):424–32.