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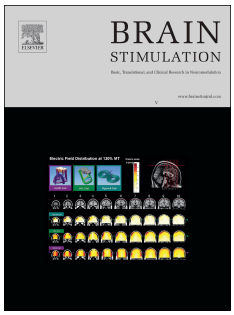

A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) on Episodic Memory

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A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) on Episodic Memory.

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ABSTRACT

Background: In the past decade, several studies have examined the effects of transcranial direct current stimulation (tDCS) on long-term episodic memory formation and retrieval. These studies yielded conflicting results, likely due to differences in stimulation parameters, experimental design and outcome measures.

Objectives: In this work we aimed to assess the robustness of tDCS effects on long-term episodic memory using a meta-analytical approach.

Methods: We conducted four meta-analyses to analyse the effects of anodal and cathodal tDCS on memory accuracy and response times. We also used a moderator analysis to examine whether the size of tDCS effects varied as a function of specific stimulation parameters and experimental conditions.

Results: Although all selected studies reported a significant effect of tDCS in at least one condition in the published paper, the results of the four meta-analyses showed only statistically non-significant close-to-zero effects. A moderator analysis suggested that for anodal tDCS, the duration of the stimulation and the task used to probe memory moderated the effectiveness of tDCS. For cathodal tDCS, site of stimulation was a significant moderator, although this result was based on only a few observations.

Conclusions: To warrant theoretical advancement and practical implications, more rigorous research is needed to fully understand whether tDCS reliably modulates episodic memory, and the specific circumstances under which this modulation does, and does not, occur.

Keywords: meta-analysis; episodic memory; long-term memory; recall; recognition; transcranial direct current stimulation; non-invasive brain stimulation

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1. INTRODUCTION

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Over the past fifteen years, transcranial direct current stimulation (tDCS) has rapidly become one of the most widely used methods of non-invasive brain stimulation among neuroscientists. In humans, tDCS involves the delivery of weak electrical currents (usually ranging from 1 to 2 mA) to the scalp by means of two electrodes, a positively-charged anode and a negatively-charged cathode. The current is thought to modulate the resting membrane potential of neurons depending on the polarity of the electrode, such that anodal stimulation induces depolarization of the membrane potential and increases cortical excitability, and cathodal stimulation induces hyperpolarization and decreases cortical excitability [1]. The rapidly-growing interest for this technique is linked to its potential to enhance cortical excitability and improve the cognitive functions associated with the stimulated brain regions, as shown across multiple cognitive domains in healthy and neuropsychiatric populations, from Alzheimer's to stroke patients [2, 3].

More recently however, several authors expressed the need to re-evaluate the effectiveness of tDCS. There are a number of reasons for this scepticism. First, like other disciplines, tDCS studies struggle with issues of reproducibility, small sample sizes, p-hacking [4], publication bias [5], and HARKing (Hypothesising After the Results are Known, [6]), which contribute to inflate effect sizes. Furthermore, large differences exist across studies in terms of stimulation parameters and other methodological aspects, which contribute to inconsistencies in findings. A number of recent meta-analyses in the working memory and language domains aimed to address this heterogeneity and examined the reliability of tDCS effects by pooling together studies that differed in stimulation parameters or other methodological aspects. However, even in this case the results were not consistent across studies,

some found tDCS effects in accuracy or reaction times [7, 8, 9, 10 11], while others found no effect [12, 13, 14].

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To date, no systematic review or meta-analysis has examined the effects of tDCS on long-term episodic memory, a memory system that involves conscious recollection of past experiences along with their temporal and spatial details [15]. Episodic memory is one of the mental functions that are most vulnerable to the effects of healthy aging and neurodegenerative diseases [16]. As pharmacological interventions have to date proven ineffective in countering this decline, understanding the extent to which memory functions can be improved by anodal tDCS is certainly of clinical relevance. Such understanding cannot be easily gained with a qualitative comparison across studies, because the findings are mixed and, just like with other cognitive domains, there is large heterogeneity in experimental designs, tasks and stimulation protocols. The results of these studies can be integrated in a meta-analysis to reveal not only the general efficacy of tDCS effects as indicated by a summary effect size, but also the variables that influence the magnitude of those effects by means of moderator analyses. This is especially relevant for tDCS studies because it is reasonable to assume that specific stimulation parameters such as stimulation duration, density, and time of administration influence the effects of tDCS.

In the present study, we examined the effects of a single session of tDCS on long-term episodic memory in healthy adults. We conducted four meta-analyses to assess the effects of anodal and cathodal stimulation on memory accuracy and reaction times, respectively. We further examined whether the size of tDCS effects varied as a function of specific stimulation parameters and experimental conditions. The main meta-analyses and the moderation analyses were performed on the same outcome measure, namely the percentage of correctly remembered items (hits),

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regardless of the measures that were analysed or reported in the articles. This information was provided by the authors when not available in the published paper. By doing so we were able to avoid possible publication bias and sub-optimal synthesis of data based on the information available on published work, therefore increasing the accuracy of summary effect size.

2. METHODS

2.1 Literature search

We conducted a literature search on the MEDLINE (PubMed), Web of Science and Scopus databases. We looked for articles published from the first date available to September 27th, 2018. We used the following keywords or Boolean terms: ("tDCS" OR "transcranial direct current stimulation" OR "non-invasive brain stimulation") AND "memory". In addition, we conducted additional searches in retrieved articles and reviews.

2.2 Eligibility criteria

We included studies if *(i)* they were written in English, *(ii)* they were performed on healthy young (> 18 years of age) or older human subjects, *(iii)* they included a control condition, *(iv)* the stimulation was delivered in a single session, *(v)* the outcome measures were quantitatively reported or available upon request. To restrict inclusion to studies that investigated long-term episodic memory, we also included studies if *(vi)* the outcome measures referred to recall or recognition memory performance for material encoded in a preceding learning phase of the study (in other words, studies that constrained memory retrieval to the encoding context of the study), and if *(vii)* the number of to-be-remembered items, the delay between the learning and test phase, or both, were large enough to rule out any major

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involvement of short-term memory processes. We included studies that tested memory performance for long lists of items (>25), regardless of the delay, or for medium-length lists of items (15-25) tested after a delay of at least five minutes. Tasks involving the immediate recall or recognition of pairs of stimuli (e.g., matching-to-sample tasks), or of very short lists of items (< 15 items, e.g., span tasks) did not qualify as long-term episodic tasks (see [17]). We therefore excluded studies, or subset of analyses, that measured memory performance on those tasks.

2.3 Long-term episodic tasks and dependent variables

We used the percentage of correctly remembered items (hits) in a recall or recognition memory task as dependent variable. Although memory accuracy in recognition memory tasks can also be indexed by performance for new items and composite indices such as the *d'* or the discrimination index [18], we focused on the hit rate to allow comparison between recall and recognition memory tasks. We also performed a separate analysis on reaction times, although this information was not available for all studies, either because reaction times were not collected (mainly in recall tasks), or because reaction times were not reported and were not made available by the authors.

2.4 Quality assessment

To assess the methodological quality of the studies, we assessed the following criteria: sham method, randomization and blinding (modified from [19]).

2.5 Data extraction

For each study, we extracted means and standard deviations of the outcome measures of interest, along with the sample size. In case of missing or unclear information, we obtained the values from the authors of the paper. When the experimental variables were not of primary interest, we averaged the results across

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different variables (affective valence [20, 21], encoding instructions [22, 23 Exp 3, 24], number of items a studied item was presented in the study list [25, 26], semantic relation across items in the study list [27], stimulus formats [28], type of recollection task [29, 30], repeated encounter with the item before the test phase [31]).

Many of the studies included in the current review tested multiple experimental variables within subjects or involved other types of non-independent statistical comparisons. We treated scalp site, memory test, time of administration with respect to encoding or retrieval and delay of the memory test for encoding stimulation as independent data. We were aware that computing different effect sizes for the same or overlapping sets of participants and treating them as completely unrelated effect sizes violate the basic assumptions of traditional meta-analytic method. However, the variables mentioned above were of primary interest and were included as moderators, therefore we reasoned that data reduction would have resulted in a loss of relevant information. To address this, we fitted a two-level model with random effects at the study level, using the rma.mv function of the "metafor R" package [32]. This strategy allowed us to control for dependencies in the data set, while at the same time preserving the information conveyed by each individual effect sizes. To confirm the validity of our results, we repeated all the analyses with an alternative library, metaSEM [33], which relies on a different algorithm to fit multi-level meta-analytic models. Here, we only reported the models fitted with metafor, since the results obtained with metaSEM were virtually identical to those of metafor.

2.6 Statistical Analyses

We run four separate meta-analyses: effects of anodal (vs sham) and cathodal (vs sham) stimulation on memory accuracy, and effects of anodal (vs sham) and cathodal (vs sham) stimulation on reaction times for hits. We calculated standardised

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mean differences (SMD), specifically Hedges' *g*, as measure of effect size. For studies with within-participants designs, we used the standard deviation of the sham condition to standardise the difference of means. We computed the variances of effect sizes using the equations provided by Morris and DeShon [34]. For within-participants designs, the computation of effect size variances requires an estimation of the correlation between dependent measures. This information is usually missing in most studies. Therefore, in all the analyses reported in the Results section we assumed a correlation of $r = .50$. We also conducted sensitivity analysis assuming a lower ($r = .30$) and higher ($r = .70$) correlation. In general, these sensitivity analyses yielded the same pattern of results and led to the same conclusions as the default analysis and, therefore, we do not report them in detail. A small-scale meta-analysis of twelve comparisons that did report sufficient information to compute this correlation (only for the effects of the anodal vs. sham manipulation on memory performance, and using the equations provided by Morris and DeShon [34], p. 118), yielded an average correlation of $r = .55$, providing support for our choice of .50 as a default assumption.

We conducted a moderation analysis using eight moderator variables treated as factor variables, six were selected a-priori (*i-vi*), and two were defined post-hoc (*vii* and *viii*). *(i) stimulation site* (seven levels, coded as left frontal, right frontal, left parietal, right parietal, left temporal, right temporal and midline occipital area). We analysed the stimulation site as moderator, rather than restricting our study selection to one stimulation site as in previous meta-analytical work (e.g. [9, 10]), given the variety of stimulation sites targeted in episodic memory studies. Furthermore, *(ii) stimulation duration* (two levels, coded as ≤ 10 minutes or > 10 minutes, as in [11], *(iii) current density* (two levels, coded as ≤ 0.029 mA/cm^2 or > 0.029 mA/cm^2, as in [11]) and *(iv) time of stimulation with respect to the memory phase* (seven levels, coded as offline before encoding, partly offline (<5min)/partly online encoding,

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entirely online encoding, offline – between encoding and retrieval, partly offline (<5min)/partly online retrieval, online retrieval, entirely online during encoding and retrieval) were included in the moderation analysis because these parameters influenced the effects of tDCS in previous meta-analyses [10, 11]. We further tested the effect of *(v) montage* (two levels, coded as unilateral, bilateral) to examine if unilateral and bilateral montages affect tDCS effects to a different degree; *(vi) retrieval task* (two levels, coded as recognition, recall) because recall and recognition memory tasks involve different memory processes [35] and tDCS may differentially affect memory in the two tasks; *(vii) delay between the end of the stimulation and the start of the memory test* (four levels, coded as less than five minutes, between five minutes and one hour, between one hour and 24 hours, more than 24 hours) for studies that administered the stimulation during encoding to examine tDCS after-effects and *(viii) age of the participants* (two levels, young and older adults, using the studies' group allocation criteria) to assess age-related difference in tDCS effects, since there is some indication in the literature that tDCS effects are stronger for older adults [36]. . Following the recommendations in [37], we only report moderator analyses with ten or more effect sizes (see Supplementary Table 1 for analyses with less than ten effect sizes).

3. RESULTS

3.1 Study selection

Figure 1 depicts the electronic database search strategy. We identified a total of 3033 studies matching the search criteria (after removal of duplicates). Screening of the title excluded 2877 articles, and a screening of the abstract further excluded 103 articles because they: *(i)* used a clinical sample, *(ii)* used a different brain stimulation method (TMS, tACS, tRNS), *(iii)* were reviews, meta-analyses or consensus papers,

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(iv) did not use a long-term episodic memory task, *(v)* used multiple sessions of tDCS, or *(vi)* other reasons. We therefore examined the full-text version of the remaining 53 articles, of those we further excluded 13 articles because they *(i)* used a different brain stimulation method (TMS, tACS, tRNS), *(ii)* did not use a long-term episodic memory task, *(iii)* did not include a control condition, *(iv)* used the same dataset as previous papers, and *(v)* the stimulation was too short compared to previous work. Two further studies were excluded because the papers did not contain the necessary information and the authors did not provide them upon request. The remaining 38 studies all met the inclusion criteria and were included in the meta-analysis.

3.2 Quality assessment

Table 1 shows the characteristics of the studies included in this meta-analysis, including the criteria for quality assessment. Most studies followed appropriate methodological procedures for randomization, blinding and sham condition. Altogether then, the studies can be considered of good quality.

3.3 Effects of tDCS on memory accuracy and reaction times

3.3.1 Effect of anodal tDCS: memory accuracy. Three effect sizes were extreme outliers with absolute values larger than 5. We considered that such extreme effect sizes were likely due to a reporting error and, consequently, we decided to remove them from subsequent analyses. Among the remaining effect sizes (k = 113), the effects of anodal tDCS (vs. sham) on memory accuracy were mostly small, in both positive and negative direction, close to a zero value. Overall, we found a small positive meta-analytical effect, Hedge's g = 0.11, 95% *CI* [-0.02, 0.24] that was not statistically significant, z = 1.65, p = .098. In other words, anodal tDCS did not significantly increase memory accuracy compared to sham. It is important to note, however, that there was a substantial amount of heterogeneity across effect sizes,

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$Q(112) = 246.25$, $p < .001$, $\sigma^2 = 0.111$. We therefore tested moderation effects of *(i)* stimulation site, *(ii)* montage, *(iii)* time of stimulation, *(iv* retrieval task, *(v)* time of stimulation with respect to the memory phase, *(vi)* current density, *(vii)* delay of memory task after stimulation, and *(viii)* age of participants. Each of these moderators was tested in a separate mixed-effects meta-analysis. Only two moderators were statistically significant (Table 2). We found a significant effect of retrieval task. The effect sizes for recall tasks were significantly larger compared to recognition tasks. We also found a statistically significant moderation effect of stimulation duration, indicating that longer stimulations led to higher performance.

3.3.2 Effect of anodal tDCS: response times. The average effect of anodal tDCS (vs. sham) on reaction times in the memory test, computed on the basis of 35 effect sizes, was $g = 0.07$, 95% CI [-0.11, 0.25], which again was statistically non-significant, $z = 0.78$, $p = .435$. Unlike the meta-analysis on the percentage of hits, heterogeneity failed to reach statistical significance, $Q(34) = 43.44$, $p = .129$, $\sigma^2 = 0.06$, and none of the moderator analyses returned significant results (see Table 2).

3.3.3 Effect of cathodal tDCS: memory accuracy. Among the 13 effect sizes included in the analysis, the average effect size of cathodal tDCS (vs. sham) on the percentage of hits was $g = -0.26$, 95% CI [-0.85, 0.33], that failed to reach statistical significance, $z = -0.87$, $p = .383$. The amount of heterogeneity was significantly larger than chance, $Q(12) = 74.84$, $p < .001$, $\sigma^2 = 0.73$, suggesting that the variability across studies cannot be solely attributed to sampling error. It was not possible to run moderator analyses of montage and age of participants because all studies were conducted on young adults using a unilateral montage. Only stimulation site explained a significant proportion of heterogeneity. The effect sizes for left parietal locations were higher than the remaining locations, although this pattern must be interpreted with caution, given the small number of studies included in most

subgroups (see Table 2). The moderator effect of delay could only be tested with 9 studies and is reported in Supplementary Table 1.

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3.3.4. Effect of cathodal tDCS: response times. Among the 8 effect sizes included in the analysis, the average effect of cathodal (vs. sham) stimulation on reaction times was g = 0.22, 95% CI [-0.31, 0.75], which was not significantly different from zero, z = 0.81, p = .421. The heterogeneity analysis did reveal a significant amount of unexplained heterogeneity, Q(7) = 25.02, p < .001, σ2 = 0.32. Moderator analyses are reported in Supplementary Table 1.

3.4 Publication and reporting biases

Figure 2 depicts the effect sizes of the four meta-analyses against their standard errors. The grey contour denotes the area where the effects would be statistically non-significant in a two-tailed test. An asymmetric distribution of effect sizes (e.g., the tendency of studies with lower precision to yield larger effect sizes) is usually taken as suggestive of publication or reporting biases, particularly when there is a disproportionate number of effect sizes just beside the border of statistical significance. To account for dependences among effect sizes, we tested for funnel plot asymmetry by fitting a mixed-effects multi-level model, similar to the ones used in the previous moderator analyses, but with the standard error of each study as the only moderator. These analyses only revealed significant evidence for funnel plot asymmetry in the case of studies exploring the effect of anodal (vs. sham) stimulation on the proportion of hits, *b* = 3.51, 95% CI [2.03, 4.98], *z* = 4.67, *p* < .001, suggesting that the observed average effect size of this meta-analysis might be inflated due to the selective publication of significant effects.

4. DISCUSSION

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The present meta-analysis aimed to examine the effects of tDCS on episodic memory accuracy and response times. We conducted separate meta-analyses for anodal and cathodal tDCS. Our results showed that when all selected studies were pooled together, the effects of tDCS were small and non-significant. These results add to a growing body of meta-analytical work that failed to show an effect of tDCS on the accuracy of working memory [12, 13] and language tasks ([14], but see [7, 8]). Three previous meta-analyses suggested that tDCS may exert its influence on the time taken to perform a task, rather than on its accuracy [9, 10, 11]. Our meta-analysis on response times showed that the response times for episodic memory judgements were unaffected by either anodal or cathodal tDCS.

One question that may arise is why meta-analytical work does not provide robust evidence of the effectiveness of tDCS, despite a proliferation of studies showing tDCS-induced changes. This observation also applies to the studies selected for the current work. All of the 38 studies included reported at least one significant effect of tDCS in the published article, despite a lack of general effect in the summary effect size reported here. There are many plausible reasons for this discrepancy. The first one concerns the sample size. The mean sample size for between-subjects designs was 21.5 (SD 8.7); however, when a parallel design was used to compare different experimental conditions, the mean size of the group was 14.9 (SD 3.7). The small sample size may have resulted in a greater probability to detect a large, spurious result by chance. Second, most of the studies included here tested multiple experimental conditions and revealed an effect in one condition, but not others. For instance, as a function of the emotional valence of the stimuli [20, 21], of whether memories were reactivated or not [38], or of the delay of the memory test [39, 40]. Other studies found effects in one memory outcome and not another, for example, in source memory and not old/new recognition [41]. Finally, in some studies the effects were specific to some stimulation parameters, for instance, they

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were specific to the brain region under investigation and did not extend to other stimulated regions [20, 29, 42-46]. On the one hand, it is a straightforward assumption that tDCS may exert its effects under specific circumstances. There are good reasons to expect an effect of tDCS on the left but not on the right DLPFC while individuals learn verbal materials, given the involvement of the left DLPFC in verbal memory formation [42, 47]. However, these findings should not be taken as evidence of the *general* effectiveness of tDCS, which, as shown in the current meta-analysis, is relatively poor. Rather, they should be taken as an indication that tDCS exerts its influence under specific conditions, and that there should be well-reasoned hypotheses and systematic examinations of the conditions that induce tDCS-related changes in memory. Of note, only 18 out of the 38 studies selected for this work reported experimental hypotheses, some of them very general (e.g., an improvement of memory performance without reference to specific experimental conditions). The exploratory nature of the studies may have increased the likelihood of false positives, especially because all possible conditions may be tested.

Meta-analyses in this field have the advantage of not only providing a general indication of the effectiveness of tDCS with the summary effect size, but also an indication on the specific factors that modulate the effectiveness by means of moderation analyses. Because the neurophysiological and behavioural effects of tDCS may depend on a number of factors, for instance, the state of the stimulated brain region at the time of tDCS application, the dosage of the stimulation, or the difficulty of the task [48, 49], understanding which factors influence the effectiveness of tDCS is of relevance. Our moderation analysis revealed that although tDCS effects were not significant in the summary effect size, the duration of stimulation and the task used to probe memory influenced the effects of anodal tDCS on episodic memory accuracy.

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More specifically, we found that longer durations (above 10 minutes) with anodal tDCS led to higher memory accuracy compared to shorter durations, which instead had decreasing effects. The idea that longer durations determine larger effects is consistent with previous meta-analyses that found that longer stimulations enhanced working memory performance [11] and corticospinal excitability [50]. It is unclear though why shorter durations would lead to significant decreases in memory performance. This could be due to a larger variability in the five studies that used stimulation durations of 10 minutes or less, perhaps associated with BDNF genotype [51]. More studies are needed in the episodic memory domain that systematically address the effect of stimulation duration on memory performance.

In line with work included in this meta-analysis [26, 52], we also found that anodal tDCS effects on episodic memory accuracy were larger with recall tasks. This finding is intriguing in light of the different strategies, processes and task difficulties involved in recall and recognition tasks [35]. One hypothesis is that anodal tDCS selectively enhances processes that are involved in recall, as opposed to recognition. In recognition tasks, the judgement of previous occurrence could be based on familiarity or perceptual fluency [53], whereas performance on recall tasks relies primarily on recollection [54]. Therefore, anodal tDCS could have a selective effect on recollection. Alternatively, the effects of anodal tDCS may be more prominent when the task is more difficult and overall performance is lower. This would be consistent with the idea that with cognitively-demanding tasks the effects of anodal tDCS are larger [55]. As typically observed, the studies included in this work reported on average a lower baseline performance on recall compared to recognition tasks (hit rate of 49.2% vs 74.4%, respectively, in the sham condition). The baseline performance on the recognition task could have been too high in some studies to reveal any further performance improvement due to tDCS administration, and/or there could have been too little variability for tDCS effects to emerge. Finally, the

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moderator analysis for cathodal tDCS revealed that the effects were larger when the stimulation was delivered over left parietal areas. This effect, however, should be interpreted with caution. Only one study stimulated the left parietal region with cathodal tDCS, therefore the small sample limits the reliability of these effects.

Three aspects of the current work deserve attention. First, our meta-analysis only pooled together studies that assessed the effects of one single session of tDCS. We are aware of only three published studies [56-58] that examined the effects of multiple sessions of tDCS on episodic memory and met the criteria described in the Methods section. Given the translational appeal of this type of research, and the evidence that multiple sessions of tDCS may be more effective than single sessions [59-61], a priority for future research will be to further examine tDCS effects on long-term episodic memory with longer courses of tDCS. We also restricted our selection to studies with young and older healthy individuals, but it should be noted that tDCS may be more effective with clinical populations [9]. Finally, although our strategy of pooling together studies with the same outcome measure was aimed at increasing the accuracy of summary effect sizes and reducing publication bias, it left open the possibility that tDCS may have affected other outcome measures. For instance, anodal tDCS may not only exert its effects by increasing the memorability of previously experienced items (i.e., hit rate), but also by decreasing the false recognition of new ones (i.e., false alarms). Interestingly, a few studies reported a selective modulation of the false alarm rate, but not hit rate, following anodal tDCS. Although this finding took the form of a decrease in some studies [23, 62], and an increase in others [22], it suggests that there are multiple ways in which tDCS may affect episodic memory.

Our analysis revealed publication bias in the studies reporting effects of anodal tDCS on episodic memory. It is perhaps not surprising that such a bias was

found for the stimulation condition with the highest clinical expectations given the potential of anodal tDCS to enhance memory functions. Meta-analyses are relevant tools to address publication bias. In meta-analyses publication bias can be analysed and corrected for (e.g., [12]). Publication bias can also be controlled by adopting a strict data extraction procedure. In the present meta-analysis, we reduced the influence of publication bias by selecting the same measure of memory accuracy across studies, the percentage of hits, regardless of the aims and the measures reported in the published article. We obtained this information from authors when it was not available in the original study. This is especially relevant for recognition memory tasks, in which there is a variety of measures available (hits, false alarms, misses, correct rejections, or composite indices such as *d'*). Only a minority of episodic memory studies report all measures regardless of the focus and outcome of the analyses, making it hard to compare results across studies.

The general sentiment expressed in our and other meta-analyses is not that tDCS, or electrical brain stimulation in general, is not effective and should be discontinued. tDCS is an important neuro-tool for causally investigating brain functions. Studies have already showed reproducible tDCS effects on the motor cortex at rest [48], and more effort should be made to conduct more systematic and replication studies in the cognitive domain, and to understand the circumstances under which tDCS does and does not exert its effects.

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FIGURE CAPTIONS:

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Figure 1: Flow-chart of the online database search strategy.

Figure 2. Contour-enhanced funnel plot of the four data sets included in the meta-analysis. The gray area represents studies with p values larger than .05

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Study	**Exp**	**Total sample size**	**Age**	**Design** (active/ control)	**Random**	**Blind**	**Control**	**Montage Polarity**[1]	**Anode || Cathode**	**Duration (min)**	**Current Density (mA/cm^2)**	**Phase of administration**	**Memory task**
Boggio et al., 2009 [62]	1	30	Y	Parallel[2]	Yes	SB	Sham[3]	Bilateral and unilateral a-tDCS	T3 || T4	10	0.06	5 min before and 5 min during encoding and retrieval	Recognition
Elmer et al., 2009 [42]	1	20	Y	Crossover	NR	NR	No tDCS	a-tDCS, c-tDCS	F3 || mastoid (n=10) F4 || mastoid (n=10)	5	0.05	During short-term encoding and retrieval; long-term retrieval offline	Recall
Penolazzi et al., 2010 [20]	1	12	Y	Crossover	N/A	NR	Sham[3]	Bilateral	Between F3 and C3 || between F4 and C4 Between F3 and C3 || between F4 and C4	20	0.03	5 min before and 15 min during encoding	Recall
Floel et al., 2012 [39]	1	20	E	Crossover	N/A	DB	Sham[3]	a-tDCS	CP4 || LSO	20	0.03	During encoding	Recall
Jacobson et al., 2012 [44]	1	24	Y	Parallel (12/12)	No	DB	No tDCS	Bilateral	P3 || P6 P6 || P3	10	0.04	7 min before and 3 min during encoding	Recognition
Javadi and Walsh, 2012 [66]	1	16	Y	Crossover	N/A	SB	Sham[3]	a-tDCS, c-tDCS	F3 || RSO RSO || F3	20	0.08	During encoding	Recognition
Javadi and Walsh, 2012 [66]	2	16	Y	Crossover	N/A	SB	Sham[3]	a-tDCS, c-tDCS	F3 || RSO RSO || F3	20	0.08	During retrieval	Recognition
Javadi and Cheng, 2013 [38]	1	30	Y	Crossover	Yes	NR	Sham[3]	a-tDCS, c-tDCS	F3 || RSO RSO || F3	20	0.12	Between encoding and retrieval (during memory reactivation in the *consolidation group*)	Recognition
Lafontaine et al., 2013 [67]	1	11	Y	Crossover	N/A	SB	Sham[3]	Bilateral	F3 || P4 F4 || F3	15	0.04	Before encoding	Recognition
Manenti et al., 2013 [68]	1	64	Y (n=32) E (n=32)	Crossover	Yes	SB	Sham[4]	a-tDCS	F3 || RSO and F4 || LSO (n=16) P3 || RSO and P4 || LSO (n=16)	6	0.04	2 min before and 4 min during retrieval	Recognition

Jones et al., 2014 [64]	1	20	Y	Crossover	N/A	NR	Sham[4]	a-tDCS	P3 || RC	15	0.04	3 min before and 12 min during encoding	Recognition and recall
Jones et al., 2014 [64]	2	20	Y	Crossover	N/A	NR	Sham[4]	a-tDCS	P3 || RC	15	0.04	Between encoding and retrieval	Recognition and recall
Jones et al., 2014 [64]	3	20	Y	Crossover	N/A	NR	Sham[4]	a-tDCS	P4 || LC	15	0.04	3 min before and 12 min during encoding	Recognition and recall
Jones et al., 2014 [64]	4	20	Y	Crossover	N/A	NR	Sham[4]	c-tDCS	P4 || LC	15	0.04	3 min before and 12 min during encoding	Recognition and recall
Sandrini et al., 2014 [65]	1	36	E	Parallel (24/12)	Yes	SB	Sham[4]	a-tDCS	F3 || RSO	15	0.04	Between encoding and retrieval (during memory reactivation in the *reminder group*)	Recall
Zwissler et al., 2014 [22]	1	96	Y	Parallel (48/48)	Yes	DB	Sham[3]	a-tDCS (n= 24)/ c-tDCS (n=24)	F3 || RS RS || F3	15	0.03	5 min before and 10 min during encoding	Recognition
England et al., 2015 [69]	1	12	Y	Crossover	N/A	SB	Sham[3]	a-tDCS	P3 || P4 P4 || P3	20	0.08	Before encoding	Recognition
Gray et al., 2015 [29]	1	96	Y	Parallel (72/24)	NR	NR	Sham[4]	a-tDCS	F3 || RSO (n=24) F4 || LSO (n=24) P5 || RSO (n=24)	20	0.06	Between encoding and retrieval	Recognition
Lu et al., 2015 [70]	1	20	Y	Crossover	N/A	SB	Sham[3]	Bilateral	FC5 || FP2	20	0.06	Before encoding	Recognition
Lu et al., 2015 [70]	2	17	Y	Crossover	N/A	SB	Sham[3]	Bilateral	Oz || FP2	20	0.06	Before encoding	Recognition
Matzen et al., 2015 [52]	1	24	Y	Parallel (12/12)	NR	DB	Sham[5]	a-tDCS	F9 || RUA	30	0.18	During encoding	Recognition and recall
Nikolin et al., 2015[6] [63]	1	16	Y	Crossover	N/A	SB	Sham[3]	HD-tDCS	P9 F3 CP5	20	0.18	5 min before and 15 min during encoding	Recognition and recall
Pergolizzi and Chua, 2015 [71]	1	52	Y	Parallel (26/26)	NR	NR	Sham[5]	Bilateral	CP3 || CP4	10	0.06	5 min before and 5 min during retrieval	Recognition
Pergolizzi	2	72	Y	Parallel	NR	NR	Sham[5]	Bilateral	CP3 || CP4 (n=24)	20	0.06	5 min before and	Recognition

and Chua, 2015 [71]				(48/24)					CP4 || CP3 (n=24)			15 min during retrieval	
Pisoni et al., 2015a [72]	1	44	Y	Parallel (30/14)	NR	SB	Sham[4]	Bilateral	P3 || P4 (n=15) T3 || T4 (n=15)	15	0.04	During retrieval	Recognition
Pisoni et al., 2015b [46]	1	12	Y	Crossover	N/A	SB	Sham[3]	a-tDCS	T3 || RSO	20	0.08	14 min before and 6 min during encoding	Recall
Pisoni et al., 2015b [46]	2	12	Y	Crossover	N/A	SB	Sham[3]	c-tDCS	T3 || RSO	20	0.08	14 min before and 6 min during encoding	Recall
Pisoni et al., 2015b [46]	3	12	Y	Crossover	N/A	SB	Sham[3]	a-tDCS	F5 || RSO	20	0.08	14 min before and 6 min during encoding	Recall
Smirni et al., 2015 [73]	1	20	Y	Crossover	N/A	NR	Sham[3]	c-tDCS	F3 || RS F4 || LS	20	0.03	Between encoding and retrieval	Recognition
Smirni et al., 2015 [73]	2	16	Y	Crossover	N/A	NR	Sham[3]	a-tDCS	F3 || RS F4 || LS	20	0.03	Between encoding and retrieval	Recognition
Sandrini et al., 2016 [40]	1	28	E	Parallel (14/14)	Yes	DB	Sham[4]	a-tDCS	F3 || RSO	15	0.04	During encoding	Recall
Balzarotti and Colombo, 2016 [21]	1	42	Y	Parallel (28/14)	Yes	SB	Sham[3]	a-tDCS (n= 14)/ c-tDCS (n=14)	F3 || LM LM || F3	15	0.03	5 min before and 10 min during encoding	Recall
Chen et al., 2016 [41]	1	36	Y	Crossover	Yes	NR	Sham[3]	a-tDCS (n= 18)/ c-tDCS (n=18)	P3 || RC RC || P3	10	0.04	2 min before and 8 min during retrieval	Recognition
Gaynor and Chua, 2016 [43]	1	72	Y	Parallel (48/24)	Yes	NR	Sham[5]	Bilateral and unilateral a-tDCS	F3 || RSO (n=24) CP3|| CP4 (n=24)	25	0.06	5 min before and 20 min during encoding	Recognition
Manuel and Schnider, 2016 [28]	1	26	Y	Crossover	Yes	SB	Sham[3]	Bilateral	F3 || RSO and F4 || LSO (n=13) P3 || RSO and P4 || LSO (n=13)	24	0.03	4 min before and 20 min during encoding	Recognition
Pergolizzi and Chua, 2016 [45]	1	54	Y	Parallel (36/18)	Yes	NR	Sham[5]	Bilateral	CP3 || CP4 (n=18) F3 || F4 (n=18)	20	0.06	5 min before and 15 min during retrieval	Recognition
De Lara et al., 2017[6]	1	30	Y	Crossover	Yes	DB	Sham[3]	HD-tDCS	AF3	20	0.33	12 minutes before and 8 minutes	Recall

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[74]												during encoding (n=15) or 15 minutes before and 5 minutes during retrieval (n=15)	
Diez et al., 2017 [27]	1	65	Y	Parallel (43/22)	Yes	NR	Sham[3]	a-tDCS (n= 22)/ c-tDCS (n=21)	FT9 || RS RS || FT9	20	0.06	7 minutes before, 8 minutes during and 2 minutes after encoding	Recognition
Habich et al., 2017 [75]	1	43	Y	Parallel (22/21)	Yes	DB	Sham[3]	a-tDCS	F3 || RSO	20	0.03	5 minutes before encoding, 10 minutes during encoding/test cycles, 5 minutes after encoding	Recognition and recall
Leshikar et al., 2017 [26]	1	42	Y	Parallel (21/21)	Yes	DB	Sham[5]	a-tDCS	F3 || RUA	25	0.14	4 minutes before and 21 minutes during encoding	Recognition and recall
Manenti et al., 2017 [76]	1	22	E	Parallel (11/11)	Yes	DB	Sham[4]	a-tDCS	F3 || RSO	15	0.04	Between encoding and retrieval	Recognition and recall
Prehn et al., 2017 [77]	1	40	Y (n=20) E (n=20)	Crossover	N/A	DB	Sham[3]	a-tDCS	T6 || Left frontopolar cortex[7]	20	0.02	During encoding	Recall
Leach et al., 2018 [25]	1	96	Y (n=24) E (n=24)	Parallel (24/24)	NS	DB	Sham[5]	a-tDCS	F3 || RUA	25	0.14	4 minutes before and 21 minutes during encoding	Recognition and recall
Marian et al., 2018 [31]	1	66	Y	Parallel (33/33)	Yes	NS	Sham[3]	Bilateral	F4 || Cz	15	0.08	Between encoding and retrieval	Recall
Marian et al., 2018 [31]	2	52	Y	Parallel (27/25)	Yes	NS	Sham[3]	Bilateral	F4 || Cz	15	0.08	Between encoding and retrieval	Recall
Medvedeva et al., 2018 [23]	1	49	Y	Parallel (32/17)	Yes	SB	Sham[3]	a-tDCS	F7 || RS	10	0.06	Before (n=15) and during (n=17) encoding	Recognition
Medvedeva et al., 2018 [23]	2	49	Y	Parallel (31/18)	Yes	SB	Sham[3]	a-tDCS	F7 || RS	10	0.06	Before (n=15) and during (n=16) retrieval	Recognition

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Medvedeva et al., 2018 [23]	3	31	Y	Crossover	Yes	SB	Sham[3]	a-tDCS	F7 || RS (n=15) P3 || RS (n=16)	15	0.04	During encoding	Recognition
Medvedeva et al., 2018 [23]	4	22	E	Parallel (11/11)	Yes	SB	Sham[3]	a-tDCS	F7 || RS	10	0.06	During encoding	Recognition
Meier and Sauter, 2018 [24]	1	32	Y	Parallel (16/16)	Yes	SB	Sham[3]	a-tDCS	F3 || RSO	20	0.09	During encoding	Recognition
Wong et al., 2018 [30]	1	48	Y	Parallel (24/24)	NS	SB	Sham[4]	a-tDCS	F3 || RSO	20	0.06	Between encoding and retrieval	Recognition
Wong et al., 2018 [30]	2	48	Y	Parallel (24/24)	NS	SB	Sham[4]	a-tDCS	F3 || RSO	20	0.06	Between encoding and retrieval	Recognition
Wong et al., 2018 [30]	3	120	Y	Parallel (80/40)	NS	SB	Sham[4]	a-tDCS	F3 || RSO (n=40) F4 || LSO (n=40)	20	0.06	Between encoding and retrieval	Recognition
Wong et al., 2018 [30]	4	80	Y	Parallel (40/40)	NS	SB	Sham[4]	a-tDCS	F3 || RSO	20	0.06	Between encoding and retrieval	Recognition

Table 1: Overview of the studies

Note: Y = young adults; E = elderly adults; NR = not reported; N/A = not applicable; SB = single blind; DB = double blind; a-tDCS = anodal transcranial direct current stimulation; c-tDCS = cathodal transcranial direct current stimulation; RSO = right supraorbital area; LSO = left supraorbital area; RC = right cheek; LC = left cheek; RS = right shoulder; LS = left shoulder; RUA = right upper arm; LM = left mastoid; all site locations according to the International 10-20 EEG electrode placement coordinates; [1] '/' denotes polarity is varied between subjects, ',' denotes polarity is varied within subjects. [2]Number of participants per group not available in the paper [3]Stimulator turned off shortly after the start of the stimulation (15 or 30 seconds). [4]Stimulator turned off shortly after the start of the stimulation (10, 20, 30 or 90 seconds) and turned on shortly before the end of the stimulation (10, 20 or 30 seconds). [5]Current constantly delivered at 0.1 mA. [6]High-Definition tDCS. [7] 9.5x9.5 cm electrode

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Moderator / Sub-group	*G*	LL	UL	*z*	*p*	*k*	*Q*	*Df*	*p*
Moderators of memory accuracy - anodal tDCS									
Stimulation site							5.89	6	.435
Left frontal	0.19	-0.01	0.37	2.11	.035	60			
Left parietal	-0.01	-0.16	0.14	-0.11	.915	18			
Left temporal	-0.04	-0.46	0.38	-0.19	.852	9			
Midline occipital	0.22	-0.27	0.71	0.87	.382	1			
Right frontal	-0.14	-0.31	0.03	-1.64	.100	10			
Right parietal	-0.14	-0.35	-0.07	-1.33	.185	7			
Right temporal	0.04	-0.12	0.20	0.51	.607	8			
Montage							1.51	1	.220
Unilateral	0.18	-0.01	0.35	2.06	.039	82			
Bilateral	-0.05	-0.26	0.15	-0.51	.608	22			
Time of stimulation							8.31	6	.216
Entirely offline before encoding	0.18	-0.06	0.42	1.44	.150	5			
Partly offline, partly online during encoding	0.35	-0.47	1.16	0.84	.401	11			
Entirely online during encoding	0.10	-0.07	0.26	1.17	.241	42			
Offline between encoding and retrieval	0.20	-0.06	0.45	1.51	.131	32			
Partly offline, partly online during retrieval	0.58	-0.50	1.67	1.06	.290	2			
Entirely online during retrieval	-0.01	-0.28	0.27	-0.06	.956	17			
Online during encoding and retrieval	-0.47	-1.00	0.07	-1.71	.086	4			

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*Retrieval task**							5.50	1	.019
Recognition	0.06	-0.10	0.21	0.70	.483	71			
Recall	0.23	0.03	0.45	2.24	.025	42			
*Stimulation duration**							4.96	1	.026
≤ 10 minutes	-0.19	-0.33	-0.06	-2.79	.005	18			
> 10 minutes	0.16	0.03	0.31	2.34	.019	95			
Current density							1.44	1	.231
≤ 0.029 mA/cm^2	-0.02	-0.14	0.10	-0.29	.768	19			
> 0.029 mA/cm^2	0.14	-0.01	0.30	1.89	.058	94			
Delay							2.02	3	.568
Less than 5 minutes	0.09	-0.07	0.25	1.08	.279	12			
Between 5 and 60 minutes	0.03	-0.09	0.15	0.41	.679	40			
Between 61 minutes and 24 hours	0.11	-0.08	0.29	1.14	.252	22			
More than 24 hours	0.38	-0.06	0.81	1.70	.089	15			
Age							0.63	1	.428
Young	0.05	-0.07	0.16	0.78	.436	94			
Elderly	0.41	0.00	0.83	1.97	.049	19			
Moderators of memory accuracy - cathodal tDCS									
*Stimulation site**							11.74	4	.019
Left frontal	-0.45	-1.38	0.48	-0.95	.343	8			
Left parietal	-0.69	-1.23	-0.16	-2.56	.011	1			
Left temporal	-0.03	-0.61	0.55	-0.10	.916	1			

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Right frontal	0.80	-0.38	1.98	1.32	.187	2			
Right parietal	-0.19	-0.64	0.26	-0.82	.413	1			
Time of stimulation							3.04	5	.694
Partly offline, partly online during encoding	-0.91	-2.56	0.73	-1.09	.277	3			
Entirely online during encoding	0.62	-0.19	1.44	1.49	.136	2			
Offline between encoding and retrieval	-0.13	-0.44	0.19	-0.80	.424	4			
Partly offline, partly online during retrieval	-2.37	-3.42	-1.32	-4.43	<.001	1			
Entirely online during retrieval	-0.69	-1.23	-0.16	-2.56	.011	1			
Online during encoding and retrieval	-0.14	-0.62	0.35	-0.56	.577	2			
Retrieval task							0.36	1	.551
Recognition	-0.45	-1.57	0.67	-0.79	.430	8			
Recall	-0.09	-0.36	0.17	-0.68	.499	5			
Stimulation duration							0.06	1	.803
≤ 10 minutes	-0.40	-0.95	0.14	-1.46	.145	3			
> 10 minutes	-0.23	-1.00	0.55	-0.57	.569	10			
Current density							2.46	1	.117
≤ 0.029 mA/cm^2	0.55	-0.36	1.46	1.19	.235	3			
> 0.029 mA/cm^2	-0.49	-1.13	0.14	-1.52	.128	10			
Moderators of response times - anodal tDCS									
Stimulation site							0.51	4	.972
Left frontal	0.02	-0.21	0.24	0.15	.883	19			
Left parietal	0.02	-0.27	0.23	-0.15	.882	6			

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Left temporal	0.26	-0.35	0.88	0.84	.399	2			
Right frontal	-0.08	-0.36	0.20	-0.57	.570	4			
Right parietal	0.00	-0.29	0.28	-0.03	.973	4			
Montage							1.49	1	.222
Unilateral	0.03	-0.16	0.22	0.30	.763	31			
Bilateral	0.35	-0.02	0.72	1.83	.067	4			
Time of stimulation							3.66	5	.599
Entirely offline before encoding	-0.04	-0.71	0.64	-0.11	.916	1			
Partly offline, partly online during encoding	0.33	0.00	0.67	1.95	.051	5			
Entirely online during encoding	0.09	-0.27	0.45	0.49	.627	12			
Offline between encoding and retrieval	-0.15	-0.43	0.12	-1.10	.271	5			
Partly offline, partly online during retrieval	0.07	-0.43	0.57	0.28	.782	1			
Entirely online during retrieval	-0.05	-0.35	0.26	-0.30	.765	11			
Retrieval task							1.30	1	.254
Recognition	0.03	-0.15	0.21	0.34	.732	32			
Recall	0.32	-0.22	0.86	1.16	.245	3			
Stimulation duration							0.05	1	.817
≤ 10 minutes	0.08	-0.57	0.74	0.25	.804	10			
> 10 minutes	0.08	-0.11	0.28	0.85	.393	25			
Current density							0.03	1	.863
≤ 0.029 mA/cm^2	0.10	-0.38	0.58	0.42	.580	8			
> 0.029 mA/cm^2	0.05	-0.14	0.24	0.51	.607	27			
Delay							0.99	2	.611
Less than 5 minutes	0.21	-0.52	0.94	0.57	.569	3			

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Between 5 and 60 minutes	0.07	-0.18	0.33	0.59	.554	14			
Between 61 minutes and 24 hours	0.02	-0.45	0.49	0.07	.940	7			
More than 24 hours									
Age							0.76	1	.385
Young	0.06	-0.12	0.25	0.67	.506	30			
Elderly	0.08	-0.51	0.66	0.25	.801	5			

Table 2: Results of moderation analyses

Note: *g* = effect size; LL = lower limit of the 95% CI; UL = upper limit of the 95% CI; *z* = *z*-score associated with the *g* value in the same row; *p* = *p*-value associated with the *z*-score in the same row; *k* = number of effect sizes contributing to *g* in the same row; *Q* = result of the *Q*-test for moderation; *df* = degrees of freedom of the *Q*-test for moderation; *p* = *p*-value of the *Q*-test for moderation. [a] The two effect sizes in the Right parietal condition of memory accuracy - cathodal tDCS belong to the same study. Consequently, these two effects sizes cannot be collated using a multi-level model. The reported effect size and 95% CI was computed with a univariate meta-analysis. * $p < .05$, ** $p < .01$, *** $p < .001$. See Supplementary Table 1 for the moderators of response times with cathodal tDCS and for the moderating role of Delay on the effects of cathodal tDCS on memory accuracy.

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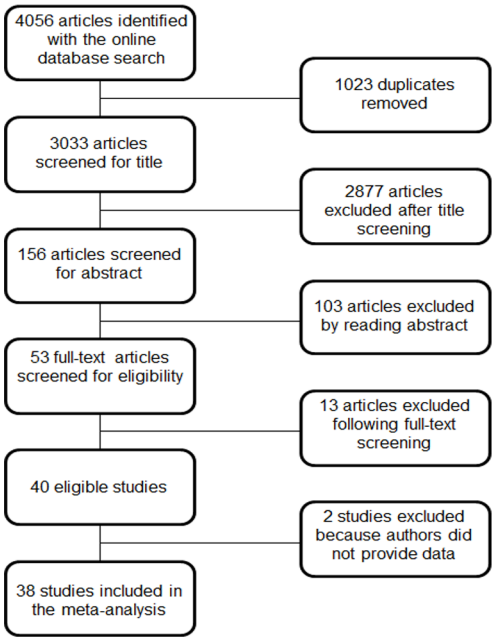

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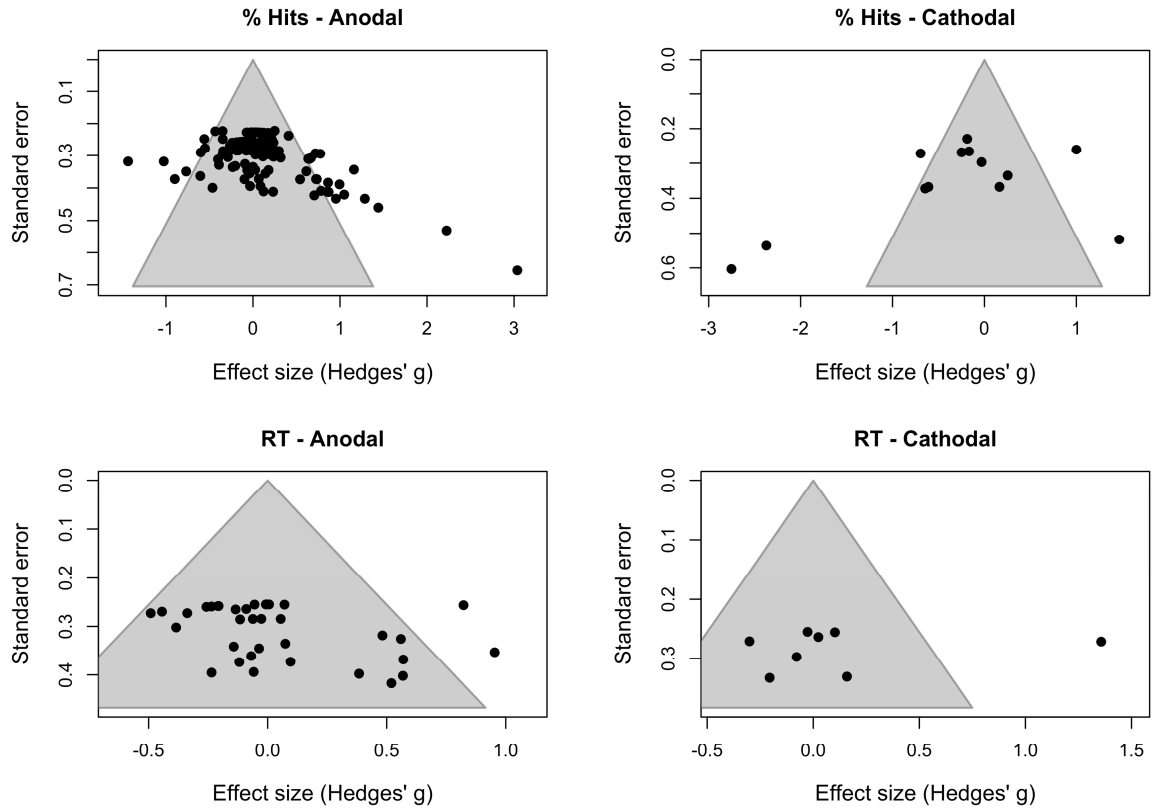

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- We conducted four meta-analyses to assess the effects of tDCS on episodic memory
- We examined the effects of anodal and cathodal tDCS
- We found no effects of tDCS on episodic memory accuracy or response times
- Specific stimulation parameters moderated the effects of tDCS

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AUTHOR DECLARATION

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Giulia Galli April 17th 2018

Miguel Vadillo April 17th 2018

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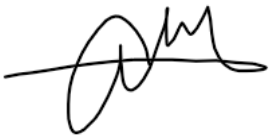

Angela Medvedeva April 17th 2018

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