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Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis

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Abstract

Recent studies have used non-invasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), to increase dorsolateral prefrontal cortex (DLPFC) activity and, consequently, working memory (WM) performance.. However, such experiments have yielded mixed results, possibly due to small sample sizes and heterogeneity of outcomes. Therefore, our aim was to perform a systematic review and meta-analyses on NIBS studies assessing the n-back task, which is a reliable index for WM. From the first data available to February 2013, we looked for sham-controlled, randomized studies that used NIBS over the DLPFC using the n-back task in PubMed/MEDLINE and other databases. Twelve studies (describing 33 experiments) matched our eligibility criteria. Active vs. sham NIBS was significantly associated with faster response times (RT), higher percentage of correct responses and lower percentage of error responses. However, meta-regressions showed that tDCS (vs. rTMS) presented an improvement only in RT. This could have occurred in part because almost all tDCS studies employed a crossover design (possibly more employed in tDCS over rTMS due to the reliable tDCS blinding) – this factor (study design) was also associated with no improvement in correct responses in the active vs. sham groups. To conclude, rTMS over the DLPFC significantly improved all measures of WM performance whereas tDCS significantly improved RT, but not the percentage of correct and error responses. Mechanistic insights on the role of DLPFC in WM are further discussed, as well as how NIBS techniques could be used in neuropsychiatric samples presenting WM deficits, such as major depression, dementia and schizophrenia.

Keywords

Non-invasive brain stimulation; repetitive transcranial magnetic stimulation; transcranial direct current stimulation; working memory; n-back task; prefrontal cortex.

Abbreviations

DLPFC, dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; NIBS, non-invasive brain stimulation; WM, working memory; RT, response times; SD, standard deviation.

1. Introduction

WM is generally defined as a system that comprises temporary storage and online manipulation and control of information (Baddeley, 1986). In early research, Baddeley and Hitch (1974) proposed to distinguish between short-term and working memory. These authors conceptualized WM as a three-component system consisting of an attentional controller, a central executive and two subsidiaries aiding systems, being the sketchpad and the phonological loop (Baddeley, 1986). In addition, recent research provided evidence that WM is a system not only involved in cognitive, "cold" processing, but also in "hot" affective processing (Hofmann, Schmeichel, & Baddeley, 2012; Ochsner & Gross, 2005), being therefore a critically and relevant function in daily activities (e.g., which emotional thoughts should be given attention and which should be ignored). Moreover, several psychiatric disorders are associated with WM impairment, and these deficits in the transient 'online' manipulation of emotional thoughts information seem to be essential information in the quest for effective therapies (Millan et al., 2012).

The prefrontal cortex seems to act as an important neural structure in WM operations and, more specifically, its dorsolateral area (DLPFC) is particularly involved in updating goal representations based on context information or task related demands (Barch, Sheline, Csernansky, & Snyder, 2003; D'Esposito et al., 1995; D'Esposito, Postle, & Rypma, 2000). Moreover, the DLPFC maintains and updates comprehensive representations of the task context by encoding task relevant rules and associated responses, stimulus features and conflict (Mansouri, Tanaka, & Buckley, 2009).

In recent years, non-invasive brain stimulation techniques have been used to explore the impact of increasing DLPFC activity on WM performance. Two of these techniques are tDCS and rTMS (for a complete review, see Dayan et al. (2013)). TDCS consists in applying a weak, direct electric current that flows from the anode to the cathode. These electrodes are placed over the scalp with the goal of, respectively, increasing and decreasing cortical excitability (Nitsche et al., 2003; Nitsche & Paulus, 2000); although tDCS effects on neuronal processing are in fact more complex (Rahman et al., 2013) and may even invert according to the nature of ongoing activity (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013). TDCS generates low-intensity

electric fields (Datta et al., 2009) in the brain leading to small changes (<1 mV) (Radman, Ramos, Brumberg, & Bikson, 2009) in the membrane potential, thus influencing the frequency of spike timing and modifying net cortical excitability (Purpura & McMurtry, 1965) without triggering action potentials *per se* (Brunoni et al., 2012; Nitsche et al., 2008). In turn, rTMS causes disruptions in brain activity by delivering strong magnetic pulses to the cortex that pass through the skull and depolarize the underlying neurons of particular areas in the brain Repetitive TMS over the motor cortex facilitates or inhibits brain excitability according to the frequency of stimulation (respectively >1Hz and <1Hz) (Fregni & Pascual-Leone, 2007; George & Aston-Jones, 2010; Hallett, 2007) For cognitive functions, however, there are also other factors that determine rTMS effects, particularly the baseline activity state of the stimulated region ("state-dependency") (Sandrini, Umilta, & Rusconi, 2011; Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008; van de Ven & Sack, 2013). For instance, Soto et al. (2012) observed that the application of TMS during a WM task respectively increased and decreased accuracy whether the cues were valid or invalid.

Both brain stimulation techniques have been used to demonstrate the fundamental role of DLPFC activation in WM operations, with most studies using the n-back task. Importantly, when the brain stimulation technique and the WM task are coincident in time (i.e., when the variable is collected during the rTMS/tDCS session), the experiment is said to evaluate the "online" effects of the technique. Conversely, when they the WM task is applied *after* the brain stimulation session, it is said that the experiment is applying tDCS/rTMS in an "offline" protocol.

During the n-back task, participants are asked to indicate whether the current stimulus matches the one that was presented "n" trials back in the sequence. The load on WM can be manipulated by varying the number of letters that needs to be sequentially stored and updated in WM. The n-back task is a frequently studied task as it provides simple and comparable measures of performance, such as the response time (RT) for stimulus detection and the rate of correct and error responses. Owen et al. (2005), in a meta-analysis of functional neuroimaging studies, showed that the performance on the n-back task is robustly associated with prefrontal cortex activation.

Nonetheless, tDCS and rTMS studies assessing n-back performance have shown mixed results (Boggio et al., 2006; Esslinger et al., 2012; Teo, Hoy, Daskalakis, & Fitzgerald, 2011), possibly due to different study designs, small sample sizes, multiple clinical conditions and distinct n-back tasks. Thus, the capacity of non-invasive brain stimulation techniques in modulating WM has yet to be determined. Hence, our aim is twofold: (1) to further determine the robustness of the causal and beneficial role of the DLPFC in WM operations; and (2) to assess whether NIBS improves WM in neuropsychiatric disorders that are characterized by WM impairments. This latter is important for interventions that enhance neural correlates of WM in order to target mechanisms that underlie psychiatric disorders(Siegle, Ghinassi, & Thase, 2007; Wallace, Ballard, Pouzet, Riedel, & Wettstein, 2011). Considering the available studies in literature and their mixed findings, our chosen methodology was a systematic review of these studies and, further, a meta-analytic synthesis of their results in single-estimate measures of effect.

2. Methods

We performed a systematic review and meta-analysis according to the recommendations of the Cochrane group (Higgins & Green, 2009), which involves the procedures of literature review, selection of eligible articles according to inclusion/exclusion criteria, quality assessment of the included studies, data extraction of outcomes and relevant variables and, finally, quantitative synthesis (meta-analysis) of the results, as described below.

This report follows PRISMA guidelines (Liberati et al., 2009). The authors independently extracted the data according to an *a priori* elaborated data extraction checklist (see 2.4). Discrepancies were resolved by consensus.

2.1 Literature review

We reviewed PubMed/MEDLINE, Web of Science, SCOPUS and Google Scholar databases. We looked for articles published from the first date available to February 2013 (including articles available online only at the time of the search). The

following key words and Boolean terms were used: ("n-back" OR "working memory") AND ("transcranial direct current stimulation" OR "brain polarization" OR "tDCS" OR "electric stimulation" OR "non-invasive brain stimulation" OR "transcranial magnetic stimulation" OR "TMS" OR "rTMS"). We also looked for additional references in retrieved articles and reviews.

2.2 Eligibility criteria

The included studies had to: (a) be written in English (in fact we found no articles in other languages); (b) enroll either healthy volunteers or neuropsychiatric patients; (c) provide data (on the manuscript or upon request) of at least one of our outcome measures; (d) perform brain stimulation in the prefrontal cortex (i.e., studies testing the effects of tDCS/rTMS in other brain areas were not included); (e) have a sham group – therefore we excluded non sham-controlled trials; (f) perform either tDCS or rTMS; (g) use a n-back task.

2.3 Quality assessment

To assess study quality, we assessed the following criteria that can negatively impact study criteria according to Cochrane guidelines (Higgins & Green, 2009): (a) sham method – the method used for sham tDCS and rTMS; (b) randomization – whether randomization was performed; (c) blinding – whether subjects and investigators were blinded to the allocation group; (d) for crossover designs (carry over bias) – the time period between sessions; (e) sample selection – which instruments were used to enroll healthy volunteers and patients; (f) methodology used for the n-back task procedure.

2.4 Data extraction

From each article, we extracted data regarding sample characteristics, study design, characteristics of the brain stimulation technique and of the n-back task. For the primary outcomes we extracted the following data: (a) RT and standard deviation

(SD) of RT; (b) percentage of correct responses and the corresponding SD and; (c) percentage of errors and the corresponding SD.

2.5 Quantitative analysis

All analyses were performed using Stata software version 12 (Statacorp, TX, USA). For each outcome we calculated the standardized mean difference and the pooled standard deviation for each comparison. We used Hedges' *g* as the measure of effect size. Hedges' *g* is a variation of Cohen's *d* that corrects for biases associated with small sample sizes (Hedges & Olkin, 1985) and can be interpreted in the same way as the standard Cohen's *d* i.e., values of 0.2, 0.5 and 0.8 respectively represent small, medium and large effect sizes (Cohen, 1988). The pooled effect size, weighted by the inverse variance method, was measured using a random-effects model.

For each outcome we assessed heterogeneity with the Chi-square test. Risk of publication bias was assessed through the Begg's funnel plot and Egger's test (1997). Sensitivity analysis and meta-regression were also used to assess heterogeneity. The former assesses the influence of each particular study in the net results by calculating the resulting effect size after the exclusion of that study; the latter is used to identify moderators of our results. The following variables were meta-regressed: type of stimulation (tDCS or rTMS); gender (% females); study design (parallel or crossover); test difficulty (number of letters in the n-back task –dichotomized in low [$n \leq 1$] vs. high [$n \geq 2$] difficulty); clinical condition (healthy vs. psychiatric subjects). For tDCS studies, we meta-regressed for current density (i.e., current [A] divided by electrode size [m^2], dichotomized in low [density=0.28 A/m^2] vs. high [density$\geq$0.57A/m^2]) and electrode position (anode at F3 vs. other positions). For rTMS studies, we performed no meta-regressions since all studies used high-frequency rTMS and coil position differed from F3 in one study only (Esslinger et al., 2012). We meta-regressed only one variable at a time.

Finally, we performed separated meta-analyses considering the experiments not doing the 0-back task (i.e., those using the 1-, 2- and 3-back task) as to explore the influence of NIBS in tasks that assess WM load.

3. Results

3.1 Overview

Our search criteria yielded 231 references in PubMed/Medline database. Of those, 183 references were excluded after title/abstract review because they were: (a) non-controlled trials; (b) trials that assessed working memory using other techniques than n-back task; (c) studies using other methods of brain stimulation; (d) editorials, letters to the editor and review articles; (e) studies in animals; (f) other reasons. We therefore examined the full-text of 48 articles, of those 36 were further excluded because they also did not match our eligibility criteria. For example, the study of Sandrini et al. (2012) was excluded because the parietal cortex was stimulated. Another four studies were not included because they had no sham group (Daskalakis et al., 2008; Imm et al., 2008; Mottaghy et al., 2002; Oliveri et al., 2001). Regarding the n-back task, Meiron et al. (2012) used a modified n-back version; Andrews et al. (2011) did not collect n-back data and Barr et al. (2011; 2013; 2009) studies also used a different n-back version. In sum, 12 studies were included in our review. However, most reported more than one experiment (for instance, brain stimulation in different intensities or in different samples) – in these cases, each one was considered a different dataset. Therefore, we examined data from 33 experiments – 19 (57.6%) of tDCS and 14 (42.4%) of rTMS (Supplementary Figure 1 and Table 1).

(Table 1)

3.2 Quality assessment

Quality assessment revealed that all studies used a random assignment for allocating patients to the different stimulation conditions. For tDCS, all experiments except one were crossover and for rTMS all studies except one were parallel (Table 2). All crossover studies employed counterbalanced designs, except for the rTMS study (Esslinger et al., 2012) in which the order of stimulation session was randomized.

Regarding sham procedures, sham tDCS was performed using a procedure in which the electric current was turned off shortly after stimulation onset, although this short period ranged from 5 (Fregni et al., 2005) to 60 (Oliveira et al., 2013)seconds. One tDCS study (Berryhill & Jones, 2012) performed 20 seconds of electric current at

the start and at the end of the sham stimulation period in order to mimic the tingling associated with the current change. The sham rTMS procedure was more heterogeneous. One study used a sham procedure using the same stimulation parameters as the real stimulation, although with the coil held in a single wing-tilt position at 90 degrees(Barr et al., 2013), or with the coil positioned 5 cm latero-caudal to F3 and with one wing angled 45 degrees away from the skull (Guse et al., 2013). Two rTMS studies used a sham coil (Esslinger et al., 2012; Gaudeau-Bosma et al., 2012).

Regarding blinding, half of the studies were double-blinded (Barr et al., 2013; Gaudeau-Bosma et al., 2012; Guse et al., 2013; Keeser et al., 2013; Oliveira et al., 2013; Teo et al., 2011) and the other half were double single-blinded, i.e., the subject and the evaluator were blinded to the allocation group, but not the person applying the stimulation. The time period between stimulation conditions ranged from at least one hour (Fregni et al., 2005) to more than one week (Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011).

Most studies reported no adverse or side effects of the stimulation. Two studies reported that a minority of their participants did not complete the study and withdrew because of side effects such as treatment intolerance (Barr et al., 2013) and headache (Mylius et al., 2012). Data of these participants were not analyzed. In addition, Gaudeau-Bosma et al. (2012) also reported one case of post-rTMS headache although the subject completed the experiment, and data was included in the analyzes. All studies analyzed only data of completers since, as mentioned, attrition was minimal.

Most studies included only right-handed subjects, except for some studies that tested a clinical sample (Boggio et al., 2005; Oliveira et al., 2013) and Teo et al. (2011) who included two (of 12) left handed healthy volunteers. Other exclusion criteria were more diverse, but were in general in accordance with the existing safety guidelines of tDCS (Nitsche et al., 2008) and rTMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

Clinical samples of the included studies were either not taking psychiatric drugs (e.g.(Boggio et al., 2006) and (Oliveira et al., 2013))or were on a stable dose (Barr et al., 2013; Guse et al., 2013). Psychiatric patients were screened using

standard questionnaires and/or psychiatric interviews. Only some studies reported that healthy volunteers were not on medication that could affect the central nervous system(Keeser et al., 2013; Mylius et al., 2012), but these subjects were, in most studies, screened to exclude a psychiatric diagnosis (Esslinger et al., 2012; Gaudeau-Bosma et al., 2012; Keeser et al., 2013; Teo et al., 2011). Importantly, tDCS studies enrolled more healthy volunteers and rTMS, more neuropsychiatric patients.

In summary, all studies used standard procedures for the methods of randomization, blinding and sham stimulation. Eligibility criteria were generally well specified and attrition was minimal. Therefore, the included studies can be considered of good quality. Notably, most rTMS studies used a parallel (between-subjects) design whereas almost all tDCS studies were crossover (within-subjects). This is further discussed.

(Table 2)

3.3 Main Results

3.3.1 Response times

Participants after active vs. sham non-invasive brain stimulation were significantly faster in responding accurately (random-effects Hedges' g = - 0.220, 95% CI -0.362 to -0.078; heterogeneity not significant [I^2=0%, p=0.99]) (Figure 1). Further, Egger's test was not significant and the Begg's funnel plot displayed that all studies were symmetrically distributed inside the boundaries of the plot (Supplementary Figure 2), both pointing in the same direction of low risk of publication bias. Finally, sensitivity analysis showed that no study significantly influenced the results, with the net effect size varying from -0.21 to -0.24 when the experiments of the study of Mylius et al. (2012)were respectively excluded.

(Figure 1)

3.3.2 Percentage of correct responses

Active vs. sham brain stimulation presented a higher percentage of correct responses (g=0.254, 95% CI 0.112 to 0.395, heterogeneity not significant [I^2=1%, p=0.45]) (Figure 2). We also found that the Egger's test was not significant. Further, the funnel plot revealed that all studies were inside the boundaries of the funnel and symmetrically distributed (Supplementary Figure 3) and no particular study substantially changed the net result according to sensitivity analysis, which ranged from 0.234 to 0.276 after excluding experiments of Boggio et al. (2006) and Mylius et al. (2012).

(Figure 2)

3.3.3 Percentage of error responses

We found a lower percentage of error responses in participants receiving active vs. sham brain stimulation (g=-0.287, 95% CI -0.146 to -0.427) (Figure 3). We also identified a non-significant between study heterogeneity (I^2=0%, p=0.83). Funnel plot visualization (Supplementary Figure 4) and sensitivity analysis revealed respectively that the risk of publication was low and that no study particularly influenced the net results, which ranged from --0.26 to -0.3 after excluding experiments of Gaudeau-Bosma et al. (2012) and Keeser et al (2013).

(Figure 3)

3.3.4 Meta-regression

We also ran univariate meta-regression analyses to identify possible variables associated with our results (Table 3). Although no variable was associated with the RT results, we identified that type of stimulation was associated with the effect size for correct responses and error responses – suggesting that only rTMS (but not tDCS) improved performance in these variables. Moreover, our results suggest that the factor "study design" was also associated with correct responses. This is important because

study design was unevenly distributed between groups – indeed, almost all tDCS trials except for Oliveira et al. (2013)used a crossover design whereas most rTMS designs were parallel. Therefore, we further meta-regressed both variables (type of stimulation and study design) simultaneously as to account for this unbalance. We found that, both for the percentage of correct and error responses, the two factors were not significant in the multivariate model (for correct responses: $\beta = 0.3$, $p=0.1$ and $\beta = 0.26$, $p=0.13$; for error responses: $\beta = -0.33$, $p=0.07$ and $\beta = -0.04$, $p=0.79$, for type of stimulation and study design, respectively). This suggests that the lack of effects of tDCS (vs. rTMS) in improving the percentage of correct and error responses could have been observed due to the crossover study design employed in most of these tDCS studies, as we discuss below.

For rate of correct responses, meta-regression also detected differential effects between healthy vs. clinical samples, with effect sizes of 0.14 (95%CI -0.01 to 0.3) and 0.25 (95%CI 0.11 to 0.39). In other words, when only considering healthy participants, the effect sizes of active stimulation on the percentage of correct responses was small and borderline significant, whereas for clinical samples (i.e., major depression, Parkinson's disease and schizophrenia) the effect sizes were medium and significant.

(Table 3)

3.3.5 Studies using higher WM load

Finally, we assessed only the experiments using the 1-, 2- and 3-back. We found significant effects for RT (random-effects Hedges's g = -0.22; 95%CI -0.06 to -0.39), rate of correct responses (g=0.26; 95%CI 0.08 to 0.44) and rate of error responses (g=-0.3, 95%CI -0.14 to -0.46). In other words, the NIBS effects on WM performance remained significant after the exclusion of the experiments using the 0-back version of the n-back task.

4. Discussion

In this first meta-analysis of WM neuromodulation using non-invasive brain stimulation; we enrolled 12 randomized, sham-controlled studies (33 experiments) using rTMS and tDCS over the DLPFC to determine the relationship between DLPFC stimulation and performance on the n-back task, which is a well-established index of WM. We demonstrated that participants receiving active rTMS, as compared to those receiving sham stimulation, were faster and more accurate (i.e., presented more correct responses and less error responses) in the n-back task; whereas those receiving active vs. sham tDCS were faster. When all the results are pooled together, we found that non-invasive brain stimulation of the dorsolateral prefrontal cortex induces WM improvement in both healthy and clinical samples. Quality assessment revealed that studies could be considered of good quality, since all of them used standard methods of randomization and blinding and overall adequately described the employed methodology. Funnel plot analyses also displayed that the risk of publication analyses was low, while sensitivity analyses found that the exclusion of no particular study modified the single-point estimates of our meta-analyses.

Meta-regression analyses found that participants receiving active tDCS were faster albeit not more accurate, in contrast to rTMS. The meta-regression also showed that studies using crossover (within-subjects) vs. parallel (between-subjects) designs presented no improvement in accuracy. Because all tDCS studies, except one (Oliveira et al., 2013), used a crossover design, it is possible that the lack of tDCS effects and the type of study design are associated. Hypothetically, performing the same experiment at multiple timepoints could have increased accuracy due to learning effects of task repetition. However, other reasons might explain why tDCS and rTMS presented different effects in WM accuracy:

1) first; it is not possible to assess whether the “doses” used for rTMS and tDCS were comparable, for instance, whether “doses” of 1mA anodal tDCS and 10Hz rTMS are similar in terms of neurobiological effects;

2) second; although all includes studies targeted the DLPFC; rTMS has greater spatial precision than tDCS and therefore rTMS could have been more focused in this brain area (Dayan et al., 2013).

3) third; tDCS studies enrolled more healthy volunteers and rTMS enrolled more neuropsychiatric patients, and we observed that the effects of brain stimulation

on correct responses were larger in patients. In fact, brain stimulation effects are state-dependent of the initial neuronal activation state (Silvanto, Muggleton, & Walsh, 2008). For instance, the effects of online TMS on behavior can turn from inhibitory to facilitatory whether the targeted brain area had been initially suppressed (Silvanto, Cattaneo, et al., 2008). It is reasonable to assume that the cortical activity of healthy vs. neuropsychiatric patients assessed in our study are different in many aspects, such as the clinical conditions assessed being associated with hypodopaminergic states (Stahl, 2009) and major depression and schizophrenia with inhibitory deficits as well (Radhu et al., 2013).

Importantly, our review focused on the off-line rTMS effects on WM – experiments that, in fact, evaluate the after-effects of brain stimulation on WM. On-line rTMS paradigms usually show worsening of cognitive performance due to disruption of cortical activity (Sandrini et al., 2011); although several exemptions exist, for instance, accordingly to state-dependent activity (as exemplified above in (Silvanto, Cattaneo, et al., 2008)), or when TMS is delivered early in the time course of the trial, before the brain region was supposed to be activated (Grosbras & Paus, 2003).

Our findings have clinical and research implications. First, we suggest that non-invasive brain stimulation over the prefrontal cortex, particularly rTMS, is associated with WM improvement. Therefore, non-invasive brain stimulation techniques seem to be useful techniques to assess the functional, causal, role of the prefrontal cortex in cognitive functioning. Second, non-invasive brain stimulation techniques presented superior improvement in clinical populations, which pose such techniques as interesting tools to be further investigated in clinical samples. Interestingly, several studies have shown that non-invasive brain stimulation is associated with cognition improvement in healthy samples, although such improvement has not been sufficiently investigated in neuropsychiatric patients (Burt, Lisanby, & Sackeim, 2002; Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2012; Utz, Dimova, Oppenlander, & Kerkhoff, 2010). Moreover, WM is becoming increasingly considered as a fundamental target for therapeutical interventions, and the causal enhancement of WM via neurostimulation might be important information for achieving optimal treatment outcomes. Finally, we observed differential effects for rTMS vs. tDCS. Although this was probably

associated with the crossover designs used for tDCS vs. parallel designs for rTMS, it is still unclear whether the effects of tDCS and rTMS on cognition are different. Future studies comparing these two neuromodulatory techniques and/or more tDCS parallel-design studies for WM are needed to assess whether tDCS provides improvement in RT only or also in accuracy as observed for rTMS.

5. Conclusion

In this systematic review and meta-analysis we found that active vs. sham rTMS over the prefrontal cortex was associated with a significant improvement in working memory as indexed by the n-back, with a medium effect size in terms of RT, correct responses and error responses; whereas tDCS was associated with a significant improvement for RT only. Although the risk of publication bias was low and sensitivity analyses revealed that no particular study influenced the results, meta-regression findings suggested that the effects might be more prominent for rTMS than tDCS. However, it is also possible that this was an artifact due to study design, since almost all tDCS studies were crossover, which might have induced learning effects and increased the accuracy in the sham group. Our results provide further evidence that these neuromodulatory tools can be used to assess and explore cognition and also that patients with neuropsychiatric disorders could particularly benefit from such gains in cognition.

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Figure Captions

Figure 1. Forest plot showing effect sizes from the comparison between active vs. sham non-invasive brain stimulation in terms of response time.

Figure 2. Forest plot showing effect sizes from the comparison between active vs. sham non-invasive brain stimulation in terms of percentage of correct responses.

Figure 3. Forest plot showing effect sizes from the comparison between active vs. sham non-invasive brain stimulation in terms of percentage of error responses.

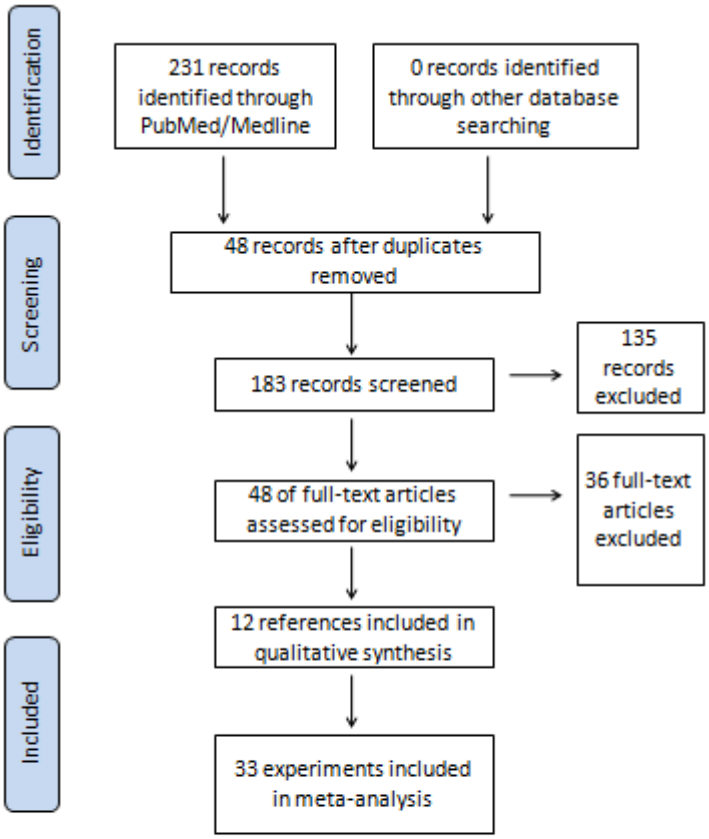
Figure captions : supplement material

Supplementary Figure 1. Flow chart used in our review to identify and include relevant studies.

Supplementary Figure 2. Funnel plot for RT.

Supplementary Figure 3. Funnel plot for percentage of correct responses.

Supplementary Figure 4. Funnel plot for percentage of error responses.


Identification
Screening
Eligibility
Included
231 records identified through PubMed/Medline
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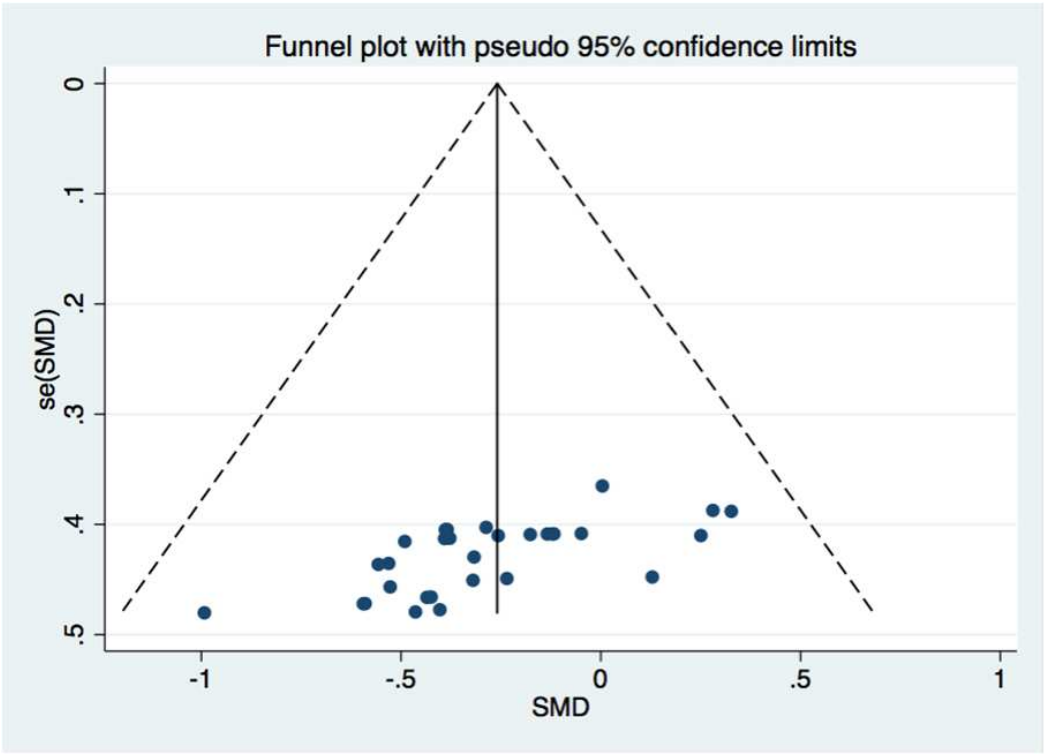
36 full-text articles excluded
12 references included in qualitative synthesis
33 experiments included in meta-analysis

Figure 1



Supp Figure 1

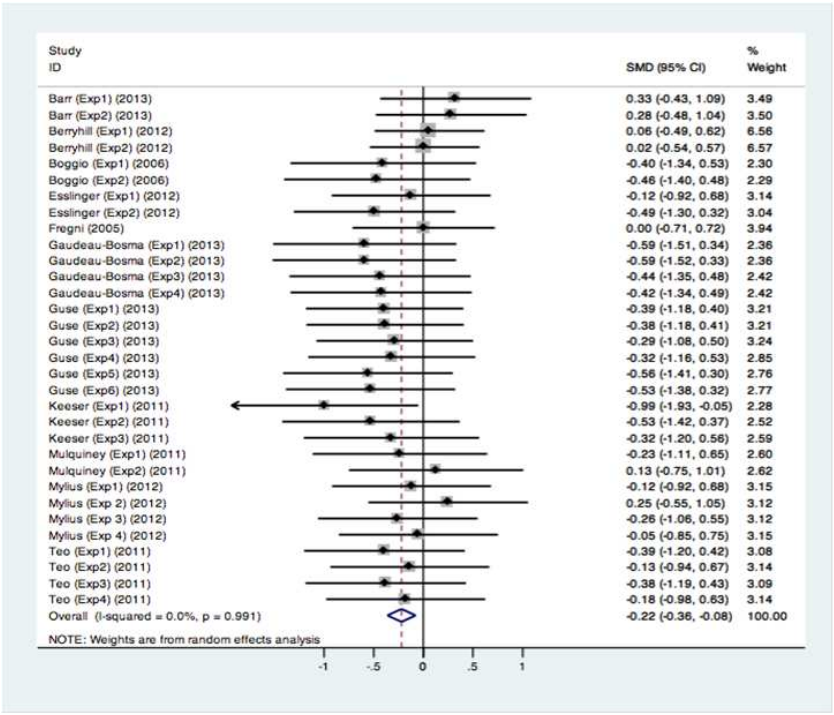
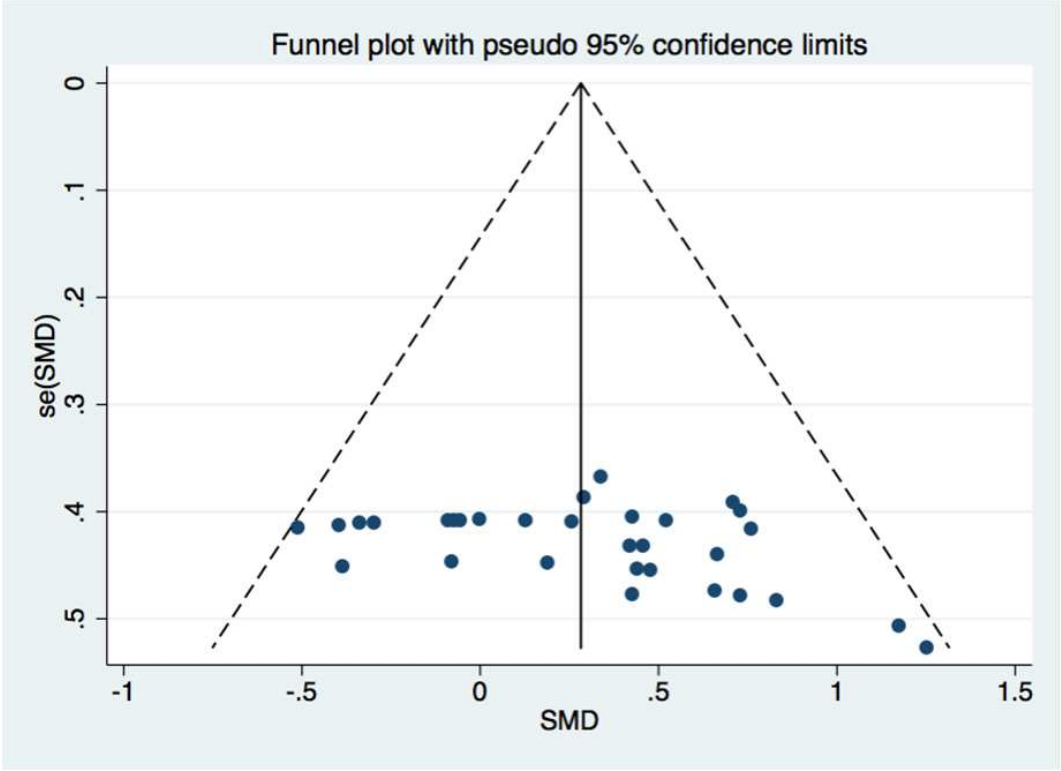
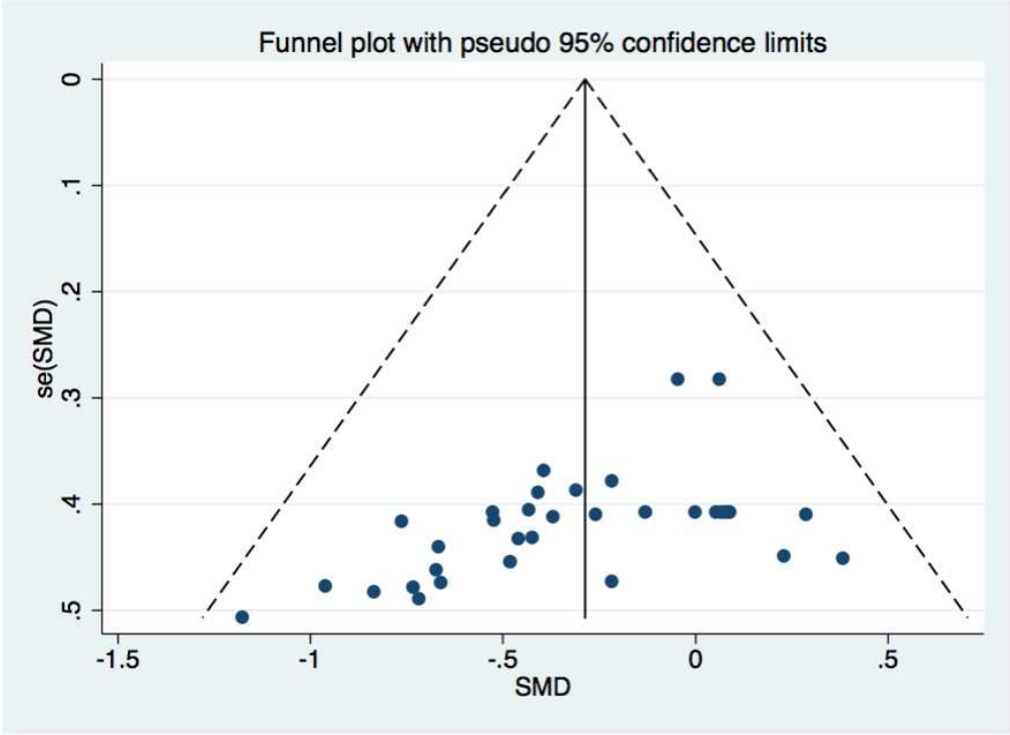

Study
ID
SMD (95% CI)
% Weight
Barr (Exp1) (2013) 0.33 (-0.43, 1.09) 3.49
Barr (Exp2) (2013) 0.28 (-0.48, 1.04) 3.50
Berryhill (Exp1) (2012) 0.06 (-0.49, 0.62) 6.56
Berryhill (Exp2) (2012) 0.02 (-0.54, 0.57) 6.57
Boggio (Exp1) (2006) -0.40 (-1.34, 0.53) 2.30
Boggio (Exp2) (2006) -0.46 (-1.40, 0.48) 2.29
Esslinger (Exp1) (2012) -0.12 (-0.92, 0.68) 3.14
Esslinger (Exp2) (2012) -0.49 (-1.30, 0.32) 3.04
Fregni (2005) 0.00 (-0.71, 0.72) 3.94
Gaudeau-Bosma (Exp1) (2013) -0.59 (-1.51, 0.34) 2.36
Gaudeau-Bosma (Exp2) (2013) -0.59 (-1.52, 0.33) 2.36
Gaudeau-Bosma (Exp3) (2013) -0.44 (-1.35, 0.48) 2.42
Gaudeau-Bosma (Exp4) (2013) -0.42 (-1.34, 0.49) 2.42
Guse (Exp1) (2013) -0.39 (-1.18, 0.40) 3.21
Guse (Exp2) (2013) -0.38 (-1.18, 0.41) 3.21
Guse (Exp3) (2013) -0.29 (-1.08, 0.50) 3.24
Guse (Exp4) (2013) -0.32 (-1.16, 0.53) 2.85
Guse (Exp5) (2013) -0.56 (-1.41, 0.30) 2.76
Guse (Exp6) (2013) -0.53 (-1.38, 0.32) 2.77
Keeser (Exp1) (2011) -0.99 (-1.93, -0.05) 2.28
Keeser (Exp2) (2011) -0.53 (-1.42, 0.37) 2.52
Keeser (Exp3) (2011) -0.32 (-1.20, 0.56) 2.59
Mulquiney (Exp1) (2011) -0.23 (-1.11, 0.65) 2.60
Mulquiney (Exp2) (2011) 0.13 (-0.75, 1.01) 2.62
Mylius (Exp1) (2012) -0.12 (-0.92, 0.68) 3.15
Mylius (Exp 2) (2012) 0.25 (-0.55, 1.05) 3.12
Mylius (Exp 3) (2012) -0.26 (-1.06, 0.55) 3.12
Mylius (Exp 4) (2012) -0.05 (-0.85, 0.75) 3.15
Teo (Exp1) (2011) -0.39 (-1.20, 0.42) 3.08
Teo (Exp2) (2011) -0.13 (-0.94, 0.67) 3.14
Teo (Exp3) (2011) -0.38 (-1.19, 0.43) 3.09
Teo (Exp4) (2011) -0.18 (-0.98, 0.63) 3.14
Overall (I-squared = 0.0%, p = 0.991) -0.22 (-0.36, -0.08) 100.00
NOTE: Weights are from random effects analysis
-1
-.5
0
.5
1

Figure 2



Supp 1 Figure 2



Supp 2 Figure 2

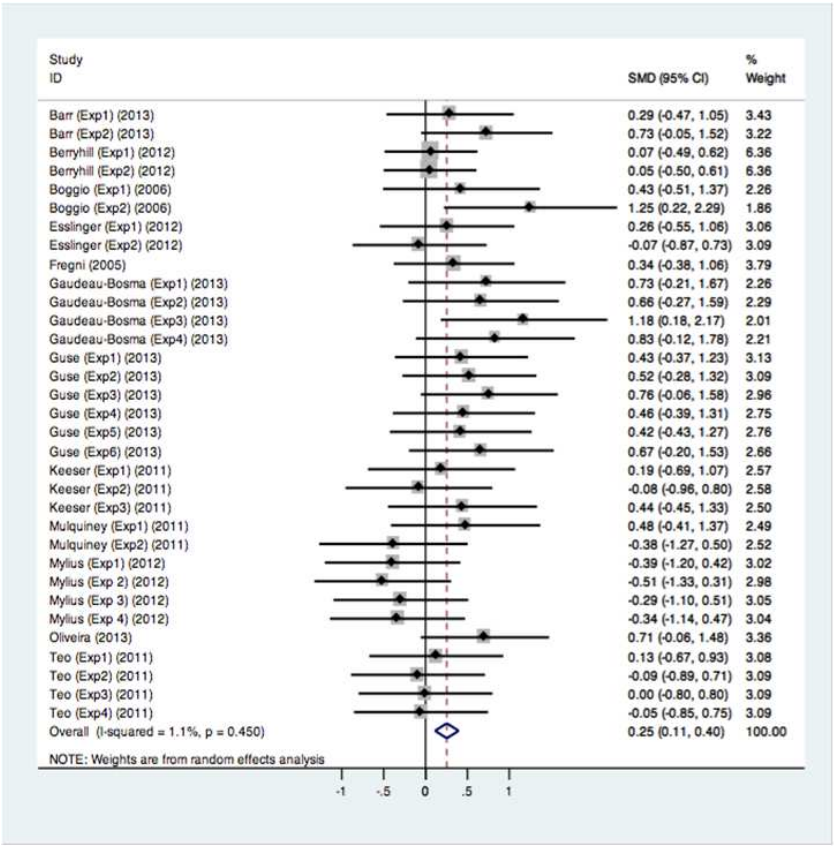

Study ID
SMD (95% CI)
% Weight
Barr (Exp1) (2013) 0.29 (-0.47, 1.05) 3.43
Barr (Exp2) (2013) 0.73 (-0.05, 1.52) 3.22
Berryhill (Exp1) (2012) 0.07 (-0.49, 0.62) 6.36
Berryhill (Exp2) (2012) 0.05 (-0.50, 0.61) 6.36
Boggio (Exp1) (2006) 0.43 (-0.51, 1.37) 2.26
Boggio (Exp2) (2006) 1.25 (0.22, 2.29) 1.86
Esslinger (Exp1) (2012) 0.26 (-0.55, 1.06) 3.06
Esslinger (Exp2) (2012) -0.07 (-0.87, 0.73) 3.09
Fregni (2005) 0.34 (-0.38, 1.06) 3.79
Gaudeau-Bosma (Exp1) (2013) 0.73 (-0.21, 1.67) 2.26
Gaudeau-Bosma (Exp2) (2013) 0.66 (-0.27, 1.59) 2.29
Gaudeau-Bosma (Exp3) (2013) 1.18 (0.18, 2.17) 2.01
Gaudeau-Bosma (Exp4) (2013) 0.83 (-0.12, 1.78) 2.21
Guse (Exp1) (2013) 0.43 (-0.37, 1.23) 3.13
Guse (Exp2) (2013) 0.52 (-0.28, 1.32) 3.09
Guse (Exp3) (2013) 0.76 (-0.06, 1.58) 2.96
Guse (Exp4) (2013) 0.46 (-0.39, 1.31) 2.75
Guse (Exp5) (2013) 0.42 (-0.43, 1.27) 2.76
Guse (Exp6) (2013) 0.67 (-0.20, 1.53) 2.66
Keeser (Exp1) (2011) 0.19 (-0.69, 1.07) 2.57
Keeser (Exp2) (2011) -0.08 (-0.96, 0.80) 2.58
Keeser (Exp3) (2011) 0.44 (-0.45, 1.33) 2.50
Mulquiney (Exp1) (2011) 0.48 (-0.41, 1.37) 2.49
Mulquiney (Exp2) (2011) -0.38 (-1.27, 0.50) 2.52
Mylius (Exp1) (2012) -0.39 (-1.20, 0.42) 3.02
Mylius (Exp 2) (2012) -0.51 (-1.33, 0.31) 2.98
Mylius (Exp 3) (2012) -0.29 (-1.10, 0.51) 3.05
Mylius (Exp 4) (2012) -0.34 (-1.14, 0.47) 3.04
Oliveira (2013) 0.71 (-0.06, 1.48) 3.36
Teo (Exp1) (2011) 0.13 (-0.67, 0.93) 3.08
Teo (Exp2) (2011) -0.09 (-0.89, 0.71) 3.09
Teo (Exp3) (2011) 0.00 (-0.80, 0.80) 3.09
Teo (Exp4) (2011) -0.05 (-0.85, 0.75) 3.09
Overall (I-squared = 1.1%, p = 0.450) 0.25 (0.11, 0.40) 100.00
NOTE: Weights are from random effects analysis
-1
-.5
0
.5
1

Figure 3