

Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS)

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ABSTRACT

Background: Over the last 15-years, transcranial direct current stimulation (tDCS), a relatively novel form of neuromodulation, has seen a surge of popularity in both clinical and academic settings. Despite numerous claims suggesting that a single session of tDCS can modulate cognition in healthy adult populations (especially working memory and language production), the paradigms utilized and results reported in the literature are extremely variable. To address this, we conduct the largest quantitative review of the cognitive data to date.

Methods: Single-session tDCS data in healthy adults (18–50) from every cognitive outcome measure reported by at least two different research groups in the literature was collected. Outcome measures were divided into 4 broad categories: executive function, language, memory, and miscellaneous. To account for the paradigmatic variability in the literature, we undertook a three-tier analysis system; each with less-stringent inclusion criteria than the prior. Standard mean difference values with 95% CIs were generated for included studies and pooled for each analysis.

Results: Of the 59 analyses conducted, tDCS was found to not have a significant effect on any – regardless of inclusion laxity. This includes no effect on any working memory outcome or language production task. **Conclusion:** Our quantitative review does not support the idea that tDCS generates a reliable effect on cognition in healthy adults. Reasons for and limitations of this finding are discussed. This work raises important questions regarding the efficacy of tDCS, state-dependency effects, and future directions for this tool in cognitive research.

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Introduction

Since its modern resurgence at the turn of the century, transcranial direct current stimulation (tDCS) – a noninvasive neuromodulatory device – has been steadily growing in popularity within both the academic and clinical research sectors. Current theory suggests that tDCS, via time-dependent and polarity specific modulation of neuronal firing patterns, can markedly and predictably enhance a number of higher-order cognitions and behaviors. However, a recent systematic review of the neurophysiologic literature undertaken by this group [1] questions the reliability and significance of tDCS effects on all but one neurophysiologic measure tested. Here, we undertake a quantitative review of the cognition literature to determine if tDCS shows a reliable effect on any cognitive tasks.

A brief review of proposed tDCS mechanisms of action

tDCS is most commonly delivered via 2 electrodes – 1 anode and 1 cathode – affixed to the scalp overlying cortical regions relevant to the outcome measure of interest [2]. It is believed that passing a weak electric current (typically 0.5–2.0 mA) between these two electrodes modulates neuronal firing patterns in the cortical regions underlying the electrodes via two mechanisms of actions. The first occurs *during* stimulation and involves ionic concentration shifts within the extracellular fluid which serve to modulate neuronal resting membrane potentials thereby hypo- and hyperpolarizing neurons underlying the anode and cathode, respectively [3]. The second occurs *following* long duration (>7 min) stimulation and involves long-term potentiation and depression-like mechanisms at the synaptic level thereby effecting hyper- and hypo-communicative activity in neurons underlying the anode and cathode, respectively [3]. To account for these different mechanisms, in this paper we divide studies according to whether

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the outcome measures were obtained during stimulation (online protocols) or following stimulation (offline protocols).

Quantitative-review structure

The poolable cognitive tasks in the literature can be grouped into 4 broad categories: executive functions, language, memory, and miscellaneous. Accordingly, the methods and results sections will be structured around these domains. To be included in this review, the effects of tDCS on a given task must have been explored by at least two different research groups using a comparable tDCS protocol. A full list of studies that assessed the relevant aspects of cognitive function but did not meet these inclusion criteria can be found in [Supplemental Material \(Fig. S1; Table S3\)](#). Each poolable outcome measure that satisfied our inclusion criteria is introduced briefly below.

Executive functions

Executive functions (EFs) are often regarded as a coordinated set of cognitive processes which allow an individual to override more instinctual or automatic responses in order to achieve a specified goal [4]. The following three EF measures met inclusion criteria for this review.

Set-shifting

Individuals must determine which target/s amongst a series of targets are “correct” based on an unspecified rule-set via arbitrarily guessing (e.g. – red fruit amongst a series of food-based images). Occasionally, and without warning or explication, the rule-set will change (e.g. – round vegetables amongst a series of food-based images). Improved performance on this task is reflected by a reduction in the time taken to notice this change, abandon the prior rule-set, and learn the new rule-set [5].

Stop signal task

Individuals are repeatedly presented with a target (e.g. – a visual circle) and asked to respond as quickly as possible each time it appears. Occasionally, however, the target will be paired with a secondary stimulus (e.g. – an auditory beep); in this instance, the individual should *not* respond to the target. This task is a measure of automatic response inhibition [6].

Stroop task

Individuals are presented with stimuli which contain multiple, uniquely processed dimensions (e.g. – the word ‘red’ written in a green colored font), of which the individual must respond to only one. The speed with which a person can accurately respond is a measure of selective attention and goal maintenance [7].

Language

Linguistic-based cognitive tasks utilize language production speed and accuracy to explore the psychological and neurobiological factors that enable humans to produce and comprehend speech [8]. The following three language measures met inclusion criteria for this review.

Picture-to-word novel-language learning

Individuals are presented with paired images and pseudo-words or words from an unfamiliar language and must learn the pairing of the two. The accuracy with which one can respond to correctly- or incorrectly-joined pairs is thought to be a measure of linguistic learning [9].

Picture naming

Individuals are presented with a series of images (either simple line drawings or photos) and asked to name them as quickly as possible. The time taken to accurately name each object is a measure of lexical access, or ‘word-finding ability’ [10].

Verbal fluency

Individuals are presented with a phonemic category (e.g. – the letter ‘p’) or a semantic category (e.g. – animals) and asked to name as many words as possible from said category within a specified time limit. The number of words produced is a measure of semantic access [11].

Memory

Memory-based cognitive tasks utilize memorization and recall speed/accuracy to explore the structures and processes involved in the effective storage and retrieval of information [12]. The following five memory measures met inclusion criteria for this review.

Digit-span recall

Individuals are sequentially presented with verbal strings of numbers which sequentially increase in length and are asked to verbally report the numbers following each presentation. The length of the final number string an individual is able to accurately report back is a measure of digit-span recall WM [13].

Verbal episodic memory

Individuals are presented with a list of words several times and asked to memorize it (encoding). Following a delay period (consolidation), during which time the individual is distracted with non-relevant tasks, the individual is presented with ‘target’ words and asked whether or not each was present in the prior memorized list. The accuracy with which an individual responds to the targets is a measure of verbal episodic recognition memory. An identical procedure, though replacing words with visual images, is utilized as a measure of visual episodic recognition memory [14].

Visual WM

Individuals are sequentially presented with a string of visual images. Following each string, a single target is visually presented and the individual must respond whether or not said target was in the prior string. The speed and accuracy with which an individual responds to the target is a measure of visual WM [15].

N-back WM

Individuals are presented with a sequential string of stimuli (e.g. – letters or numbers) and asked to generate a response if a stimulus is identical to the one presented ‘N’ items prior. The accuracy and speed with which an individual responds to targets is a measure of WM according to the modality of the stimuli utilized [16].

Miscellaneous

An additional four measures met inclusion criteria for this review but could not be grouped into any single cognitive domain.

Mental arithmetic

Individuals are asked to complete simple arithmetic math problems in their head. The speed and accuracy with which an individual can complete these problems is a measure of computational efficiency [17].

Picture viewing/rating

Individuals are asked to view and rate a series of images of differing valences (typically negative and neutral). The average

Table 1

Studies and values for executive function task primary analyses.

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Set shifting tasks – anode/offline: ERRORS								
[25]	30	IDLPC	rORBIT	0.0286	Cog	0.20 (–0.21, 0.61)	0.978	0.328
	30	IDLPC	rORBIT	0.0286	Motor	–0.30 (–0.81, 0.21)	–1.150	0.250
[26]	46	IDLPC	rORBIT	0.0286	Cog	0.08 (–0.42, 0.59)	0.325	0.745
Fixed effect model						0.03 (–0.27, 0.32)	0.207	0.836
Stop signal task – anode/offline: NO STOP REACTION TIME								
[27]	11	rIFG	lORBIT	0.04	–	–0.10 (–0.93, 0.74)	–0.225	0.822
[28]	10a/12s	rIFG	lORBIT	0.0429	–	–0.91 (–1.79, –0.03)	–2.023	0.043
Fixed effect model						–0.48 (–1.09, 0.13)	–1.555	0.12
Stop signal task – anode/offline: STOP SIGNAL REACTION TIME (IFG)								
[27]	11a/22s	rIFG	lORBIT	0.04	–	–0.21 (–0.93, 0.52)	–0.554	0.580
[28]	10a/12s	rIFG	lORBIT	0.0429	–	–0.13 (–0.97, 0.71)	–0.300	0.764
Fixed effect model						–0.17 (–0.72, 0.38)	–0.615	0.538

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized mean difference; A = Active; S = Sham; DLPFC = Dorsolateral prefrontal cortex; ORBIT = Orbitofrontal location; IFG = Inferior frontal gyrus.

Set shifting: Two studies from [25] were omitted due to targeting M1 (no comparable work elsewhere).

Stop signal: All sham participants were pooled for [27].

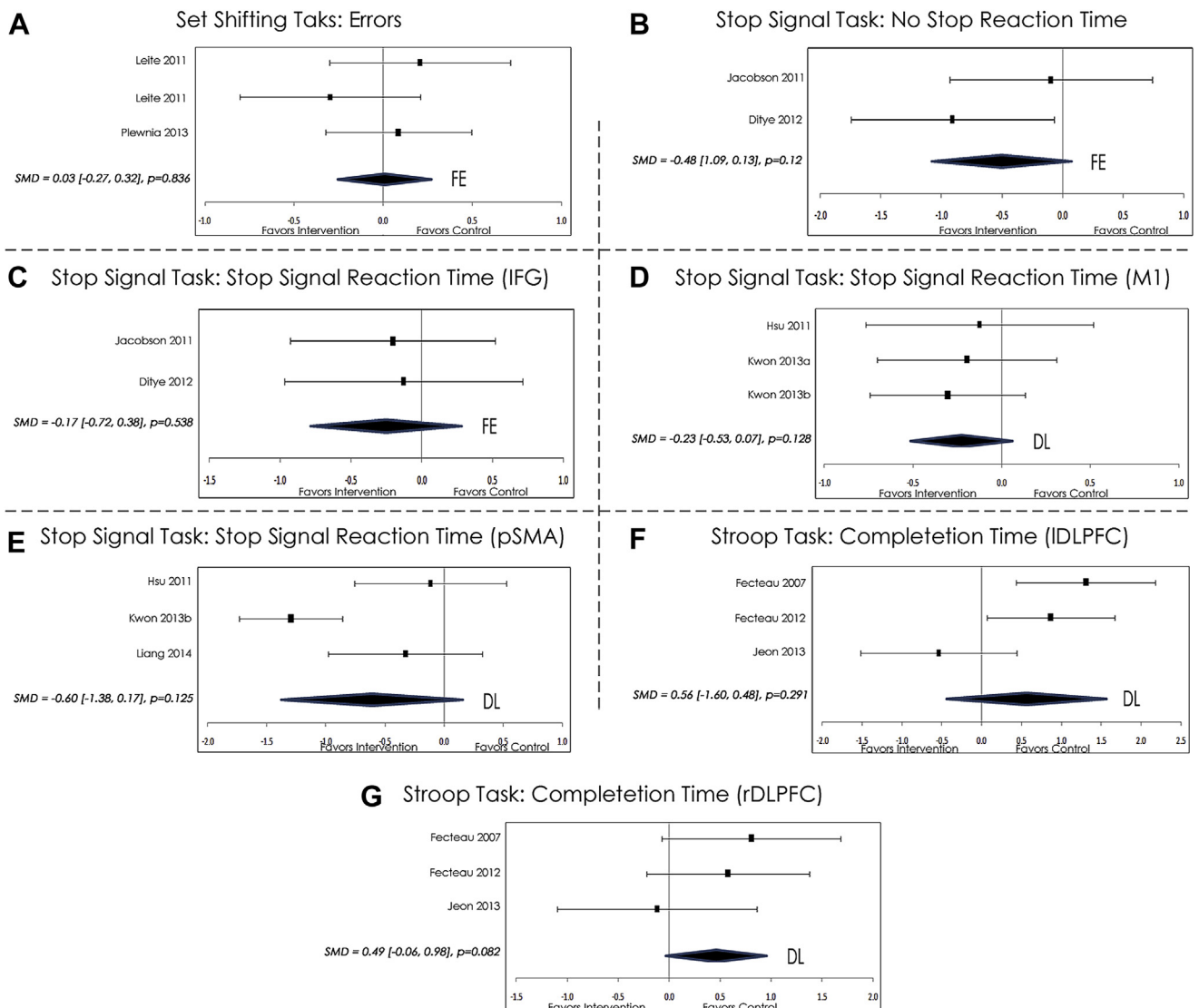


Figure 1. Forest plots for both primary and secondary executive function analyses (SMD = Standard mean difference; FE = Fixed effect model for primary analyses; DL = DerSimonian-Laird mixed-effect model for secondary analyses; Parentheses represent 95% CI).

Table 2
Studies and values for executive function task secondary analyses.

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Stop signal task – anode/offline: STOP SIGNAL REACTION TIME (M1)								
[32]	14a/28s	rM1	ICHK	0.0938	–	–0.13 (–0.77, 0.52)	–0.381	0.704
[30]	30	rM1	IORBIT	0.0286	–	–0.20 (–0.70, 0.31)	–0.753	0.451
[33]	40	rM1	IORBIT	0.0286	–	–0.30 (–0.75, 0.14)	–1.353	0.176
				DL model		–0.23 (–0.53, 0.07)	–1.521	0.128
Stop signal task – anode/offline: STOP SIGNAL REACTION TIME (pSMA)								
[32]	14a/28s	rpSMA	ICHK	0.0938	–	–0.11 (–0.76, 0.53)	–0.347	0.728
[33]	40	rpSMA	IORBIT	0.0286	–	–1.30 (–1.78, –0.81)	–5.267	<0.001
[34]	18	rpSMA	ICHK	0.0938	–	–0.33 (–0.98, 0.33)	–0.973	0.331
				DL Model		–0.60 (–1.38, 0.17)	–1.532	0.125
Stroop task – anode/offline: COMPLETION TIME (IDL PFC)								
[35]	10	IDL PFC	rDLPFC	0.0571	–	1.31 (0.34, 2.27)	2.650	0.008
[36]	12	IDL PFC	rDLPFC	0.0571	–	0.87 (0.03, 1.70)	1.032	0.042
[37]	8	IDL PFC	rORBIT	0.0286	–	–0.54 (–1.54, 0.46)	–1.059	0.290
				DL model		0.56 (–1.60, 0.48)	1.056	0.291
Stroop task – anode/offline: COMPLETION TIME (rDLPFC)								
[35]	10	rDLPFC	IDL PFC	0.0571	–	0.81 (–0.11, 1.72)	1.734	0.083
[36]	12	rDLPFC	IDL PFC	0.0571	–	0.58 (–0.24, 1.40)	1.387	0.165
[37]	8	rDLPFC	IORBIT	0.0286	–	–0.12 (–1.10, 0.86)	–0.236	0.831
				DL model		0.49 (–0.06, 0.98)	1.737	0.082

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized mean difference; A = Active; S = Sham; DLPFC = Dorsolateral prefrontal cortex; ORBIT = Orbitofrontal location; IFG = Inferior frontal gyrus; CHK = Cheek; pSMA = Pre-supplementary motor area.

Stop signal: All sham participants were pooled for [32]. [30] presented conflicting data regarding the number of participants: we used the N presented in the results section (n = 30).

Stroop task: [38] and [39] were omitted due to utilizing a 6-day and 5-day multiple-day stimulation protocol, respectively (no day 1 data); though, each reported no effect of stimulation on the Stroop task.

rating generated within each valence is a measure of emotional processing [18].

Gambling based risk taking

Individuals participate in a ‘gambling-type’ scenario whereby different actions carry varying, yet clearly understood, consequences (e.g. – choose between two boxes, the first of which has a 90% probability of containing \$1 whilst the second has a 10% chance of containing \$10). The number of low-probability/high-reward choices an individual selects is a measure of risk-taking propensity [19,20].

Rumination

Individuals are asked to report about the frequency and intensity of mentally generated self-referential thoughts (typically following a pre-arranged negative valence-type scenario, such as receiving a negative grade on an exam) [21].

Methods

Study selection

Papers included in this quantitative review were obtained from a PubMed database search (June 12th, 2014). The search term “transcranial direct current stimulation” generated 1156 papers. The abstract of each of paper was then read to determine which outcome measures were included and what type of population was utilized. This initial review narrowed the study pool to 417 (see Supplemental Material: Fig. S1 for complete study selection flow chart).

Following this, each article was read and the tasks/outcome measures utilized were noted and organized to identify all outcome measures utilized by at least two different research groups. We chose to exclude measures that have only been replicated by a

Table 3
Studies and values for language-based task primary analyses.

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Novel language learning task (Pictures to words) – anode/offline: ACCURACY								
[40]	19	WNKE	rORBIT	0.0286	–	0.18 (–0.46, 0.82)	0.553	0.580
[41]	10	WNKE	rORBIT	0.0286	–	0.28 (–0.60, 1.16)	0.624	0.533
				Fixed effect model		0.21 (–0.30, 0.73)	0.814	0.416
Picture naming task – anode/offline: RT								
[42]	12	IDL PFC	rSHLD	0.0571	–	–0.09 (–0.89, 0.71)	–0.217	0.829
[43]	20	IDL PFC	rSHLD	0.0429	–	0.04 (–0.58, 0.66)	0.135	0.893
				Fixed effect model		–0.01 (–0.50, 0.48)	–0.026	0.979
Verbal fluency task – anode/offline: NUMBER OF WORDS GENERATD								
[44]	12	IDL PFC	rORBIT	0.0613	PHN	0.23 (–0.57, 1.4)	0.568	0.570
[45]	10	IDL PFC (+Broca)	rORBIT	0.0571	SMT	1.00 (0.07, 1.93)	2.110	0.035
	10	IDL PFC (+Broca)	rORBIT	0.0571	PHN	0.63 (–0.27, 1.53)	1.381	0.167
[46]	18	IDL PFC	rORBIT	0.0571	SMT	–0.23 (–0.89, 0.42)	–0.700	0.484
	18	IDL PFC (+Broca)	rORBIT	0.0571	SMT	0.43 (–0.29, 1.09)	1.283	0.199
	18	IDL PFC (+Broca)	rORBIT	0.0571	SMT	–0.27 (–0.93, 0.39)	–0.809	0.418
				Fixed effect model		0.20 (–0.11, 0.50)	1.259	0.208

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized mean difference; A = Active; S = Sham; WNKE = Wernicke's area; RT = Reaction time; DLPFC = Dorsolateral prefrontal cortex; ORBIT = Orbitofrontal location; PHN = Phonemic; SMT = Semantic.

Picture naming: [37] was omitted from analysis as no quantitative RT data was reported.

Verbal fluency: [47] was omitted from analysis as the young cohort only undertook sham stimulation. [48] did not supply quantitative data for the phonemic fluency task, though they verbally reported no effect of stimulation.

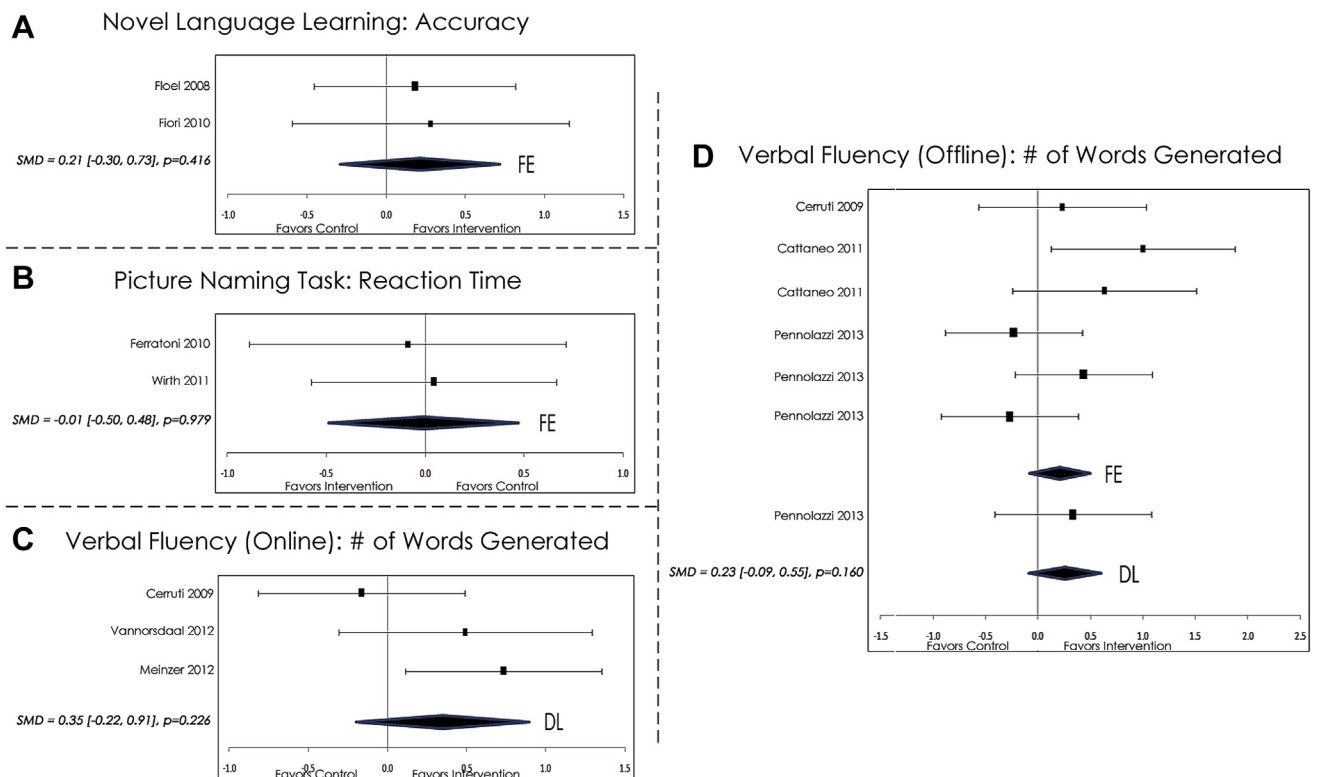


Figure 2. Forest plots for both primary and secondary language analyses (SMD = Standard mean difference; FE = Fixed effect model for primary analyses; DL = DerSimonian-Laird mixed-effect model for secondary analyses; Parentheses represent 95% CI).

single research group to ensure all data included in and conclusions generated by this review accurately reflect the effects of tDCS itself, rather than any unique device, protocol, or condition utilized in a single lab. Examples of non-experimentally based systematic errors reliably influencing the results generated by a single research group can be found in all the sciences, from physics (see: Ref. [22]), to biology (see: Ref. [23]), to medicine (see: Ref. [24]). Due to this inclusion criterion, a number of cognitive outcome measures extant in the literature were omitted due to only being reported by a single research group (see [Supplemental Material: Table S2](#)). We want to emphasize that this *does not* suggest said research is in any way faulty or incorrect; rather, that inter-group replication is necessary in order to eliminate any potential non-tDCS influential outcome factors.

Next, the stimulation-to-task relationship was determined for each study. As the mechanism of tDCS is thought to differ *during* and *following* stimulation (see above), included papers were divided into those which utilized an ‘online’ protocol and those which utilized an ‘offline’ protocol. Following this, we further divided studies according to the location chosen for the active stimulating tDCS electrode and whether or not anodal or cathodal stimulation was utilized. Finally, all studies not including a sham condition were omitted.

Analysis

Our initial intention was to pool only studies which utilized identical stimulation current densities and electrode montages. However, a look at the results section reveals there is very little direct replication in the literature. Accordingly, we decided to dichotomize current density values (low = 0.0286 mA/cm²; high > 0.0286 mA/cm²) and assessed the respected effects independently.

Next, continuous mean and variation data was extracted from each included study. If continuous numerical data was not included, values were extracted from included images (achieved by exporting images to an image editing program, overlaying a standardized grid, and counting relevant values by hand). For each included study, active stimulation values were compared to sham (control) values and a standard mean difference (SMD) with 95% confidence interval (95% CI) effect size was determined. These values were grouped and analyzed using two different meta-analytic software tools to ensure accuracy (Comprehensive Meta-Analysis – v2.0, Biostat, Englewood, NJ, USA; MetaEasy – v1.0.4, Statanalysis, Manchester, UK). No differences were found in obtained values from either program; included images were exported from Meta-Easy v1.0.4. Due to the wide paradigmatic variation and unknown effect of multiple-day stimulation protocols (e.g. – 10 consecutive days of anodal stimulation during a learning task), we only analyzed day 1 data from any study utilizing a multiple-day protocol.

Due to parametric variations within papers, we undertook two levels of analyses to balance the tradeoff between the maximum homogeneity achieved by including a smaller number of studies and our desire to also look for any more generalized effects seen across a broader sample of studies. Our primary analysis was limited to studies utilizing the same cognitive task with identical tDCS current densities and reference electrode locations. For this analysis, a fixed-effect (FE) model was utilized since, as the tDCS parameters and task were the same between studies, one would expect fairly homogenous results.

For our secondary analysis, all studies which utilized the same outcome measure were pooled and analyzed, regardless of current density and/or reference electrode location. This analysis included both the studies utilized in the first analysis and any additional study that used different current density and/or electrode montage. For this larger analysis, a DerSimonian-Laird (DL) mixed-effects

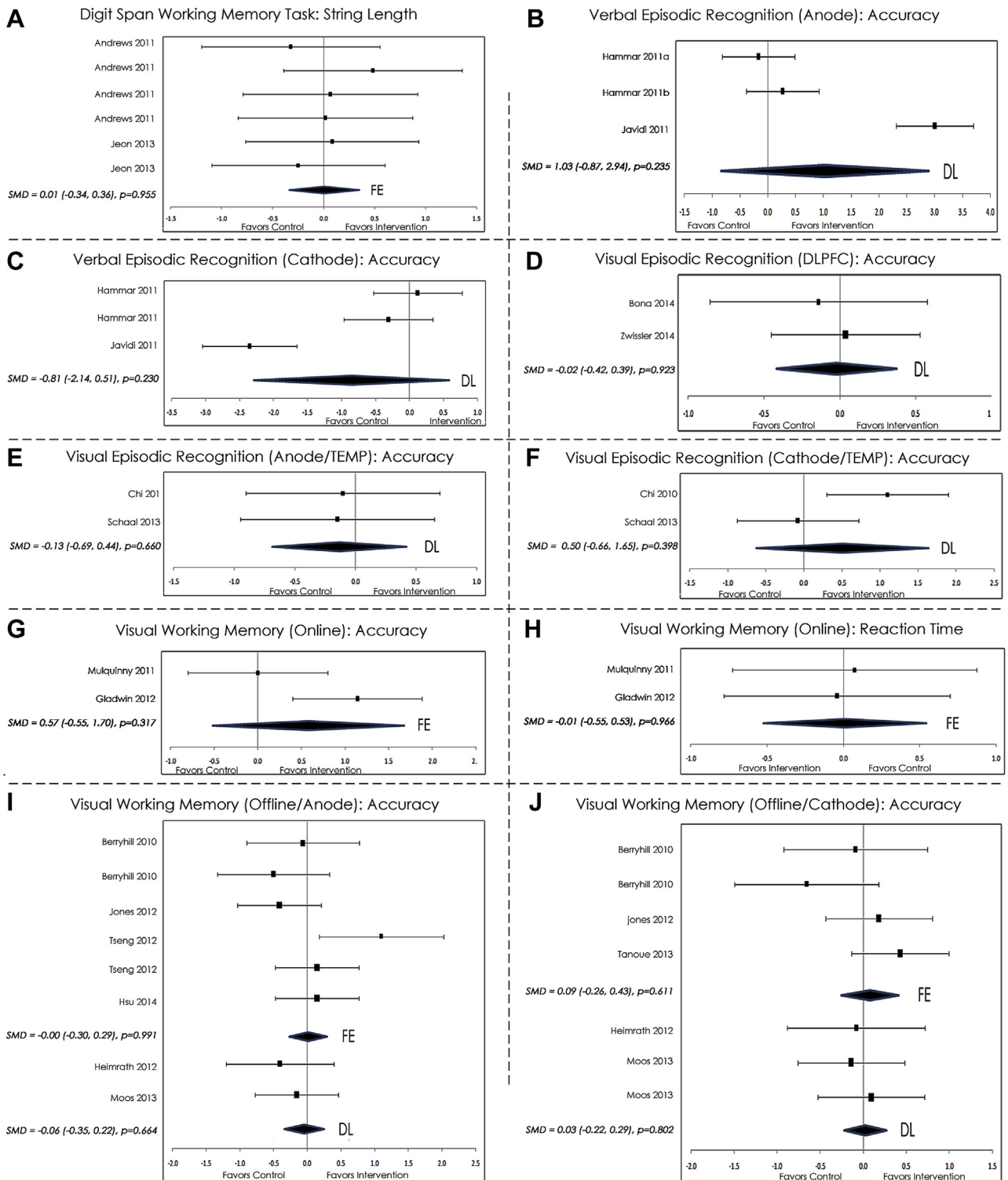


Figure 3. Forest plots for both primary and secondary memory task analyses (n-back excluded) (SMD = Standard mean difference; FE = Fixed effect model for primary analyses; DL = DerSimonian-Laird mixed-effect model for secondary analyses; Parentheses represent 95% CI).

model was selected since, as current density and reference electrode location parameters were variable, one would expect more heterogenous results. As these parameters were chosen prior to analysis, homogeneity I^2 values will not be reported below.

Several studies in the literature have explored outcome measures included in the analysis below whilst targeting a neural

region not replicated by a second group. Unfortunately, as these studies did not meet our inclusion criteria, we were unable to pool or meaningfully analyze them. For a list of these studies which have explored one of the outcome measures included in this paper but which targeted a different, non-replicated neural region, please see [Supplementary Material \(Table S2\)](#)

Table 4

Studies and values for executive function task secondary analyses.

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Verbal fluency task – anode/online: NUMBER OF WORDS GENERATD								
[44]	18	IDLPCF	rORBIT	0.0613	PHN	–0.17 (–0.82, 0.49)	–0.494	0.621
[48]	12	IDLPCF	Cz	0.0370	SMT	0.49 (–0.32, 1.30)	1.185	0.236
[51]	20	IDLPCF (+Broca)	rORBIT	0.0286	SMT	0.73 (0.09, 1.38)	2.247	0.025
				DL model		0.35 (–0.22, 0.91)	1.210	0.226
Verbal fluency task – anode/offline: NUMBER OF WORDS GENERATD								
[44]	12	IDLPCF	rORBIT	0.0613	PHN	0.23 (–0.57, 1.4)	0.568	0.570
[45]	10	IDLPCF (+Broca)	rORBIT	0.0571	SMT	1.00 (0.07, 1.93)	2.110	0.035
	10	IDLPCF (+Broca)	rORBIT	0.0571	PHN	0.63 (–0.27, 1.53)	1.381	0.167
[46]	18	IDLPCF	rORBIT	0.0571	SMT	–0.23 (–0.89, 0.42)	–0.700	0.484
	18	IDLPCF (+Broca)	rORBIT	0.0571	SMT	0.43 (–0.29, 1.09)	1.283	0.199
	18	IDLPCF (+Broca)	rORBIT	0.0571	SMT	–0.27 (–0.93, 0.39)	–0.809	0.418
[46]	18	IDLPCF (+Broca)	rDLPCF	0.0571	SMT	0.29 (–0.37, 0.95)	0.869	0.385
				DL model		0.23 (–0.09, 0.55)	1.406	0.160

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized mean difference; A = Active; S = Sham; WNKE = Wernicke's area; RT = Reaction time; DLPFC = Dorsolateral prefrontal cortex; ORBIT = Orbitofrontal location; PHN = Phonemic; SMT = Semantic.

Verbal fluency: [47] was omitted from analysis as the young cohort only undertook sham stimulation. [48] did not supply quantitative data for the phonemic fluency task, though they verbally reported no effect of stimulation. 1 study from [48] was omitted as it did not include numerical data (though they did verbally report no effect of stimulation on the total number of words generated).

Results

Executive functions: primary analysis

Set shifting

The directly-replicated anode/offline studies revealed a non-significant SMD effect size for the number of errors generated during task completion (Table 1; Fig. 1a). Only 1 study explored cathodal/offline stimulation [25] and only 1 study explored online tDCS on this task [29]; accordingly, no analysis was undertaken for these measures.

Stop signal task

The directly-replicated anode/offline studies revealed a non-significant SMD effect size for inhibitory reaction time to stop-signal stimuli (Table 1; Fig. 1c). In addition [27], and [28] further reported values for reaction time (RT) to non-stop-signal stimuli; analysis of this measure revealed a non-significant SMD effect size (Table 1; Fig. 1b). Only 1 study explored the effect of anodal/online stimulation [30] and only 1 explored the effect of cathodal/offline stimulation on this task [31]; accordingly, no analysis was undertaken for these measures.

Executive functions: secondary analysis

Stop signal task

Six non-directly comparable studies explored this task; 3 targeted M1 and 3 targeted pSMA. Analysis of the different locations revealed no significant SMD effect sizes for inhibitory reaction time to stop-signal stimuli (Table 2; Fig. 1d,e).

Stroop task

The non-directly comparable studies revealed no significant SMD effect sizes for task completion time (Table 2; Fig. 1f,g). 2 studies explored the effects of cathodal/offline stimulation [35,36]. As each came from the same research group, no analysis was undertaken. No studies have explored the effect of online stimulation on this measure.

Language: primary analysis

Novel language learning task

The directly-replicated anode/offline studies revealed a non-significant SMD effect size for task accuracy (Table 3; Fig. 3a).

Interestingly, although [41] noted an effect of stimulation on RT [40], noted no effect of stimulation on RT: as this later group did not include any numeric data for this measure (only a verbal report), no analysis could be undertaken for this measure. No studies have explored the effect of online or cathodal stimulation on this task.

Picture naming task

Three studies explored the effect of tDCS on this outcome measure by targeting the temporal lobes (2 from [49], 1 from [50]). Unfortunately [49], only reported numerical data for accuracy (verbally noted no effect of stimulation on RT) whilst [50] only reported numerical data for RT (verbally noted no effect of stimulation on accuracy). Accordingly, no analysis was undertaken for these papers. In addition, 4 studies from 3 papers have explored the effect of tDCS on this outcome measure by targeting the left DLPFC [37,42,43]. Unfortunately [42], and [43] both reported only numerical data for RT (though [42] verbally noted no effect of stimulation on accuracy) whilst [37] only reported numerical data for Accuracy. Accordingly, an analysis could only be undertaken exploring RT. Analysis of this measure revealed a non-significant SMD effect size (Table 3; Fig. 3b). Although 4 studies from 3 papers have explored the effect of anodal/online stimulation on this task, each targeted a different neural region; accordingly, no analysis could be undertaken. Finally, although 4 studies from 3 papers have explored the effect of cathodal stimulation on this task, each targeted a different neural region; accordingly, no analysis was undertaken.

Verbal fluency

The directly-replicated anode/offline studies revealed a non-significant SMD effect size for word generation (Table 3; Fig. 3d). Three comparable studies have explored the effect of anode/online stimulation on this task; however, as the current density and reference electrode location differed between each, we will explore this in the secondary analysis (below). No study has explored the effect of cathodal stimulation on this measure.

Language: secondary analysis

Verbal fluency

The non-directly comparable anode/online and anode/offline studies revealed no significant SMD effect size for word generation (Table 4; Fig. 2c,d). No study explored the effect of cathodal stimulation on this measure.

Table 5
Studies and values for memory task primary analyses (N-Back excluded).

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Digit span working memory task (forward & backward) – anode/offline: SPAN								
[52]	10	IDL PFC	rORBIT	0.0286	Forward	–3.22 (–1.21, 0.56)	–0.716	0.474
	10	IDL PFC	rORBIT	0.0286	Backward	0.483 (–0.41, 1.37)	1.065	0.287
	11a/10s	IDL PFC	rORBIT	0.0286	Forward	0.065 (–0.79, 0.92)	0.148	0.882
	11a/10s	IDL PFC	rORBIT	0.0286	Backward	0.018 (–0.84, 0.87)	0.040	0.968
[37]	8a/16s	IDL PFC	rORBIT	0.0286	Forward	0.084 (–0.77, 0.93)	0.194	0.846
	8a/16s	IDL PFC	rORBIT	0.0286	Backward	–0.25 (–1.10, 0.60)	–0.574	0.566
				Fixed effect model		0.01 (–0.34, 0.36)	0.056	0.955
Visual working memory – anode/online: ACCURACY								
[53]	12	IDL PFC	rORBIT	0.0286	STRNBRG	0.000 (–1.62, 0.86)	0.000	1.000
[54]	14	IDL PFC	rORBIT	0.0286	STRNBRG	1.14 (0.34, 1.94)	2.803	0.005
				Fixed effect model		0.57 (–0.55, 1.70)	1.000	0.317
Visual working memory – anode/online: RT								
[53]	12	IDL PFC	rORBIT	0.0286	STRNBRG	–0.07 (–0.87, 0.73)	–0.177	0.859
[54]	14	IDL PFC	rORBIT	0.0286	STRNBRG	0.04 (–0.70, 0.78)	0.107	0.915
				Fixed effect model		–0.01 (–0.55, 0.53)	–0.042	0.966
Visual working memory – anode/offline: ACCURACY								
[55]	11	rPPC	ICHK	0.0429		–0.07 (–0.90, 0.77)	–0.153	0.878
	11	rPPC	ICHK	0.0429		–0.50 (–1.35, 0.35)	–1.160	0.246
[56]	20	rPPC	ICHK	0.0429		–0.42 (–1.04, 0.21)	–1.298	0.194
[57]	9	rPPC	ICHK	0.0938		1.06 (0.07, 2.04)	2.099	0.036
	20	rPPC	ICHK	0.0938		0.14 (–0.48, 0.76)	0.451	0.652
[58]	20	rPPC	ICHK	0.0938		0.14 (–0.48, 0.76)	0.451	0.652
				Fixed effect model		–0.00 (–0.30, 0.29)	–0.012	0.991
Visual working memory – cathode/offline: ACCURACY								
[55]	11	rPPC	ICHK	0.0429		–0.09 (–0.93, 0.75)	–0.211	0.833
	11	rPPC	ICHK	0.0429		–0.66 (–1.52, 0.20)	–1.504	0.133
[56]	20	rPPC	ICHK	0.0429		0.18 (–0.44, 0.80)	0.569	0.569
[59]	24	rPPC	ICHK	0.0429		0.43 (–0.14, 1.00)	1.468	0.142
				Fixed effect model		0.09 (–0.26, 0.43)	0.509	0.611
Two-back working memory task – anode/offline: RT								
[53]	12	IDL PFC	rORBIT	0.02857	2-Back	–0.45 (–1.26, 0.36)	–1.095	0.274
[60]	18	IDL PFC	rORBIT	0.02857	2-Back	–0.29 (–0.95, 0.37)	–0.868	0.385
				Fixed effect model		–0.39 (–0.90, 0.12)	–1.364	0.173
[61]	10	IDL PFC	rORBIT	0.05714	2-Back	–0.33 (–1.22, 0.55)	–0.741	0.459
[60]	18	IDL PFC	rORBIT	0.05714	2-Back	–0.02 (–0.68, 0.63)	–0.073	0.942
				Fixed effect model		–0.13 (–0.66, 0.40)	–0.499	0.617
Three-back working memory task – anode/online: ACCURACY								
[62]	15	IDL PFC	rORBIT	0.02857	3-Back	0.31 (–0.41, 1.03)	0.855	0.393
[63]	12	IDL PFC	rORBIT	0.02857	3-Back	0.05 (–0.71, 0.81)	0.125	0.901
				Fixed effect model		0.19 (–0.33, 0.71)	0.706	0.480
[64]	15	IDL PFC	rORBIT	0.04	3-Back	0.36 (–0.37, 1.08)	0.966	0.334
[63]	12	IDL PFC	rORBIT	0.05714	3-Back	–0.05 (–0.81, 0.71)	–0.128	0.898
				Fixed effect model		0.16 (–0.36, 0.69)	0.612	0.541
Three-back working memory task – anode/online: RT								
[62]	15	IDL PFC	rORBIT	0.02857	3-Back	0.00 (–0.71, 0.72)	0.011	0.991
[63]	12	IDL PFC	rORBIT	0.02857	3-Back	–0.30 (–1.11, 0.50)	–0.736	0.462
				Fixed effect model		–0.13 (–0.67, 0.40)	–0.481	0.631
[64]	15	IDL PFC	rORBIT	0.04	3-Back	0.01 (–0.70, 0.73)	0.032	0.974
[63]	12	IDL PFC	rORBIT	0.05714	3-Back	–0.32 (–1.13, 0.48)	–0.781	0.435
				Fixed effect model		–0.14 (–0.67, 0.40)	–0.495	0.621

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized mean difference; A = Active; S = Sham; DLPFC = Dorsolateral prefrontal cortex; ORBIT = Orbitofrontal location; DELT = Deltoid muscle; ATL = Anterior temporal lobe; SMG = Supramarginal gyrus; STRNBRG = Sternberg working memory task; PPC = Posterior parietal cortex; CHK = Cheek; IPS = Inferior parietal sulcus; RT = Reaction time.

Digit span: Two sham groups were pooled in Jeon 2013.

Visual working memory: Values collapsed across hemifields and array sizes. Values for the second study from Tseng 2012 and Hsu 2014 are collapsed across all participants (data appear to be identical for these studies). Bolognini 2010 was omitted from analysis as they did not report any data for accuracy. Tanoue 2013 utilized a cueing paradigm – only the data from the cue-less trials was utilized.

N-back tasks: Data for [64] and [63] were collapsed across two online blocks. [60] was omitted from both accuracy and RT analysis due to no discernable quantitative data being made available. A description in the text noted no effect of either low- or high-density stimulation on accuracy or RT. [52] was omitted from analysis due to not reporting quantitative data. [65] was omitted due to utilizing a 10-day stimulation protocol (no day 1 data). 1 study from [60] was omitted due to not reporting quantitative data (though they verbally reported no effect of stimulation on accuracy or RT data during a 3-back task, and no effect on accuracy during a 2-back task).

Memory: primary analysis

Digit span working memory

The directly-replicated anode/offline studies revealed a non-significant SMD effect size for span length (Table 5; Fig. 3a). No studies explored the effects of online or cathodal stimulation on this task.

Visual working memory

The directly-replicated anode/online studies revealed a non-significant SMD effect size for task accuracy or RT (Table 5; Fig. 3g,h). Similarly, anode/offline studies revealed a non-significant SMD effect size for task accuracy (Table 5; Fig. 3i). With regards to cathode/offline stimulation, analysis of the directly-replicated cathode/offline studies revealed a non-significant SMD effect size

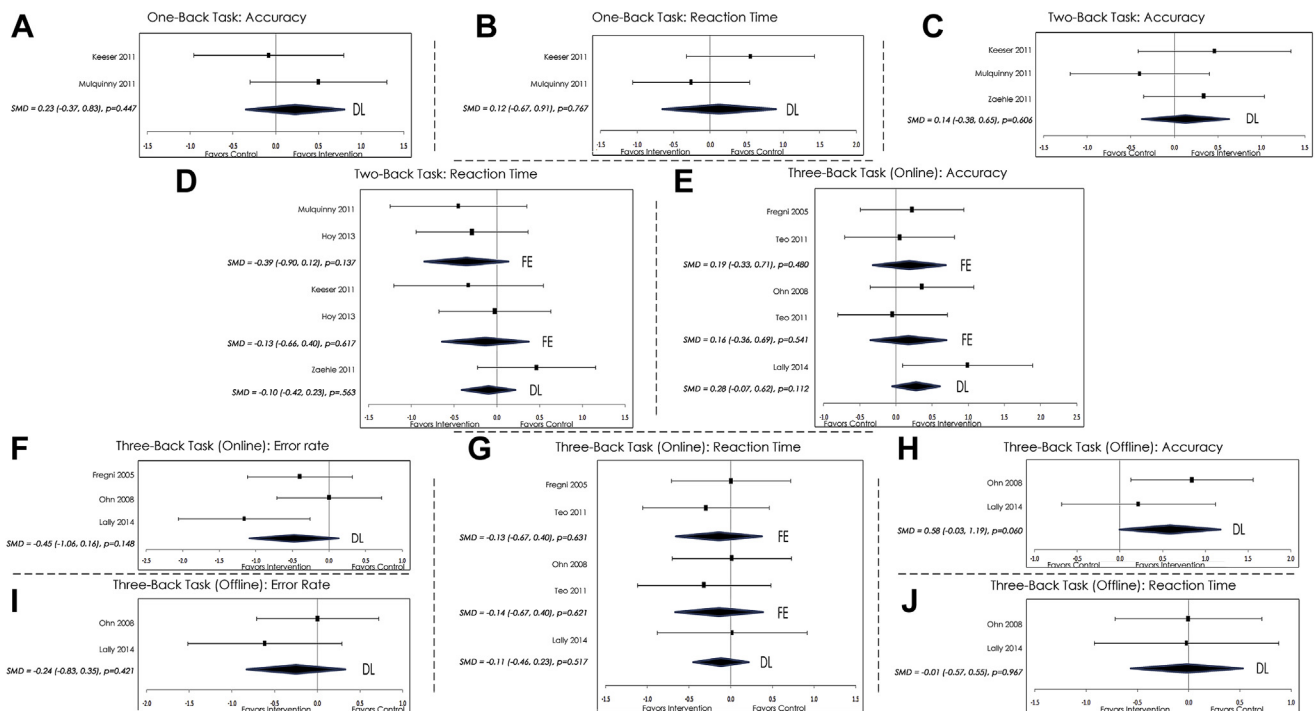


Figure 4. Forest plots for both primary and secondary n-back task analyses (SMD = Standard mean difference; FE = Fixed effect model for primary analyses; DL = DerSimonian-Laird mixed-effect model for secondary analyses; Parentheses represent 95% CI).

on task accuracy (Table 5; Fig. 3j). No studies explored the effect of cathodal/online stimulation on this task. Finally, 2 studies have explored the effect of anode/offline and cathode/offline stimulation on this task whilst targeting the cerebellum [66,67]. Unfortunately [66], only reported quantitative data for RT (verbally reported no effect on accuracy) whilst [67] only reported quantitative data for accuracy (verbally noted no effect on accuracy); accordingly, no analysis was undertaken.

N-back working memory

As task difficulty increases with N , we decided to divide and analyze the remaining studies according to N (so that the effects of stimulation during a 1-back task do not skew effects during a 3-back task). Analyses of the directly-replicated studies revealed no significant SMD effect size for any measure (Table 5; Fig. 4a,e,g).

Memory: secondary analysis

Verbal episodic memory

The non-directly comparable anode and cathode studies during encoding revealed no significant SMD effect size for task accuracy (Table 6; Fig. 3b,c). With regards to anode during recognition [69], only reported numerical data for accuracy (verbally reported no effect on RT) whilst [82] only reported numerical data for RT (verbally reported no effect on accuracy); accordingly, no analysis was undertaken.

Visual episodic memory

The non-directly comparable anodal studies at each electrode location revealed no significant SMD effect size for task accuracy (Table 7; Fig. 3d,e). Similarly, the non-directly comparable cathodal studies revealed a non-significant SMD effect size for task accuracy (Table 6; Fig. 3f).

Visual working memory

The non-directly comparable anode/offline studies revealed a non-significant SMD effect size for task accuracy (Table 6; Fig. 3i). The non-directly comparable cathode/offline studies also revealed a non-significant SMD effect size on task accuracy (Table 6; Fig. 3j). No studies explored the effect of cathodal/online stimulation on this task.

N-back working memory

Again, as task difficulty increases with N , studies were divided according to N (so that the effects of stimulation during a 1-back task did not skew effects during a 3-back task). For a full breakdown, see Table 6 and Fig. 4. Analyses of the non-directly comparable studies revealed no significant SMD effect size for task accuracy, reaction time, or false alarm rate at any level.

Memory: additional pooled analyses

As many of the aforementioned memory studies utilize tasks which explore a similar memory system (e.g. – working memory), we ran 8 additional analyses combining all studies exploring the same memory system (regardless of specific task utilized). First, we pooled all anodal/online n-back working memory tasks, regardless of the ‘ n ’ value. Analysis revealed no significant SMD effect size for accuracy SMD [95% CI] = 0.19 [–0.13, 0.51], $z = 1.187$, $P = 0.235$; Fig. 5a) or RT (SMD [95% CI] = –0.14 [–0.46, 0.18], $z = –0.851$, $P = 0.395$; Fig. 5b). Next, we pooled all anodal/offline n-back working memory tasks, regardless of the ‘ n ’ value. Again, analysis revealed no significant SMD effect size for accuracy (SMD [95% CI] = 0.29 [–0.02, 0.60], $z = 1.845$, $P = 0.065$; Fig. 5e) or RT (SMD [95% CI] = –0.16 [–0.42, 0.09], $z = –1.266$, $P = 0.206$; Fig. 5f). Next, we pooled all anodal/online tasks exploring working memory (with a similar neural target). Again, analysis revealed no significant SMD effect size for accuracy (SMD [95% CI] = 0.29 [–0.04, 0.61], $z = 1.699$, $P = 0.089$; Fig. 5c) or RT (SMD [95% CI] = –0.10 [–0.37, 0.17],

Table 6

Studies and values for memory task secondary analyses (N-Back excluded).

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Verbal episodic memory task: recognition (stim during encoding) – anode: ACCURACY								
[68]	18	IDLPFC	rORBIT	0.0286	Errorless Learning	–0.17 (–0.82, 0.49)	–0.502	0.616
	18	IDLPFC	rORBIT	0.0286	Errorful Learning	0.268 (–0.39, 0.92)	0.800	0.424
[69]	16	IDLPFC	rORBIT	0.0816	–	3.00 (1.99, 4.01)	5.821	<0.001
				DL model		1.03 (–0.87, 2.94)	1.188	0.235
Verbal episodic memory task: recognition (stim during encoding) – cathode: ACCURACY								
[68]	18	IDLPFC	rORBIT	0.0286	Errorless Learning	0.120 (–0.53, 0.77)	0.360	0.719
	18	IDLPFC	rORBIT	0.0286	Errorful Learning	–0.31 (–0.97, 0.35)	–0.932	0.351
[69]	16	IDLPFC	rORBIT	0.0816	–	–2.35 (–3.25, –1.45)	–5.117	<0.001
				DL model		–0.81 (–2.14, 0.51)	–1.201	0.230
Visual episodic memory task: recognition (stim during encoding) – anode: ACCURACY (DLPFC)								
[70]	15	IDLPFC	rORBIT	0.0286	Cued Learning	0.037 (–0.45, 0.53)	0.146	0.884
[71]	24a/48s	IDLPFC	rDELT	0.0571	–	–0.14 (–0.86, 0.58)	–0.385	0.700
				DL model		–0.02 (–0.42, 0.39)	–0.096	0.923
Visual episodic memory task: recognition (stim during encoding) – anode: ACCURACY (TEMP)								
[72]	12	IATL	rATL	0.0571	–	–0.11 (–0.91, 0.70)	–0.257	0.797
[73]	12	ISMG	rORBIT	0.08	–	–0.15 (–0.95, 0.65)	–0.365	0.715
				DL model		–0.13 (–0.69, 0.44)	–0.440	0.660
Visual episodic memory task: recognition (stim during encoding) – cathode: ACCURACY (TEMP)								
[72]	12	IATL	rATL	0.0571	–	1.10 (0.24, 1.96)	2.509	0.012
[73]	12	ISMG	rORBIT	0.08	–	–0.08 (–0.88, 0.72)	–0.198	0.843
				DL model		0.50 (–0.66, 1.65)	0.845	0.398
Visual working memory – anode/offline: ACCURACY								
[55]	11	rPPC	ICHK	0.0429		–0.07 (–0.90, 0.77)	–0.153	0.878
	11	rPPC	ICHK	0.0429		–0.50 (–1.35, 0.35)	–1.160	0.246
[56]	20	rPPC	ICHK	0.0429		–0.42 (–1.04, 0.21)	–1.298	0.194
[57]	9	rPPC	ICHK	0.0938		1.06 (0.07, 2.04)	2.099	0.036
	20	rPPC	ICHK	0.0938		0.14 (–0.48, 0.76)	0.451	0.652
[58]	20	rPPC	ICHK	0.0938		0.14 (–0.48, 0.76)	0.451	0.652
[74]	12	rPPC	IPPC	0.0286		–0.42 (–1.22, 0.39)	–1.005	0.315
[75]	20	rIPS	IORBIT	0.0286		–0.16 (–0.78, 0.46)	–0.495	0.620
				DL model		–0.06 (–0.35, 0.22)	–0.435	0.664
Visual working memory – cathode/offline: ACCURACY								
[55]	11	rPPC	ICHK	0.0429		–0.09 (–0.93, 0.75)	–0.211	0.833
	11	rPPC	ICHK	0.0429		–0.66 (–1.52, 0.20)	–1.504	0.133
[56]	20	rPPC	ICHK	0.0429		0.18 (–0.44, 0.80)	0.569	0.569
[59]	24	rPPC	ICHK	0.0429		0.43 (–0.14, 1.00)	1.468	0.142
[74]	12	rPPC	IPPC	0.0286		–0.08 (–0.88, 0.72)	–0.200	0.842
[75]	20	rIPS	IORBIT	0.0286		–0.14 (–0.76, 0.48)	–0.448	0.654
	20	rIPS	IORBIT	0.0571		0.09 (–0.53, 0.71)	0.293	0.769
				DL model		0.03 (–0.22, 0.29)	0.251	0.802
One-back working memory task – anode/offline: ACCURACY								
[61]	10	IDLPFC	rORBIT	0.05714	1-Back	–0.08 (–0.96, 0.80)	–0.184	0.854
[53]	12	IDLPFC	rORBIT	0.02857	1-Back	0.50 (–0.31, 1.31)	1.206	0.228
				DL model		0.23 (–0.37, 0.83)	0.760	0.447
One-back working memory task – anode/offline: RT								
[61]	10	IDLPFC	rORBIT	0.05714	1-Back	0.55 (–0.34, 1.44)	1.208	0.227
[53]	12	IDLPFC	rORBIT	0.02857	1-Back	–0.26 (–1.07, 0.54)	–0.638	0.524
				DL model		0.12 (–0.67, 0.91)	0.296	0.767
Two-back working memory task – anode/offline: ACCURACY								
[61]	10	IDLPFC	rORBIT	0.05714	2-Back	0.46 (–0.43, 1.35)	1.019	0.308
[53]	12	IDLPFC	rORBIT	0.02857	2-Back	–0.40 (–1.21, 0.41)	–0.970	0.332
[76]	16	IDLPFC	rMAST	0.02857	2-Back	0.39 (–0.36, 1.04)	0.949	0.343
				DL model		0.14 (–0.38, 0.65)	0.515	0.606
Two-back working memory task – anode/offline: RT								
[53]	12	IDLPFC	rORBIT	0.02857	2-Back	–0.45 (–1.26, 0.36)	–1.095	0.274
[60]	18	IDLPFC	rORBIT	0.02857	2-Back	–0.29 (–0.95, 0.37)	–0.868	0.385
[61]	10	IDLPFC	rORBIT	0.05714	2-Back	–0.33 (–1.22, 0.55)	–0.741	0.459
[60]	18	IDLPFC	rORBIT	0.05714	2-Back	–0.02 (–0.68, 0.63)	–0.073	0.942
[76]	16	IDLPFC	rMAST	0.02857	2-Back	0.46 (–0.24, 1.17)	1.293	0.196
				DL model		–0.10 (–0.42, 0.23)	–0.579	0.563
Three-back working memory task – anode/online: ACCURACY								
[62]	15	IDLPFC	rORBIT	0.02857	3-Back	0.31 (–0.41, 1.03)	0.855	0.393
[63]	12	IDLPFC	rORBIT	0.02857	3-Back	0.05 (–0.71, 0.81)	0.125	0.901
[64]	15	IDLPFC	rORBIT	0.04	3-Back	0.36 (–0.37, 1.08)	0.966	0.334
[63]	12	IDLPFC	rORBIT	0.05714	3-Back	–0.05 (–0.81, 0.71)	–0.128	0.898
[77]	9a	IDLPFC	rCHK	0.02857	3-Back	0.97 (0.01, 1.92)	1.988	0.047
	10			DL model		0.28 (–0.07, 0.62)	1.589	0.112
Three-back working memory task – anode/online: FA								
[62]	15	IDLPFC	rORBIT	0.02857	3-Back	–0.40 (–1.13, 0.32)	–1.095	0.273
[64]	15	IDLPFC	rORBIT	0.04	3-Back	0.00 (–0.72, 0.72)	0.000	1.000
[77]	9a	IDLPFC	rCHK	0.02857	3-Back	–1.16 (–2.14, –0.19)	–2.339	0.019
	10							

Table 6 (continued)

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
DL model						−0.45 (−1.06, 0.16)	−1.446	0.148
Three-back working memory task – anode/online: RT								
[62]	15	IDL PFC	rORBIT	0.02857	3-Back	0.00 (−0.71, 0.72)	0.011	0.991
[63]	12	IDL PFC	rORBIT	0.02857	3-Back	−0.30 (−1.11, 0.50)	−0.736	0.462
[64]	15	IDL PFC	rORBIT	0.04	3-Back	0.01 (−0.70, 0.73)	0.032	0.974
[63]	12	IDL PFC	rORBIT	0.05714	3-Back	−0.32 (−1.13, 0.48)	−0.781	0.435
[77]	9a	IDL PFC	rCHK	0.02857	3-Back	0.02 (−0.88, 0.92)	0.037	0.971
	10							
DL model						−0.11 (−0.46, 0.23)	−0.648	0.517
Three-back working memory task – anode/offline: ACCURACY								
[64]	15	IDL PFC	rORBIT	0.04	3-Back	0.84 (0.10, 1.59)	2.214	0.027
[77]	9a	IDL PFC	rCHK	0.02857	3-Back	0.22 (−0.69, 1.12)	0.466	0.641
	10							
DL model						0.58 (−0.03, 1.19)	1.879	0.060
Three-back working memory task – anode/offline: FA								
[64]	15	IDL PFC	rORBIT	0.04	3-Back	0.00 (−0.72, 0.72)	0.000	1.000
[77]	9a	IDL PFC	rCHK	0.02857	3-Back	−0.62 (−1.54, 0.31)	−1.312	0.190
	10							
DL model						−0.24 (−0.83, 0.35)	−0.804	0.421
Three-back working memory task – anode/offline: RT								
[64]	15	IDL PFC	rORBIT	0.04	3-Back	−0.01 (−0.72, 0.71)	−0.015	0.988
[77]	9a	IDL PFC	rCHK	0.02857	3-Back	−0.02 (−0.92, 0.88)	−0.047	0.962
	10							
DL model						−0.01 (−0.57, 0.55)	−0.041	0.967

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized mean difference; A = Active; S = Sham; DLPFC = Dorsolateral prefrontal cortex; ORBIT = Orbitofrontal location; DELT = Deltoid muscle; ATL = Anterior temporal lobe; SMG = Supramarginal gyrus; STNRBRG = Sternberg working memory task; PPC = Posterior parietal cortex; CHK = Cheek; IPS = Inferior parietal sulcus; RT = Reaction time; MAST = Mastoid; FA = False alarms.

Verbal episodic memory: [68] presented only values pooled between online and offline measures. Two studies from [69] were omitted: one for targeting M1, one for generating stimulation during recognition (no comparable work elsewhere). [78] was omitted due to using very-short duration (1.6 s) stimulation during recognition only (no comparable work elsewhere). [79] was omitted due to utilizing a 5-day stimulation protocol (no day 1 data).

Visual episodic memory: Two studies from [54] were omitted as they utilized an interference paradigm in the Sternberg task (no comparable work elsewhere). [80] was omitted due to using a 10-day stimulation paradigm (no day 1 data). Values were collapsed across array sizes.

Visual working memory: Values collapsed across hemifields and array sizes. Values for the second study from [57] and [58] are collapsed across all participants (data appear to be identical for these studies). [81] was omitted from analysis as they did not report any data for accuracy. [59] utilized a cueing paradigm – only the data from the cue-less trials was utilized.

Two-back: [60] was omitted from the accuracy analysis due to no discernable quantitative data being made available. A description in the text noted no effect of either low- or high-density stimulation on accuracy.

Three-back: Only data from day one of [77] was used for analysis. Data for [64] and [63] were collapsed across two online blocks. [60] was omitted from both accuracy and RT analysis due to no discernable quantitative data being made available. A description in the text noted no effect of either low- or high-density stimulation on accuracy or RT.

$z = -0.715$, $P = 0.474$: Fig. 5d). Next, we pooled all anodal/offline tasks exploring working memory (with a similar neural target). Again, analysis revealed no significant SMD effect size for accuracy (SMD [95% CI] = 0.17 [−0.06, 0.4], $z = 1.438$, $P = 0.151$: Fig. 5g). Finally, we pooled all anodal during encoding episodic memory tasks. Again, analysis revealed no significant SMD effect size for accuracy (SMD [95% CI] = 0.53 [−0.33, 1.38], $z = 1.211$, $P = 0.226$: Fig. 5h). Complete analyses can be found in [Supplemental Material: Table S1](#).

Miscellaneous: primary analysis

Due to a lack of directly replicable studies, no primary analysis could be undertaken on these measures.

Miscellaneous: secondary analysis

Mental arithmetic

The non-directly comparable anode/offline studies revealed a non-significant SMD effect size for task accuracy and RT (Table 7; Fig. 6a,b). Only 1 study explored the effect of online stimulation on this task [93]; accordingly, no analysis was undertaken. No studies explored the effect of cathodal stimulation on this task.

Picture viewing/rating

The non-directly comparable anode/online studies revealed no significant SMD effect size for either negative or neutral valence image ratings (Table 7; Fig. 6c,e,f,h). Similarly, the non-directly

comparable cathode/online studies revealed no significant SMD effect size for either negative or neutral valence image ratings (Table 7; Fig. 6d,g). Only 1 study explored the effect of offline stimulation on this task [94]; accordingly, no analysis was undertaken.

Risk taking

The remaining non-comparable anode/online studies revealed no significant SMD effect size for task performance (Table 7; Fig. 6i). Analysis of the non-comparable cathode/online studies revealed a non-significant SMD effect size for task performance (Table 7; Fig. 6j). Only 1 study explored the effect of offline stimulation on this task [95]; accordingly, no analysis was undertaken for this measure.

Rumination task

The non-comparable anode/offline studies revealed a non-significant SMD effect size for rumination intensity (Table 7; Fig. 6k). Only 1 study explored the effect of cathodal stimulation on this task [91]; accordingly, no analysis was undertaken. No studies explored the effect of online stimulation on this task.

Discussion

In this paper, we pooled and analyzed every cognitive outcome measure in the literature explored by at least two different research groups utilizing healthy adult populations, the same stimulation-to-task relationship, the same active electrode location, and

Table 7
Studies and values for miscellaneous task secondary analyses.

Study	N	Active	Ref	Density (mA/cm ²)	Task	SMD (95% CI)	Z value	P value
Mental arithmetic ability – anode/offline: ACCURACY								
[83]	10	rPAR	IORBIT	0.0571	MULT	0.18 (–0.70, 1.06)	0.3989	0.691
[84]	16	rPAR	IORBIT	0.0286	SUB	–0.23 (–0.93, 0.47)	–0.647	0.518
				DL model		–0.07 (–0.62, 0.47)	–0.261	0.794
Mental arithmetic ability – anode/offline: TIME TO SOLVE								
[83]	10	rPAR	IORBIT	0.0571	MULT	–0.18 (–1.06, 0.70)	–0.398	0.691
[84]	16	rPAR	IORBIT	0.0286	SUB	–0.33 (–1.03, 0.37)	–0.925	0.355
				DL model		–0.27 (–0.82, 0.28)	–0.971	0.331
Negative valence picture viewing – anode/online: NEGATIVITY RATING (IDL PFC)								
[85]	23	IDL PFC	rORBIT	0.0571	–	–0.26 (–0.84, 0.32)	–0.884	0.377
[86]	16a/32s	IDL PFC	rM1	0.0286	–	–0.37 (–0.97, 0.24)	–1.192	0.233
[87]	20	IDL PFC	rDLPFC	0.0429	–	0.14 (–0.48, 0.76)	0.438	0.661
				DL model		–0.17 (–0.52, 0.18)	–0.968	0.333
Negative valence picture viewing – cathode/online: NEGATIVITY RATING (IDL PFC)								
[86]	16a/32s	IDL PFC	rM1	0.0286	–	–0.25 (–0.86, 0.35)	–0.826	0.409
[87]	20	IDL PFC	rDLPFC	0.0429	–	0.33 (–0.30, 0.95)	1.029	0.304
				DL model		0.03 (–0.54, 0.60)	0.106	0.915
Negative valence picture viewing – anode/online: NEGATIVITY RATING (rDLPFC)								
[87]	20	rDLPFC	IDL PFC	0.0429	–	0.33 (–0.30, 0.95)	1.029	0.304
[88]	23a/25s	rDLPFC	IORBIT	0.0429	–	–0.70 (–1.28, –0.12)	–2.347	0.019
				DL model		–0.19 (–1.20, 0.81)	–0.374	0.709
Neutral valence picture viewing – anode/online: NEGATIVITY RATING (IDL PFC)								
[86]	16a/32s	IDL PFC	rM1	0.0286	–	–0.12 (–0.72, 0.48)	–0.389	0.697
[87]	20	IDL PFC	rDLPFC	0.0429	–	0.15 (–0.47, 0.77)	0.476	0.634
				DL model		0.01 (–0.42, 0.45)	0.054	0.957
Neutral valence picture viewing – cathode/online: NEGATIVITY RATING (IDL PFC)								
[86]	16a/32s	IDL PFC	rM1	0.0286	–	0.42 (–0.19, 1.02)	1.336	0.181
[87]	20	IDL PFC	rDLPFC	0.0429	–	0.33 (–0.30, 0.95)	1.026	0.305
				DL model		0.37 (–0.06, 0.81)	1.673	0.094
Neutral valence picture viewing – anode/online: NEGATIVITY RATING (rDLPFC)								
[87]	20	rDLPFC	IDL PFC	0.0429	–	0.33 (–0.30, 0.95)	1.026	0.305
[88]	23a/25s	rDLPFC	IORBIT	0.0429	–	–0.05 (–0.62, 0.52)	–0.175	0.861
				DL model		0.12 (–0.30, 0.54)	0.560	0.575
Gambling-based risk taking – anode/online: RISK PROPENSITY								
[35]	10	IDL PFC	rDLPFC	0.0571	MB	–2.95 (–4.22, –1.69)	–4.568	<0.001
[89]	12	IDL PFC	rDLPFC	0.0571	GT	0.58 (–0.24, 1.39)	1.385	0.166
[90]	16	IDL PFC	rDLPFC	?	GT	0.14 (–0.55, 0.84)	0.404	0.687
				DL model		–0.67 (–2.39, 1.06)	–0.754	0.451
Gambling-based risk taking – cathode/online: RISK PROPENSITY								
[35]	10	IDL PFC	rDLPFC	0.0571	MB	–3.38 (–4.74, –2.01)	–4.848	<0.001
[89]	12	IDL PFC	rDLPFC	0.0571	GT	–1.92 (–2.89, –0.96)	–3.895	<0.001
[90]	16	IDL PFC	rDLPFC	?	GT	0.00 (–0.69, 0.69)	0.000	1.000
				DL model		–1.70 (–3.61, 0.22)	–1.738	0.082
Rumination task – anode/offline: SELF-RUMINATION INTENSITY								
[91]	29a/33s	IDL PFC	rDLPFC	0.0571	–	0.07 (–0.43, 0.57)	0.282	0.778
[92]	32	IDL PFC	rORBIT	0.0571	–	–0.09 (–0.58, 0.40)	–0.364	0.716
				DL model		–0.01 (–0.36, 0.34)	–0.063	0.950

General notes: Active = Active electrode location; Ref = Reference electrode location; SMD = Standardized Mean Difference; A = Active; S = Sham; PAR = Parietal cortex; MULT = Multiplication task; SUB = Subtraction task; RT = Reaction time; DLPFC = Dorsolateral prefrontal cortex; MB = Monetary balloon analogue risk task; GT = Gambling Task.

Mental math: The value reported by [83] combined both RT and Accuracy – accordingly, the same value was used for both the accuracy and RT analyses. As the value represents an improvement following stimulation, it is represented as positive (higher score) in the accuracy analysis and negative (faster response) in the RT analysis.

Picture viewing: All sham participants were pooled for [86]. Two studies from [85] were omitted from analysis due to targeting M1 and V1, respectively (no comparable work elsewhere). Only the ‘maintain’ condition from [88] was analyzed.

Risk taking: Due to the unknown current density of [90], we analyzed using a DL model. Two studies from [35] were omitted for not including a sham condition.

comparing to a sham (control) condition. Of the 59 analyses undertaken, tDCS was not found to generate a significant effect on any. Taken together, the evidence does not support the assertion that a single-session of tDCS has a reliable effect on cognitive tasks in healthy adult populations.

A common criticism leveled at quantitative reviews concerns biased study selection: more specifically, through more- or less-stringent inclusion criteria, it is possible to skew analyses toward a positive result (for discussion, see: Ref. [96]). To address this issue, in this paper we undertook a two-tier analysis system. First we combined only those studies which demonstrated a direct replication of tDCS parametric values. The analysis was then expanded to combine all papers that targeted the same neural region and utilized the same task (regardless of current density and/or

reference electrode location). Finally, in the case of memory, the analysis was further expanded to combine all papers that targeted the same neural region and utilized tasks thought to measure the same cognitive skill (e.g. – working memory). None of these analyses generated significant results. This suggests that the null results found in this paper are not likely the result of any specific sampling criteria (see Limitations section below).

One potential explanation for our findings rests in state-dependency: a concept which suggests that the effect an external stimulus exerts on the brain (and, by extension, cognition) is highly influenced by the state of the brain at the time of stimulus onset [97]. For instance, there is a large body of literature that demonstrates that the outcomes of single-, paired-, and repetitive-pulse TMS can be modulated according to the initial

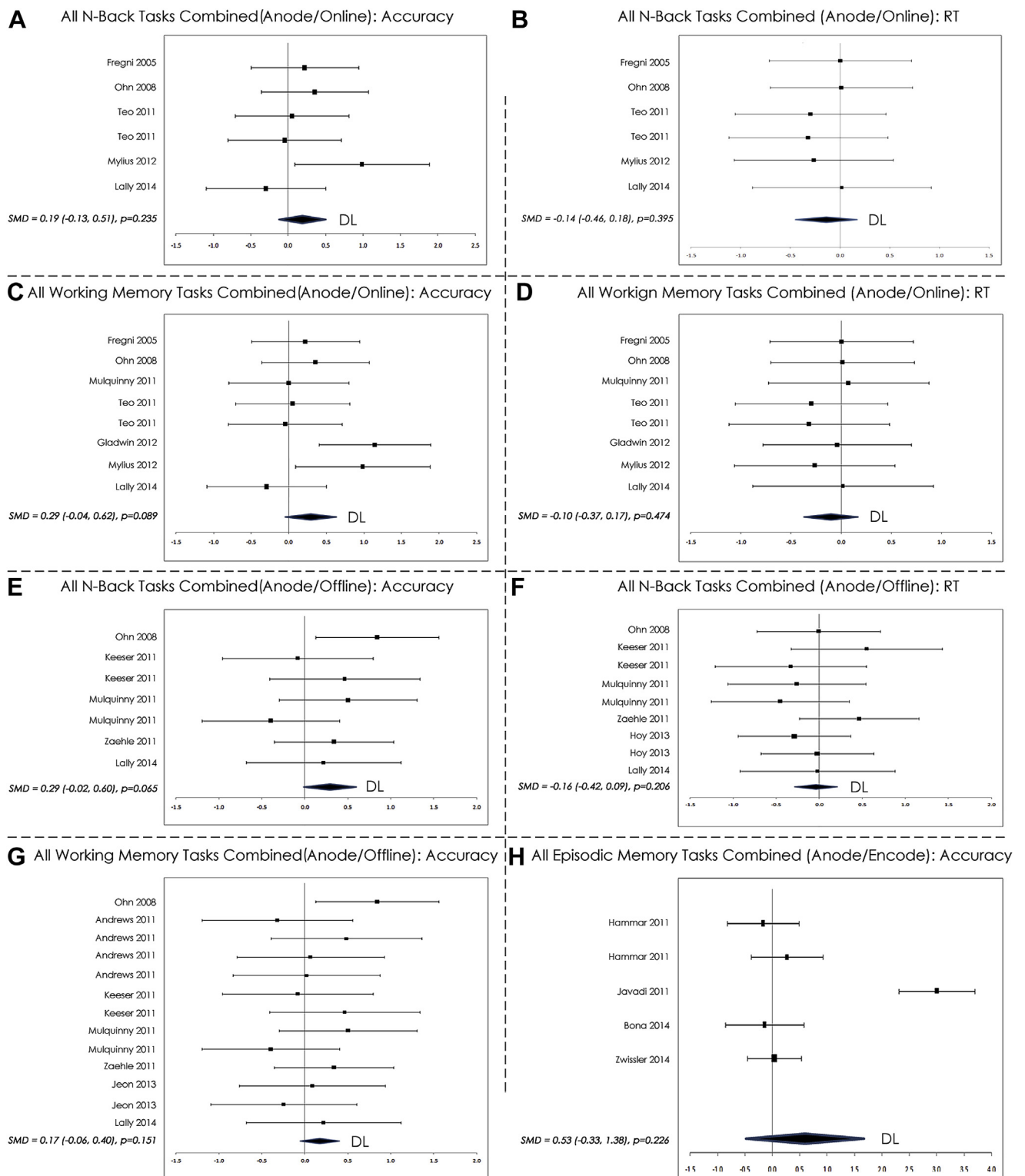


Figure 5. Forest plots for each pooled-task memory analysis (SMD = Standard mean difference; FE = Fixed effect model for primary analyses; DL = DerSimonian-Laird mixed-effect model for secondary analyses; Parentheses represent 95% CI).

cortical activation state of the targeted neural region (for review: Ref. [98]). Similarly, several studies have demonstrated that the effect of single-session tDCS on MEP amplitude can be negated following behavioral or cognitive priming [99,100] or reversed following neural priming using TMS [101]. Accordingly, it is likely that differential state-dependent effects between different

studies included in this analysis influenced the null results obtained.

Luckily, state-dependent effects can be elucidated, controlled for, and possibly even leveraged to enhance the effects of tDCS; unfortunately, there is not enough comprehensive reporting in the literature to undertake such a synthesis at this point. It would be

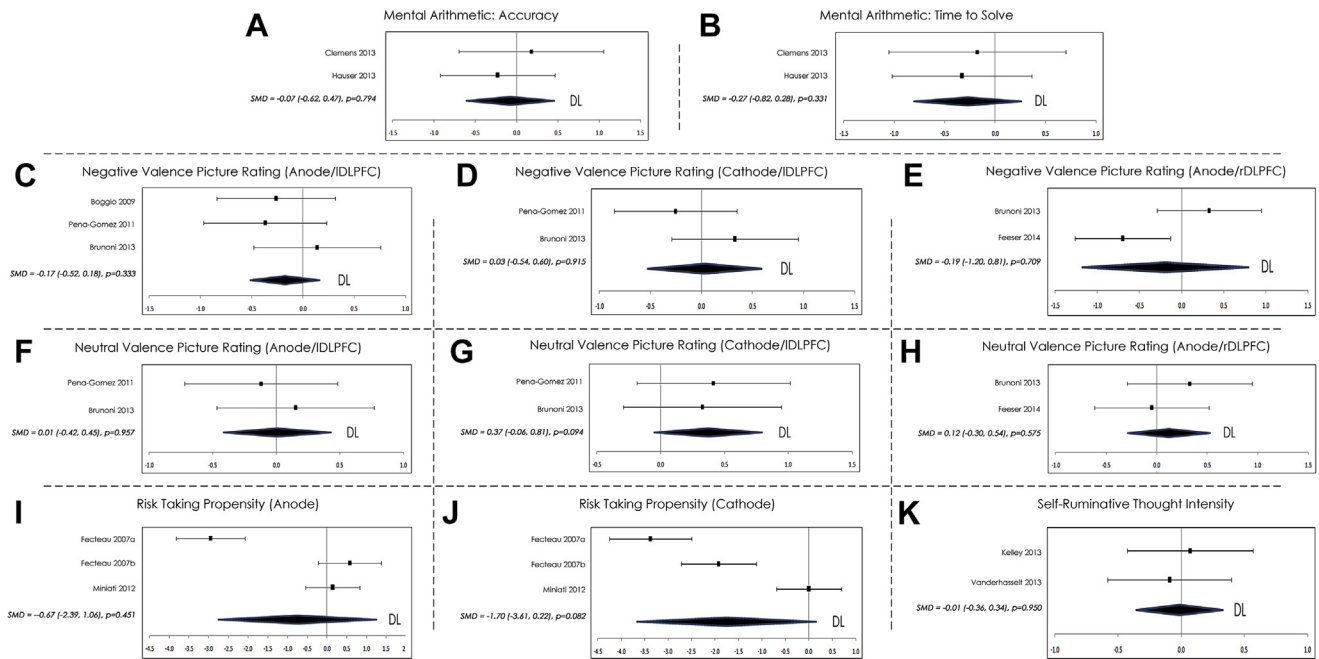


Figure 6. Forest plots for both secondary miscellaneous task analyses (SMD = Standard mean difference; FE = Fixed effect model for primary analyses; DL = DerSimonian-Laird mixed-effect model for secondary analyses; Parentheses represent 95% CI).

beneficial if future research included information concerning the time-of-day, day-of-week, duration, etc. of unique stimulation sessions and the satiation-levels, energy-levels, amount of sleep, etc. of individual participants. The inclusion of this information will not only allow for correlative and regression analyses to contextualize individual findings, but will also allow for more robust and meaningful quantitative pooling in the future.

Beyond methodological reporting, it is worth noting the relative lack of detailed data reporting in the literature. Though many studies explored for this analysis verbally reported a null finding on a particular measure, many did not offer quantitative or visual data amenable to pooling. This lack of data reporting has the undesirable effect of skewing quantitative analyses (such as this one). Accordingly, it would be beneficial if new studies included numerical data for all measures, even those with null results: only by doing so can more meaningful analyses take place in the future.

Limitations

A major limitation of this analysis is the lack of comparable research available in the current tDCS literature. Of the 50 cognitive outcome measures replicated between two different research groups included in this paper, 35 include only 2 or 3 papers. Accordingly, these analyses must be interpreted with caution. It is worth noting, however, that of these 35 outcome measures, 25 include papers report opposing effect sizes. This means > 70% of analyses which include only 2 or 3 papers contain at least 1 paper reporting enhancement and at least 1 paper reporting impairment following tDCS. As noted above, this may be due to varied state-dependency effects between different studies. Until more direct replication of older research is undertaken and more data are made available for pooling, it is difficult to conclude the true effect of this device.

Another limitation of this analysis concerns the population utilized. Although our results suggest tDCS has no reliable effect on cognitions in healthy adults, it remains to be seen whether or not tDCS can influence these measures in juvenile, elderly, or infirm

populations. It is certainly possible that tDCS (known to be a relatively 'weak' form of modulation) simply does not work in a manner which can modulate a healthy, optimally performing brain (see: Ref. [102]). This does not preclude it from being able to modulate infirm, developing, or deteriorating brains. Additional analyses exploring the impact of tDCS in these populations are certainly warranted (examples of elderly population tDCS reviews: [103,104]; examples of infirm population tDCS meta-analyses: [105–107]).

This paper only explores cognitive measures undertaken during or following one session of tDCS. As noted in the results section, there are many studies which have utilized a multiple-day stimulation paradigm (e.g. Refs. [39,65,79,108]). It is wholly possible that several sessions of tDCS are required in order for a reliable effect to be seen. In this instance, it has been argued tDCS impacts cognition via repeated exposure and, possibly, overnight consolidation (see: Refs. [109,110]). Unfortunately, there simply are not enough comparable multiple-day stimulation studies conducted by two different research groups to assess if this is the case. As before, in order to determine the effect of repeated sessions of tDCS, more work directly replicating older research is required.

Conclusion

Taken together, we have found no evidence that single-session tDCS has a reliable effect on cognitions in healthy adult populations. When this is combined with our previous work which suggested tDCS does not have a reliable effect on neurophysiologic measures beyond MEP amplitude [1], it becomes difficult avoid questions of device efficacy. It is important to note, however, that these findings may be due to state-dependency effects which, with elucidation, can be controlled for and leveraged. In addition, our findings do not preclude the possibility that tDCS has an effect on different populations (juvenile, elderly, infirm), when utilized multiple-times over several days or weeks, or on behavioral tasks. Nor does this preclude the possibility that tDCS could be effective if utilized in a novel fashion (hi-definition tDCS, spinal tDCS, pulsed

current tDCS, etc.). Despite this, as this field moves forward, it will be important future studies include measures which directly replicate prior work, explore potential state-dependent effects within and between studies, and report quantitative data for all explored outcome measures (so that a more clear picture of the state of the field can be derived).

Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.brs.2015.01.400>.

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