Systematic review and network meta-analysis of anodal tDCS effects on verbal episodic memory: Modelling heterogeneity of stimulation locations

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Abstract

There is growing interest in the study of transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, as an effective intervention to improve memory. In order to evaluate the relative efficacy of tDCS based on the location of anodal electrode sites, we conducted a systematic review examining the effect of stimulation applied during encoding on subsequent verbal episodic memory in healthy adults. We performed a network meta-analysis of 20 studies (23 experiments) with N=978 participants. Left ventrolateral prefrontal and temporo-parietal sites appeared most likely to enhance episodic memory, although any significant effects were based on findings from single studies only. We did not find evidence for verbal retrieval enhancement of tDCS versus sham stimulation where the effect was based on more than one experimental paper. More frequent replication efforts and stricter reporting standards may improve the quality of evidence and allow more precise estimation of population-level effects of tDCS.

Introduction

Episodic memory is the long-term memory for specific events or episodes (Tulving, 1983). In addition to medial temporal lobe structures of the brain, it has been shown that lateral prefrontal and temporo-parietal cortices (PFC and TPC, respectively) also contribute to episodic memory function (Spaniol et al., 2009; Dickerson & Eichenbaum, 2010; Manenti, Cotelli, Robertson, & Miniussi, 2012; Szczepanski & Knight, 2014; Rugg & King, 2017). This type of long-term memory declines with age (Ronnlund, Nyberg, Backman, & Nilsson, 2005), a process accelerated in pathological conditions such as amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD).

Over the last decade, there has been growing interest in the use of non-invasive brain stimulation techniques as a tool to enhance memory (Sandrini & Cohen, 2013, 2014), with a view to possible future applications in pathological aging. Among these techniques is transcranial direct current stimulation (tDCS), a safe and well-tolerated neuromodulation approach (Dayan, Censor, Buch, Sandrini, & Cohen, 2013). tDCS is a portable device which uses a constant low-intensity current (1-2 milliampere) delivered directly to the cortex through the cranium via surface electrode pads, anode and cathode, typically for up to a 30-minute duration (Dayan et al., 2013). Anodal tDCS applied to primary motor cortex is considered to increase cortical excitability, whereas cathodal tDCS to decrease cortical excitability (Nitsche & Paulus, 2000).

Potential positive effects of tDCS on long-term memory have been suggested using a variety of electrode locations. Javadi and Walsh (2012) reported improved performance in a verbal recognition task following stimulation with the anode over the dorsolateral prefrontal cortex (DLPFC), as opposed to motor cortex- or sham stimulation. Jones, Gözenmann and Berryhill (2014) observed similar effects following tDCS with the anode over the left, but not right posterior parietal cortex (PPC). In a more recent example, Medvedeva et al. (2018) found that stimulation with the anode over the ventrolateral prefrontal cortex (VLPFC) during intentional encoding improved delayed memory performance. These examples are indicative of the range of electrode locations which have been proposed as beneficial to enhance episodic memory in these tasks.

In their recent work Galli, Vadillo, Sirota, Feurra and Medvedeva (2018) conducted a systematic review and meta-analysis of tDCS studies targeting long-term episodic memory, addressing the occasionally conflicting results emerging in this field. The authors reported a lack of overall significant effects of tDCS on memory, despite the number of significant results in original studies. In contrast to Galli et al. (2018), our interest specifically concerned the application of tDCS in boosting learning, with enhancement of long-term verbal episodic memory. We find this question particularly relevant in order to evaluate the potential of clinical application of tDCS in pathological aging.

Research synthesis efforts in the field, whilst beneficial, encounter the problem of how to model the wide variety of electrode locations within the constraints of traditional pairwise meta-analyses. A number of solutions have been attempted, for example pooling effect sizes independently (Horvath, Forte, & Carter, 2015), grouping very different electrode placements as similar (Hsu, Ku, Zanto, & Gazzaley, 2015), or including electrode location as a moderator variable (Galli, Vadillo, Sirota, Feurra, & Medvedeva, 2018). These solutions may lead to the loss of a direct statistical comparison of treatments of interest, or statistical power when evaluating the relative effectiveness of electrode configurations.

In our current project we took a new approach and conducted a Network Meta-Analysis (NMA; see e.g. Lumley, 2002, and Lu & Ades, 2006) to address this research question. NMA has been used increasingly as a research synthesis method over the last decade, predominantly in the field of clinical trials (see Riley et al., 2017; Cipriani et al., 2018,), to make use of a combination of available direct and indirect comparisons of interventions. For example, there may be studies comparing stimulation type A with B, and B with C. In this case, pooling effect sizes results in two direct comparisons with their respective variance: the mean difference between A and B (M_{AB}, var_{AB}), B and C (M_{BC}, var_{BC}). Although there are no studies testing A against C directly, their relative difference can be estimated as an indirect comparison: $M_{AC} = M_{AB} + M_{BC}$, whilst the variance of such an estimate would be $var_{AC} = var_{AB} + var_{AC}$. Simply put, the difference between the effect of two stimulation types (e.g. different electrode locations) can be

estimated by how they perform against a common comparator, although the certainty of these indirect estimates would be lower than that of a result of a pairwise, direct comparison. In the presence of common comparators, NMA enables researchers to evaluate relative efficacy of interventions in a single analysis based on a network combining direct and indirect evidence, providing additional information compared to pairwise meta-analysis methods (for examples, see e.g. Higgins & Welton, 2015, or Riley et al., 2017). In an example from the field of tDCS, Elsner, Kwakkel, Kugler and Mehrholz, (2017) carried out NMA in order to evaluate the relative efficacy of tDCS in stroke recovery. They reported that cathodal, but not anodal or dual stimulation, improved activities of daily living capacity relative to sham.

The aim of our paper was to synthesise evidence regarding differences in episodic memory enhancement as a function of tDCS stimulation site. This may enable researchers to evaluate the potential benefits of using particular electrode locations, e.g. in the field of neuromodulation interventions for memory decline. We reviewed evidence regarding the effects of tDCS on verbal episodic memory in order to evaluate potential behavioural effects beyond the stimulation session itself. For learning and memory, synchronising the learning task with stimulation-induced plasticity may be critical. In this case, tDCS may enhance task-related activity (Martin, Liu, Alonzo, Green, & Loo, 2014; Shin, Foerster, & Nitsche, 2015). Therefore, our focus was on studies applying tDCS during encoding.

Thus, two main questions were addressed. If a single session of tDCS is applied during the learning/encoding phase, (1) which anode placement location is the most effective in enhancing delayed verbal memory retrieval, and (2) what degree of enhancement is likely to occur in setups with the most effective electrode locations? We also intended to explore the feasibility of using NMA to synthesise evidence from non-invasive brain stimulation experiments, particularly in order to compare the relative efficacy of stimulation sites.

Methods

Literature search

We followed the guidelines and checklist regarding conducting and reporting systematic reviews and network meta-analysis in the extension of the PRISMA Statement (Hutton et al., 2015). Our aim was to include studies of adult human participants based on the following primary criteria: (1) randomised controlled trials or within-subjects designs (2) applying a single session of tDCS during encoding (3) with a subsequent verbal retrieval task. We carried out a systematic review of English language publications up until 31st March 2019, using databases MEDLINE, PsychINFO, PsychARTICLES, and OpenDissertations via the search platform provided by EBSCO Information Services. The search terms used were *'tdcs OR transcranial direct current stimulation OR transcranial electric* OR tes OR non-invasive brain stimulation'*, combined with *'memory OR recall OR recognition OR retriev*'*, and *'verbal OR word OR declar* OR episod* OR associat*'*. We evaluated the sensitivity of our search strategy by comparing results to a pre-defined list of potentially eligible studies already known to us. We included all randomised studies which adopted a single- or double-blind design and contained at least two different tDCS stimulation conditions. Titles and abstracts of items identified during the search were screened independently by two authors (GB, EB) for inclusion based on criteria 1-3. Potential clashes were resolved by agreement and consulting a third reviewer (MS). Full-text versions of identified hits were read and assessed in-depth for eligibility criteria by GB and MS. Clashes were resolved by further review until agreement was reached. Corresponding authors of identified eligible articles were approached for full-text versions or data where this was not openly accessible to the reviewers.

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Figure 1. Flowchart of study screening and selection process.

Outcome variable

We were interested in the effect of tDCS applied during encoding on later episodic memory retrieval tested using both recall and recognition tasks, and the modulation of this effect by

anodal electrode placement. We included both traditional tDCS studies using one anode and one cathode, as well as high definition (HD) tDCS montages where one polarity is represented by multiple electrodes (Datta et al., 2009). For instance, in the case of one anode and multiple cathodes, it may be plausible to assume that current density is more focalised in regions proximal to the anodal stimulation site (Villamar et al., 2013).

Our key criteria regarding inclusion were that studies conducted an encoding session of material having at least one verbal element (words, pseudo-words, sentences, names) with concurrent application of tDCS, and employed a subsequent, delayed retrieval task. Studies testing performance from concurrent and immediate retrieval tasks were not included in our analysis, given our focus on delayed episodic memory effects. Data eligible for inclusion were screened and identified by two authors (GB and MS). Data were extracted from the original publications where possible. This included values reported in the manuscript text, tables, and figures. Authors were contacted when relevant data were not available. In case of studies with multiple memory measures, a pooled effect size was calculated. For example, (a) Day 1 and Day 2 scores, (b) performance of different participant groups (e.g. young and old adults), or (c) test results from recall and recognition tasks were combined into a summary measure. Corrections were made as necessary in the case of within-subject studies, using the correlation value r = .5. This was selected as a plausible value based on an earlier similar review (Galli, Vadillo, Sirota, Feurra, & Medvedeva, 2018) and data available from our own lab in similar experiments. Hedges' g was calculated as a standardised mean difference measure (SMD) for all comparisons using the Metacont function of the *Meta* package in R (Schwarzer, 2007).

NMA method

We performed a network meta-analysis using the *Netmeta* package (Rücker, & Schwarzer, 2015) in the statistical software R. Connectedness of the network was evaluated using a network diagram, and by visual exploration of experimental conditions listed in the summary data file. We evaluated the suitability of both fixed-

and random-effects models during our analysis. Consistency of direct- and indirect effects was evaluated using a node-splitting procedure (Dias, Welton, Caldwell, & Ades, 2010). Potential effect modifier parameters (e.g. task type, stimulation intensity) were extracted for all included studies and summarised in Table 1. Following the selection of the final model, we ranked tDCS based on anodal electrode location by efficacy against a common comparator using P-scores (Rücker, & Schwarzer, 2015). P-scores measure the extent of certainty that a treatment performs better than another treatment, based on network meta-analysis point estimates and standard error. They may take values from 0 to 1, with higher values representing better success (Rücker, & Schwarzer, 2015). The contrast of each electrode location placement versus sham stimulation was evaluated using 95% confidence intervals (CI) and visualised using a forest plot. Moderation analyses were run using the *Metafor* package (Viechtbauer, 2010).

Evaluation of bias

We rated studies for potential bias using the Cochrane Collaborations Risk of Bias Tool (Higgins et al., 2011). GB, EB, and MS accessed full-text versions of included studies and rated items independently. Differences between bias ratings were resolved with agreement.

Open access statement

Supporting materials are available through the online repositories Psycharchives[1] and Open Science Framework[2]. Our choice of analytic software *Netmeta* (Rücker, & Schwarzer, 2015) was motivated by enabling a free and open-access reproducibility of our analysis.

Results

Search results

[1] DOIs: http://dx.doi.org/10.23668/psycharchives.2619; http://dx.doi.org/10.23668/psycharchives.2620
[2] DOI: https://osf.io/cfyvk/

A total of 612 records were identified in the initial database search (588) and additional resources, e.g. items indexed in other reviews (24). The database search itself identified 20 out of 23 previously known potentially eligible studies, demonstrating a sensitivity of 86.95%. 397 records remained after the removal of duplicates. 370 items were excluded during abstract screening due to not meeting eligibility criteria (1-3) set out above. This left 27 records for full-text review. Two studies were removed due to describing overlapping experiments (both were PhD theses with experimental data also published in peer-reviewed articles). Four studies were removed as their design did not meet the inclusion criteria (tDCS applied *during* learning, followed by verbal episodic retrieval test) following full-text review. One study was not included in the analysis, as the relevant data was not available. This resulted in the inclusion of 20 separate publications (describing 23 experiments) in our final quantitative and qualitative synthesis.

The total sample consisted of N=978 participants. 16 studies used healthy young adult samples, 3 studies tested elderly groups, and one study included both a young and elderly group. The age of the total sample was M=29.34, SD=7.25, with a 58.76%-41.24% female-to-male ratio. The majority of studies reported encoding tasks using explicit, intentional learning instructions. The timing of the delayed retrieval task ranged from a few minutes to one week. Testing of previously learned material was conducted using free or cued recall, and recognition tasks, and in the case of some studies, a combination of the above. The selection flowchart is displayed in Figure 1.

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Table 1. Key parameters of studies included in the analyses.

Data analysis

We coded tDCS used in studies as 16 different categories based on the location of the placement of the anodal electrode, according to the International 10-20 EEG System for electrode placement (Klem, Luders, Jasper, & Elger, 1999). Key parameters including electrode placement, stimulation intensity, retrieval task, and sample characteristics of

the included studies are reported in Table 1. Figure 2 displays the network of included comparisons in our analysis. All apart from one included study reported using a sham stimulation condition as a comparator, which we chose as the primary comparison when evaluating relative efficacy.

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Figure 2. Network diagram of the final random-effects NMA model. Circles refer to the different placement locations of the anodal electrode according to the International 10-20 EEG system for electrode placement. Area of circles is proportional to included sample size per stimulation condition. Width of lines is proportional to number of studies with direct comparisons.

There was evidence of significant total heterogeneity, Q(17)=32.44, p=.013, tau^2 = 0.0935; I^2= 47.6%. Therefore, comparisons and effect sizes are reported below based on our random-effects NMA. There were no inconsistencies indicated between direct and indirect effect size estimates. Efficacy of anodal electrode placement locations versus sham stimulation are displayed in Figure 3.

tDCS with the anode over F7 (left ventrolateral PFC) had a high certainty of being more successful in inducing memory enhancement than other electrode locations (P-score = .9553). The effect of this electrode configuration, based on data from three direct comparisons (total N=71) reported in Medvedeva et al. (2018), was significantly positive: g = 1.21, 95%CI = [0.63; 1.79]. One other contrast showed significant effects of tDCS with the anode over CP5-TP7 (left inferior parietal lobule/temporal-parietal region), P-score = .9367, g = 1.22, 95%CI = [0.23; 2.21], although the sham contrast is based on a single direct comparison (N=30) only (Rivera-Urbina, Mendez Joya, Nitsche, & Molero-Chamizo, 2019). tDCS with the anode over F3 (left dorsolateral PFC), a frequently used stimulation site in the field with 10 head-to-head comparisons (total N=352) had a small, statistically non-significant effect versus sham stimulation, g = 0.16, 95%CI = [-0.1; 0.43], P-score = .5792.

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Figure 3. Forest plot of NMA results. Efficacy of each condition (anodal placement) versus sham condition is listed (Hedges' g).

We evaluated the effect of two potential moderators: blinding, and current density (at the anodal site) on our pooled outcome variable using pairwise meta-analysis on data available from sham-controlled studies. Blinding was selected as a moderator variable in order to evaluate whether effect sizes extracted from the relatively high proportion of single-blind studies (ca. 50%) differ from those with double-blind designs. Given the suggestion (Voroslakos et al., 2018) that the cortical penetration of tDCS is relatively weak, the possibility of higher current densities leading to greater enhancement was also examined as a potential moderator. Our random-effects model suggested evidence for significant heterogeneity, $Q(31)=72.23$, $p<.001.$, $tau^2 = 0.1421$, 95%CI=[0.018; 0.266]; $I^2= 58.55\%$. Including the two moderators resulted in a non-significant decrease in heterogeneity $Q(28)=58.49$, $p<.001.$, $tau^2 = 0.111$, 95%CI=[0; 0.225]; $I^2= 51.5\%$, with neither blinding (g=0.251, 95%CI=[-0.113, 0.615] nor current density (g=-0.058, 95%CI=[-0.262; 0.146]) having a significant effect.

Details of bias evaluation are summarised in Table 2. The majority of studies (16 out of 20) described using randomisation during allocation to stimulation conditions, although this process was not typically described in detail. All publications reported some form of blinding process, 11 of them double-blind. Blinding success was rarely evaluated. Drop-out rates from experiments were generally low.

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Table 2. Evaluation of bias according to the Cochrane Risk of Bias Tool. L – low, U – unclear, H – high risk of bias, respectively.

Discussion

In our review and analyses we summarised data on verbal episodic memory performance following tDCS applied during encoding from 23 experiments, with a total sample size of N=978. We deemed our search successful in identifying relevant studies based on previously set criteria.

Our random-effects NMA results indicated that tDCS applied with the anode over frontal (F7) and temporo-parietal (CP5/TP7) regions may have a higher probability in enhancing delayed retrieval when applied during encoding. These two significant effects stem from single studies or publications, and in our analyses these could be compared to the primary reference (i.e. sham condition) based only on direct evidence. The identified sites showing a potential in enhancing learning are proximal to some a priori regions of interest, e.g. left ventral TPC and left ventrolateral PFC, areas known to be involved in episodic memory processes (Spaniol et al., 2009; Manenti, Cotelli, Robertson, & Miniussi, 2012). However, there is considerable uncertainty of the mean effect size estimates in these cases. Further replications across different experimental designs and research groups would allow for better estimation of these effects, whilst also increasing their generalisability.

Importantly, we did not find any statistically significant episodic memory enhancing effects where direct and indirect evidence from multiple studies were available. For example, the frequently employed stimulation with the anode over F3 (i.e. DLPFC) ranked relatively high against other electrode locations, but we did not find evidence for significant benefit over sham. Thus, earlier findings reporting long-term memory enhancement following stimulation during encoding, for example with the anode over DLPFC (Javadi & Walsh, 2012), or PPC (Jones, Gözenmann, & Berryhill, 2014), are not corroborated by our network meta-analysis estimates. One possible reason may be differences in exact testing procedures: it has been suggested that tDCS may have differential effects during intentional versus incidental learning (Medvedeva et al., 2018), or enhance recall but not recognition (Leshikar et al., 2017). Our choice of using pooled effect sizes where multiple memory tests were available, whilst reducing potential bias due to selective inclusion of outcomes, meant that we were not able to address these suggestions for potential effect moderators. However, one plausible explanation behind the failure to find significant effects in these

cases remains the possibility of a lack of robust effects of tDCS on cognition in the long-term – an important aspect to consider when evaluating the need for clinical trials in the field.

Stimulation intensity, anode-cathode electrode locations, and the employed episodic memory tasks varied across studies, resulting in a large heterogeneity in included study designs. Direct replication attempts were not often reported. Quantifying true effects of tDCS on verbal episodic memory with more certainty would benefit from such efforts in the future. We also note a lack of pre-registered studies in our analysed sample. This particular approach (pre-registration) has been recommended as one of the tools that could improve replicability in science in general (Munafo et al., 2017) and in our cognitive neuroscience subfield in particular (Szucs & Ioannidis, 2017).

All included studies adopted some form of blinding procedure, with an approximately 50% split between single- and double-blind designs. Differences in blinding method did not appear to affect reported scores according to our moderation analyses. However, exact blinding procedures were not always described in sufficient detail. Attrition rates, where described, were generally low, corresponding with the conclusion of reviews dedicated to evaluating the safety and tolerance of tDCS methods (Bikson et al., 2016, Woods et al., 2016). Allocation concealment were not addressed in detail in the majority of studies with between-subjects designs. In future studies exploring potential therapeutic benefits of non-invasive brain stimulation methods, the adoption of commonly used clinical trial reporting guidelines, e.g. principles of the CONSORT Statement (Schulz, Altman, & Moher, 2010) could be considered in order to control for potential sources of bias.

As described earlier, the synthesis of direct and indirect effects is not new in the field of tDCS Elsner, Kwakkel, Kugler, & Mehrholz, (2017). In our case, the application of NMA is a novel approach to modelling heterogeneity of effects on cognitive performance due to differences in electrode placements and targeted areas. Some previous reviews of non-invasive stimulation studies reached different conclusions, some argued for evidence of enhancement of cognitive functions (Hsu, Ku, Zanto, & Gazzaley, 2015; Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Summers, Kang, & Cauraugh, 2016), whilst some found no evidence (Tremblay, Lepage, Latulipe-Loiselle, Fregni, Pascual-Leone, & Théoret, 2014; Horvath, Forte, & Carter, 2015). Given the strong assumption in the field that stimulation

of different sites should lead to differential neural and behavioural effects, modelling heterogeneity due to differences in stimulation sites is an important aspect of any research synthesis effort. Accounting for this variability with the right statistical synthesis method may reduce the contradiction between reviews on similar topics. We argue that NMA may be one of the most promising currently available methods to account for these differences, retaining the benefits of synthesising evidence in a single analysis, and making use of a wider (direct and indirect) evidence base.

In terms of limitations of our review, we recognise that some of the main findings (e.g. most efficient stimulation sites in memory enhancement) were tested by a single study or group only and would therefore benefit from replication. A larger number of studies addressing each head-to head comparison may also enable a meaningful evaluation of publication bias, e.g. using comparison-adjusted funnel plots as in Chaimani & Salanti (2012). Our primary interest in conducting this review was in exploring potential beneficial effects of tDCS applied during encoding in pathological aging. However, the final sample mainly consisted of young, healthy adults, reducing the generalisability of our results to key populations of interest. In addition, whilst the placement of anodal electrode – the basis of classification in our analysis – is often used in conjunction with describing targeted cortical areas in the literature, there may be significant differences in intracranial current distribution based on cathodal placement (Woods et al., 2016). Incorporating the distribution and the strength of tDCS-induced electric fields for given montages in an analysis, instead of electrode locations, may be a useful alternative in the future. However, such estimates derived using currently available modelling software have not yet been extensively tested in vivo (see e.g. Jog et al., 2016). Finally, whilst our analysis looked at memory performance enhanced by tDCS, a topic with potential therapeutic relevance, clinical outcomes were not the key focus of this review. Previous reviews provide some information on this topic (e.g. Hsu, Ku, Zanto, & Gazzaley, 2015; Summers, Kang, & Cauraugh, 2016), with at least one other related systematic review ongoing (Zhang, Liu, Li, Zhang, & Qu, 2018) in the field.

In summary, we adopted an NMA approach to conduct a novel synthesis of direct and indirect evidence of tDCS-effects on verbal memory retrieval when applied during encoding. Focussing on behavioural results, our analysis addressed the question, currently

unanswered using neuroimaging means, of whether there is a differential behavioural effect of tDCS when applied at different stimulation sites. Our current results do not suggest a conclusive modulation of memory based on the locations of the anode electrode, and further replications of studies reporting potentially effective stimulation locations would be necessary to allow more precise evaluation of these findings. At the same time we suggest the NMA framework is a useful approach to comparing the efficacy of non-invasive brain stimulation techniques (e.g. tDCS, transcranial alternating current stimulation, repetitive Transcranial Magnetic Stimulation; Dayan, Censor, Buch, Sandrini, & Cohen, 2013) in a variety of cognitive domains whilst accounting for heterogeneity in the location of targeted cortical areas.

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Figure legends

Figure 1. Flowchart of study screening and selection process.

Figure 2. Network diagram of the final random-effects NMA model. Circles refer to the different placement locations of the anodal electrode according to the International 10-20 EEG System for electrode placement. Area of circles is proportional to included sample size per stimulation condition (range 16 - 364). Width of lines is proportional to number of studies with direct comparisons (range 1 - 10).

Figure 3. Forest plot of NMA results. Efficacy of each active (anodal placement) versus sham condition is listed (Hedges' g).

Table 1. Key parameters of studies included in the analyses.

Table 2. Evaluation of bias according to the Cochrane Risk of Bias Tool. L – low, U – unclear, H – high risk of bias, respectively.

Figure 1

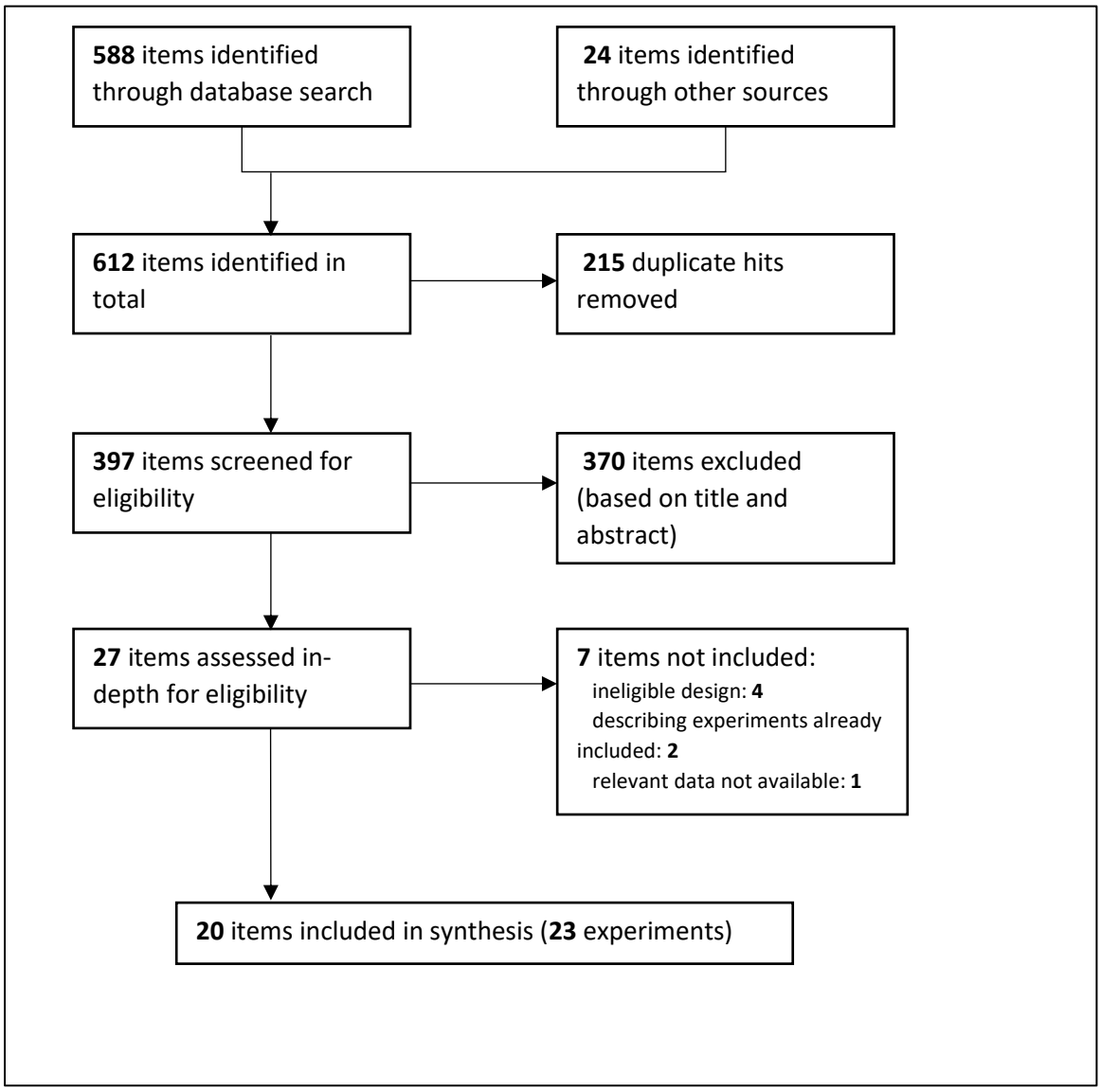
588 items identified through database search
24 items identified through other sources
612 items identified in total
215 duplicate hits removed
397 items screened for eligibility
370 items excluded (based on title and abstract)
27 items assessed in-depth for eligibility
7 items not included:
ineligible design: **4**
describing experiments already included: **2**
relevant data not available: **1**
20 items included in synthesis (**23** experiments)

Figure 2

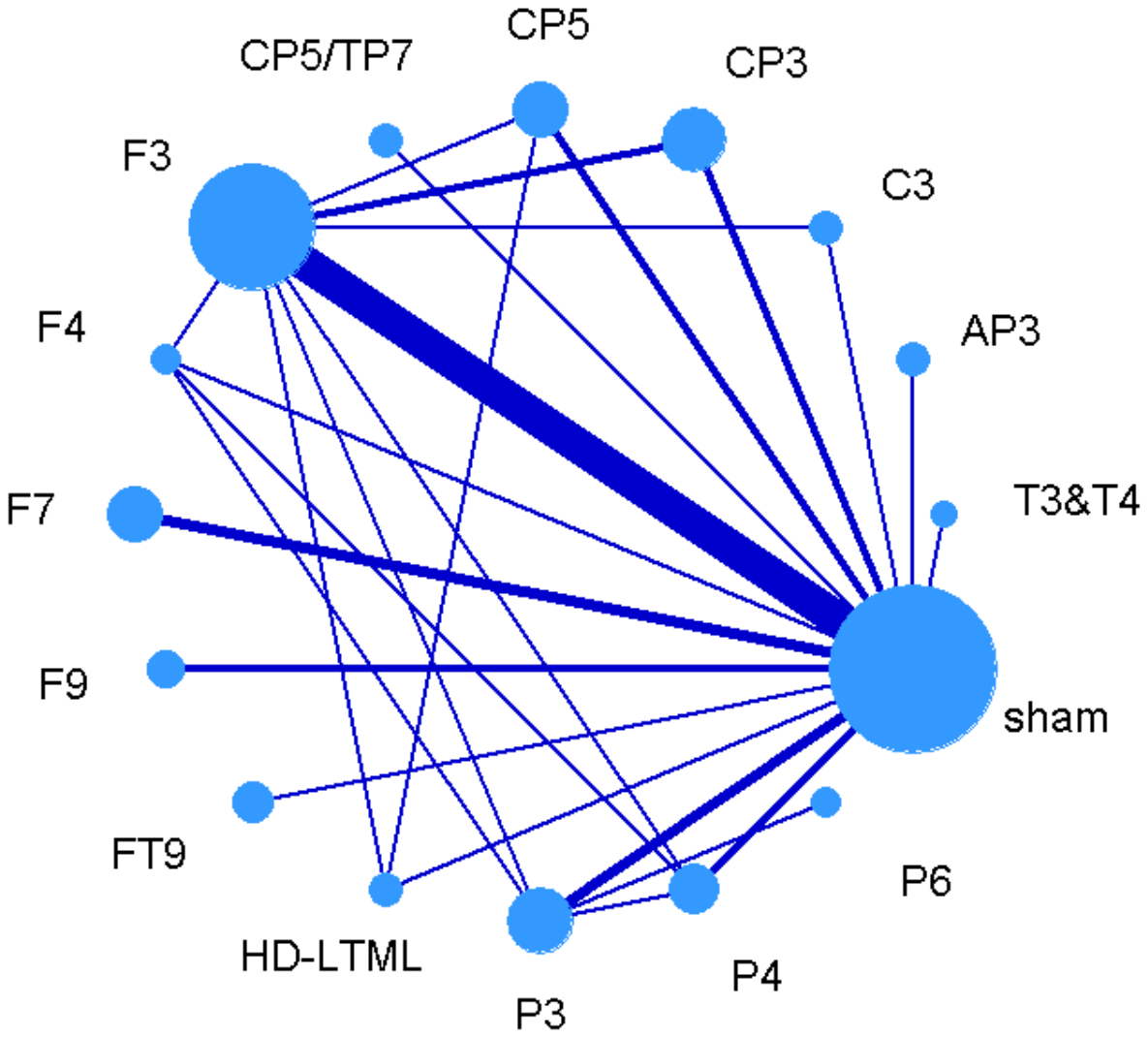

Figure 3

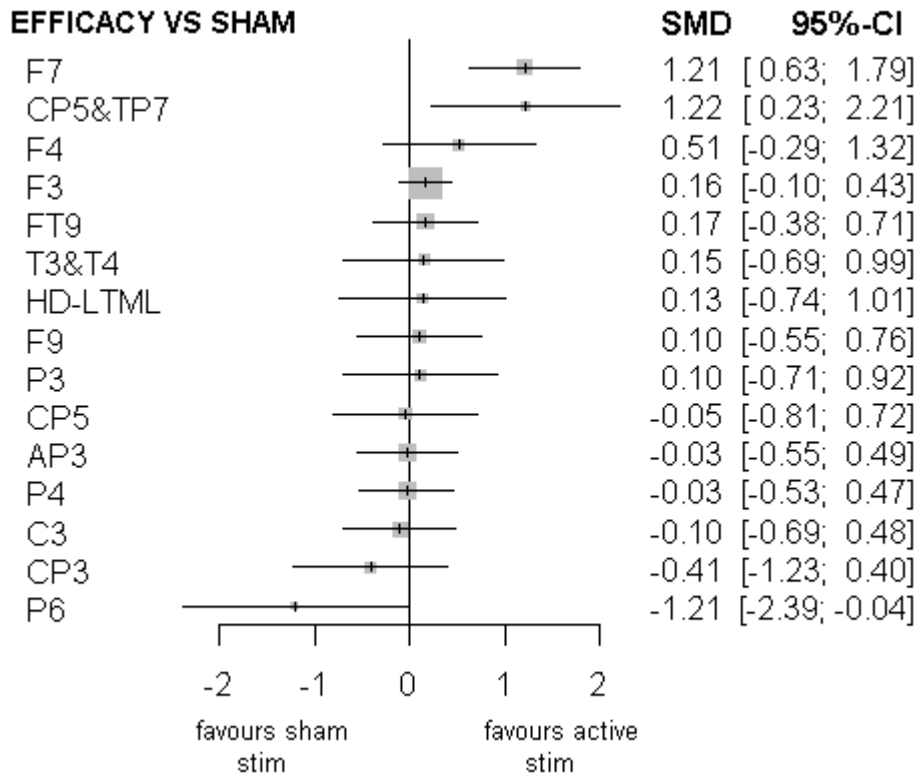
EFFICACY VS SHAM
SMD 95%-CI
F7 1.21 [0.63; 1.79]
CP5&TP7 1.22 [0.23; 2.21]
F4 0.51 [-0.29; 1.32]
F3 0.16 [-0.10; 0.43]
FT9 0.17 [-0.38; 0.71]
T3&T4 0.15 [-0.69; 0.99]
HD-LTML 0.13 [-0.74; 1.01]
F9 0.10 [-0.55; 0.76]
P3 0.10 [-0.71; 0.92]
CP5 -0.05 [-0.81; 0.72]
AP3 -0.03 [-0.55; 0.49]
P4 -0.03 [-0.53; 0.47]
C3 -0.10 [-0.69; 0.48]
CP3 -0.41 [-1.23; 0.40]
P6 -1.21 [-2.39; -0.04]
-2
-1
0
1
2
favours sham stim
favours active stim

Table 1

Study ID		Exp	N	Mean age	Design	Applied current	Electrode surface or diameter	Stimulation duration	Exp. conditions	Learning and retrieval task
1	Boggio et al., 2009	1	30	19.8	between	2mA	35cm²	10 mins	T3 to T4	word learning, followed by recognition task
2	Brunyé et al., 2018	1	150	21.2	between	1.5mA,	not specified	duration of learning	F3-Fp2, Fp2-F3, sham	word learning, delayed free recall (2 days)
3	de Lara et al., 2017*	1	15	24.8	within	1mA	3cm² anode, 4x3cm² cathode	20 mins	AF3 to 4 cathodes (active vs sham)	word pair associative learning, delayed cued recall (10 min, 24hrs)
4	Diez et al., 2017	1	69	21.8	between	2mA	35cm²	20 mins	FT9 to contralateral shoulder (active vs sham)	word learning, delayed old-new recognition task (2 mins)
5	Gaynor & Chua, 2017	1	72	20.8	between	2mA	35cm²	20 mins	F3 to Fp2, CP3 to CP4, sham	word pairs associative learning, delayed pair-recognition task (24 hour)
6	Habich et al. 2017	1	44	24.8	between	1mA	35cm²	20 mins	F3 to Fp2 (active vs sham)	word learning, delayed free recall
7	Jacobson et al., 2012***	1	12	12	within	1mA	25cm²	10 mins	P3 to P6, P6 to P3	word learning, delayed recognition task (20 mins)
8	Javadi & Walsh, 2012	1	32	22.5	within	1mA	cca. 12cm² and 30cm²	20 mins	F3-Fp2 (active vs sham), Fp2-F3, Cz-Fp2	word learning, delayed recognition task (1 hr)

9	Jones et al., 2014	1	20	23	within	1.5mA	35cm²	15 mins	P3 to contralateral cheek (active vs sham)	word learning task, delayed free recall (20 mins)
9	Jones et al., 2014	3	20	21.1	within	1.5mA	35cm²	15 mins	P4 to contralateral cheek (active vs sham)	word learning task, delayed free recall (20 mins)
10	Leach et al., 2016	1	14	71.7	between	2mA, 0.1mA	35cm²	25 mins	F9 to contralateral upper arm (active vs sham)	face-name associative learning, followed by recall and pair recognition task
11	Leach et al., 2018	1	96	44	between	1.5mA, 0.1mA	11cm²	duration of learning task	F3- contralateral upper arm (active vs sham)	face-name associative learning, delayed recognition task
12	Leshikar et al., 2017	1	42	21.6	between	1.5mA, 0.1mA	11cm²	25 mins	F3 to contralateral upper arm (active vs sham)	face name pairs associative learning (implicit), cued recall and recognition task (same day and next day)
13	Manuel & Schnider, 2016	1	26	23.5	mixed	1mA, sham	35cm²	24 mins	F3 to Fp2, F4 to Fp1, sham vs P3 to Fp2, P4 to Fp1, sham	continuous learning/recognition task (of repeated items) with pseudo-words, delayed recognition task (30 mins)

14	Matzen et al., 2015	1	24	22.3	between	2mA, 0.1mA	11cm²	30 mins	F9 to contralateral arm (active vs sham)	face-name pairs associative learning, recognition task, delayed name recall
15	Medvedeva et al., 2018	1	34	24	between	2mA, sham	35cm²	cca. 9 mins	F7 to contralateral deltoid (active vs sham)	word learning, recognition task (24 hrs)
15	Medvedeva et al., 2018	3	34	23	within	2mA	35cm²	15 mins	F7 to contralateral deltoid (active vs sham)	incidental word learning, delayed recognition task (1hr)
15	Medvedeva et al., 2018	4	22	73	between	2mA	35cm²	cca. 9 mins	F7 to contralateral deltoid (active vs sham)	word learning, recognition task (24 hrs)
16	Meier & Sauter, 2018	1	48	24.5	between	0.8mA	9cm²-35cm²	20 mins	F3 to Fp2 (active), CP3 to Fp2 (active vs sham)	implicit learning of action phrases (read or enact), followed by delayed recognition task (45 mins and 1 week)
17	Nikolin et al., 2015**	1	16	21.8	within	2mA	d=1cm electrodes (1 anode, 4 cathodes)	20 mins	F3 to AF3,F5,FC,FC3 (active) vs Cp5 to C5,TP7,Cp3,P5 (active) vs P9 to Fp1, Fp2, FC4 (active) vs F4 to Cp4, Cp6 (sham)	word learning, delayed free recall (30 mins)

18	Perceval et al., 2017**	1	50	23.2	between	1mA	d=2.5cm centre, 7.5-9.8cm ring	20 mins	CP5 centre to ring electrode (active vs sham)	novel item name learning, cued recall (last test, not overlapping with stimulation included)
19	Rivera-Urbina et al., 2019	1	45	21.9	between	1.5mA, sham	35cm² anode, 25cm² cathode	15 mins	CP5&TP7 to Fp2 (use 1.5mA and sham only for analysis)	word learning, delayed free- and semantic strategy recall (20 mins)
20	Sandrini et al., 2016	1	28	68.9	between	1.5mA	35cm²	15 mins	F3 to Fp2 (active vs sham)	word learning, delayed free recall (2 days and 30 days)

* Stimulation during encoding included only
** Denotes High Definition tDCS setup
*** Control arm of study not included due to potential lack of randomised allocation across conditions.

Table 2

Study	Selection bias Random sequence generation	Selection bias Allocation concealment	Reporting bias Selective reporting	Other bias Other sources of bias	Performance bias Blinding	Detection bias Blinding	Attrition bias ncomplete outcome data
Boggio et al., 2009	L	U	L	L	L	L	L
Brunyé et al., 2018	L	U	L	L	H	H	L
de Lara et al., 2017	L	L	L	L	L	L	L
Diez et al., 2017	L	U	L	L	H	H	L
Gaynor & Chua, 2017	L	U	L	L	H	H	L
Habich et al. 2017	L	U	L	L	L	L	L
Jacobson et al., 2012	H	L	L	L	L	L	L
Javadi & Walsh, 2012	L	L	L	L	H	H	L
Jones et al., 2014 Exp 1	U	L	L	L	H	H	L
Jones et al., 2014 Exp 3	U	L	L	L	H	H	L
Leach et al., 2016	L	U	L	L	L	L	L
Leach et al., 2018	U	U	L	L	L	L	L
Leshikar et al., 2017	L	L	L	L	L	L	L
Manuel & Schnider, 2016	L	U	L	L	H	H	L
Matzen et al., 2015	U	U	L	L	L	L	L
Medvedeva et al., 2018 Exp 1	L	U	L	L	H	H	L
Medvedeva et al., 2018 Exp 3	L	L	L	L	H	H	L
Medvedeva et al., 2018 Exp 4	L	U	L	L	H	H	L

Meier & Sauter, 2018	L	U	L	L	H	H	L
Nikolin et al., 2015**	L	L	L	L	H	H	L
Perceval et al., 2017	L	L	L	L	L	L	L
Rivera-Urbina et al., 2019	L	U	L	L	L	L	L
Sandrini et al., 2016	L	L	L	L	L	L	L