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Title page

Does transcranial electrical stimulation enhance corticospinal excitability of the motor cortex in healthy individuals? A systematic review and meta-analysis

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Abstract

Numerous studies have explored the effects of transcranial electrical stimulation (tES) – including anodal transcranial direct current stimulation (a-tDCS), cathodal transcranial direct current stimulation (c-tDCS), transcranial alternative current stimulation (tACS), transcranial random noise stimulation (tRNS) and transcranial pulsed current stimulation (tPCS) – on corticospinal excitability (CSE) in healthy populations. However, the efficacy of these techniques and their optimal parameters for producing robust results have not been studied. Thus, the aim of this systematic review was to consolidate current knowledge about the effects of various parameters of a-tDCS, c-tDCS, tACS, tRNS and tPCS on the CSE of the primary motor cortex (M1) in healthy people. Leading electronic databases were searched for relevant studies published between January 1990 and February 2017; 126 articles were identified, and their results extracted and analysed using RevMan software. The meta-analysis showed that a-tDCS application on the dominant side significantly increases CSE ($P < 0.01$), and that the efficacy of a-tDCS is dependent on current density and duration of

application. Similar results were obtained for stimulation of M1 on the non-dominant side ($P = 0.003$). The effects of a-tDCS reduce significantly after 24 hours ($P = 0.006$). Meta-analysis also revealed significant reduction in CSE following c-tDCS ($P < 0.001$) and significant increases after tRNS ($P = 0.03$) and tPCS ($P = 0.01$). However, tACS effects on CSE were only significant when the stimulation frequency was $\geq 140\text{Hz}$. The present review provides evidence that tES has substantial effects on CSE in healthy individuals for a range of stimulus parameters.

Introduction

Transcranial electrical stimulation (tES) is an umbrella term for a series of non-invasive, painless and safe neuromodulatory techniques. These techniques involve a weak current (1-2 mA) applied via two or more electrodes on the outside of the scalp (Krause and Cohen, 2013) that modulate transmembrane neuronal potentials of cortical brain areas, leading to changes in neuronal excitability (Chib et al., 2013). It has also been suggested that tES modifies synaptic transmission via glutamatergic and GABAergic activities (Stagg and Nitsche, 2011; Mondino et al., 2014). Several methods of tES have been described, including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS) and transcranial pulsed current stimulation (tPCS). Of these methods, tDCS is the most widely reported technique. tDCS modulates cortical excitability; cathodal stimulation (c-tDCS) is assumed to hyperpolarise neuronal membranes and decrease neuronal functions, while anodal stimulation (a-tDCS) causes neuronal depolarization and increases brain function (M. A. Nitsche and Paulus, 2000; Batsikadze et al., 2013; Moliadze et al., 2015). tDCS affects brain functions due to the static effects of the induced current (Jaberzadeh et al., 2015).

In contrast to tDCS, tACS is a tES technique that aims to interfere with ongoing oscillation in the brain by stimulating at a fixed frequency (e.g. 10Hz). In this method, a constantly alternating low-intensity current alternates the anode and cathode designations of electrodes to produce net zero voltage or current, meaning the effects of tACS are based on the dynamic effects of the applied current (Zaghi et al., 2010; Jaberzadeh et al., 2015). tRNS, on the other

hand, is a method that applies alternating current stimulation with random amplitude (Antal and Paulus, 2013). It has been shown that the tRNS technique produces a significant increase in corticospinal excitability (CSE) which is measured by peak-to-peak amplitude of single-pulsed transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEPs) (Terney et al., 2008; Moliadze et al., 2012; Batsikadze et al., 2013). The advantages of tRNS over tDCS include lower probability of skin sensation, and modulation of two brain regions concurrently without the inhibitory cathodal effect at the second electrode (Ambrus et al., 2011; Krause and Cohen, 2013).

Finally, tPCS is a novel neuromodulatory paradigm that involves unidirectional flow of positive pulses separated by a predetermined inter-pulse interval (IPI) (Jaberzadeh et al., 2015; Morales-Quezada et al., 2015). Thus, it induces both static and dynamic current components. Compared to other paradigms, tPCS produces different degrees of net direct current component (NDCC), depending upon the pulse duration (PD), amplitude of pulses and IPI (Jaberzadeh et al., 2014). For instance, shorter IPIs and longer PDs induce larger increases in CSE, and result in longer after-effects (Jaberzadeh et al., 2014; Jaberzadeh et al., 2015). Despite these observations, the effects of tPCS on CSE have received minimal attention and remain poorly understood.

To date, the ability of tES techniques to modulate CSE have been explored in numerous studies, though with mixed results (Antal et al., 2008; Terney et al., 2008; Chaieb et al., 2011a; Chaieb et al., 2011b; Jaberzadeh et al., 2014; Jaberzadeh et al., 2015; Vaseghi et al., 2015; Labruna et al., 2016). A systematic review and meta-analysis concluded that a-tDCS has a significant effect (0.31 [95% CI 0.14, 0.48], $p = 0.0003$) on CSE (Bastani and Jaberzadeh, 2012); however, the analysis was confined to data from only 14 studies using current intensities of 1 mA or more. Horvath et al.'s (2015) recent review of a-tDCS did not consider physiological/anatomical factors (dominant vs non-dominant side) or protocol parameters (current intensity, duration, electrode size); they pooled the findings of pharmacological studies on tDCS (a-tDCS and c-tDCS) with those of non-pharmacological studies. Consequently, the optimal CSE stimulation parameters of a-tDCS have not been established. Many studies of tDCS have been published in recent years, but no study has provided a comprehensive meta-analytic review of the literature. Moreover, previous systematic reviews did not evaluate the effects of c-tDCS, tACS, tRNS and tPCS over the primary motor cortex (M1) on CSE, making accurate judgement of the effects of these techniques on CSE extremely challenging. A carefully constructed systematic review and

meta-analysis, using properly estimated inclusion criteria, is required to assess the effect of tES over the M1 on CSE.

The primary aim of this review was to synthesize and critically evaluate the literature on the efficacy of a-tDCS over M1 and its parameters as a method to change CSE in healthy individuals. As the effects of c-tDCS, tACS, tRNS and tPCS on CSE are unclear, the secondary aim of this review was to investigate whether c-tDCS, tACS, tRNS and tPCS change CSE in healthy individuals, and if the methods' stimulation parameters are related to putative effects on CSE.

Methods

Protocol registration

The protocol for this systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Registration number: CRD42016036921).

Methods for identifying studies

Electronic databases (PubMed, AMED, CINAHL, Embase, CENTRAL (Cochrane Central Registered of Control Trials), Scopus, Science Direct, Ovid Medline and EBM reviews) were searched for article published from January 1990 to 13th February 2017 (see Supplementary Material for detailed search strategy (S1)). The search was conducted in each database using the following terms: “transcranial direct current stimulation” OR “tDCS” OR “anodal transcranial direct current stimulation” OR “a-tDCS” OR “cathodal transcranial direct current stimulation” OR “c-tDCS” OR “cranial direct current stimulation” OR “transcranial alternating current stimulation” OR “tACS” OR “transcranial random noise stimulation” OR “tRNS” OR “transcranial pulsed current stimulation” OR “tPCS” AND “transcranial magnetic stimulation” OR “magnetic stimulation” OR “TMS” AND “cortical plasticity” OR “cortical reorganization” OR “cortical excitability” OR “corticospinal excitability” OR “CSE”. These terms were used in various combinations. The reference lists of retrieved papers were searched for relevant publications not identified in the initial search.

Outcome measures

The intervention of interest was the use of tES (a-tDCS, c-tDCS, tACS, tRNS, tPCS) over M1 to increase CSE of M1 in healthy individuals, with TMS-induced peak-to-peak MEPs amplitude as the primary outcome.

Selection criteria

Each search was restricted using the inclusion and exclusion criteria listed below. Inclusion criteria: 1) application of a-tDCS or c-tDCS or tACS or tRNS or tPCS in healthy individuals; 2) participants aged over 18 years; 3) using peak-to-peak TMS-induced MEPs amplitude as an outcome measure; 4) active electrode over right or left M1 region; 5) pre-post or randomized controlled trial (RCT) study designs; and 6) availability of the full text in English. Studies with non-human samples were excluded.

The titles of the articles were initially screened by one reviewer (TDD). Determining the eligibility of the studies was undertaken independently by two reviewers (SJ and TDD) who assessed abstracts against the inclusion and exclusion criteria, and relevant articles were then retrieved for evaluation of the full texts.

Risk of bias

The risk of bias and the methodological quality of the included studies were assessed based on an adaptation of the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2008). The tool provided in the RevMan software package was used to assess the risk of bias (Deeks and Higgins, 2010). Possible publication bias was assessed using funnel plots (Sterne et al., 2001).

The quality of the included RCTs was further assessed using the PEDro scale (Moseley et al., 2002; Maher et al., 2003). The Downs and Black tool (D & B) (Downs and Black, 1998) was used for the non-RCTs.

Data extraction

A data extraction sheet was developed for details of the study design, intervention, stimulus parameters and outcome measures (mean $\pm$ standard deviation (SD)) at baseline, immediately after intervention and after two or more hours of dominant M1 stimulation. Corresponding data were gathered for non-dominant M1 stimulation. When the mean $\pm$ SD was reported graphically rather than numerically (110 of 126 studies), values were estimated from the graphs using Plot digitizer software (Joseph, 2010). This Java-based software converts the plotted values into a numerical format in a highly reliable way (Jelicic Kadic et al., 2016) and has been employed in a large number of other meta-analytical studies (Bastani and Jaberzadeh, 2012; Bulter et al., 2013; Vaseghi et al., 2015; Chung et al., 2016; Hill et al., 2016; Pisegna et al., 2016). When the standard error (SE) was reported, the SD was estimated

using the formula $SD=SE\sqrt{n}$ (n = number of subjects in each group) (Higgins and Green, 2008). If numerical data was not reported and could not be extracted from graphs, a request for information was sent to the corresponding author via email. If the data were not subsequently provided by the authors, normalized data of mean at baseline and immediately after intervention were extracted. In those studies that collected data in more than one experimental condition (different stimulation intensities, stimulation durations and electrode sizes), each experimental condition was treated as a unique dataset. Table 1 summarizes the characteristics of the studies included in this review.

Insert Table 1 near here

Meta-analysis

RevMan 5 software (version 5.2) was used to calculate the effect size (Deeks and Higgins, 2010). The weighted mean difference (WMD) or standard mean difference (SMD) was used to measure the effect size. The WMD was employed when outcome measures in all trials were measured on the same scale, and SMD was used when different outcome measures were used in different trials to measure a comparable outcome. The particular formulation of the SMD implemented by the RevMan package is Hedge's adjusted g , which is similar to Cohen's d , but includes an adjustment for small sample bias (Deeks and Higgins, 2010). Effect sizes can be interpreted as small (0.2), medium (0.5) or large (0.8) using the convention suggested by Cohen et al. (1988).

Test of heterogeneity

Heterogeneity was quantified using the I^2 statistic, which can range from 0% to 100%, where 0% denotes no heterogeneity; values between 30% and 60% indicate moderate heterogeneity, while values between 75% and 100% denote high levels of heterogeneity (Higgins and Green, 2008). In the absence of heterogeneity among studies, results were pooled in the meta-analysis using a fixed effects model. If the I^2 statistic was 30% or greater heterogeneity was considered to be substantial or high, and meta-analysis was performed using a random effects model.

Results

Description of studies

The literature search identified 397 articles; after removing duplicates, the number was reduced to 182. Screening by title and abstract identified 130 studies as potential inclusions for the review. After excluding four full-text articles due to incompatibility with inclusion criteria, 126 studies were included in the systematic review and meta-analysis, of which 73 were a-tDCS studies, 39 c-tDCS studies, five tACS studies, seven tRNS studies and the remaining two tPCS studies (Fig.1).

Insert Figure 1 near here

Risk of bias and quality assessment

Risk of bias varied among studies for all assessment criteria. None of the studies had a high risk of bias across all criteria (Fig.2). Potential publication bias was explored by plotting effect sizes against variance; the absence of publication bias is indicated by the plot's resemblance to an inverted funnel, symmetrical around the mean effect size (Egger et al., 1997), as illustrated in Fig. 3B, C and D. In the present review, some evidence (Fig.3 A and E) of asymmetry was seen in the funnel plot of effects related to a-tDCS and tPCS, suggesting potential publication bias.

Insert Figures 2 and 3 near here

PEDro scores of included studies ranged between five and 10, indicating good-quality RCTs. Likewise, the 27-item D&B quality checklist provided medium-quality scores for pre-post studies, ranging between 14 and 19.

Participants in the included studies

In a-tDCS and c-tDCS studies, sample sizes at study onsets ranged from five to 59 healthy individuals. The sample sizes ranged from eight to 12 for tACS studies and from 10 to 17 for tRNS studies. The tPCS studies recruited 23 healthy participants in total. All included studies recruited both men and women, except for three studies that recruited only men (Siebner et al., 2004; Alonzo et al., 2012; Galvez et al., 2013).

Electrode montage

Electrode montage is one of the key parameters of tES application. The weak current used in tES techniques flows from anode (positive electrode) to cathode (negative electrode).

Changes of electrode montage impose different CSE effects (Nitsche and Paulus, 2000). Sixty-seven a-tDCS studies and all of the c-tDCS, tACS, tRNS and tPCS studies used a similar electrode montage, with anode over the left M1 and cathode on the contralateral supraorbital area (for stimulation of the dominant side in right-handers). Four studies used the anode over the right M1 and the cathode on the contralateral supraorbital area (stimulation of non-dominant side). Another two studies used both montages (dominant and non-dominant side stimulation).

Duration of stimulation

The duration of stimulation varied significantly among studies. In all a-tDCS, c-tDCS and tPCS studies, the stimulation duration ranged between one and 20 minutes. Among tACS studies, four studies used stimulation duration of 10 min and one study applied tACS for 5 min. Likewise, in seven tRNS studies, the duration of stimulation was 10 min, whereas one study used 4–6 min stimulation.

Current dosage

Current intensity and the size of the active electrode are important parameters in tES applications. The intensity of current used in a-tDCS and c-tDCS studies ranged between 0.01 and 2 mA. Three of five tACS studies used an intensity of 1mA, while the other two studies had intensities of 0.4 mA and 0.2–1 mA. All of the tRNS studies applied current intensity between 0.2mA and 2 mA, while the two tPCS studies used 1.5 mA.

Current density (current intensity divided by electrode size) plays an important role in the safety of tES applications (Brunoni et al., 2012). Electrode size varied widely among studies. Sizes of active electrodes and current densities in tES studies varied from 3 to 35 cm² and 0.0002 to 0.125 mA/cm² respectively. The highest current density was applied through 16 cm² electrodes with an intensity of 2 mA (Moliadze et al., 2010a; Chew et al., 2015), whereas the lowest current densities involved a 35 cm² active electrode and 0.01 mA intensity (Nitsche et al., 2007).

Stimulation frequency in tACS and tRNS

Among the tACS studies, four used frequencies of at least 140Hz, and two applied frequencies of less than 140Hz (Antal et al., 2008; Moliadze et al., 2010b). All the tRNS studies applied high-frequency current ranging between 101 and 640 Hz.

Analysis of normalized data

Table 2 and Table 3 summarise the outcomes of quantitative analysis of normalized data from a-tDCS and c-tDCS studies using Microsoft Excel 2013. The mean increase in CSE with a-tDCS was 28% and the mean decrease with c-tDCS was 20%. In addition, calculation of means of normalized data showed enhancement of CSE after a-tDCS and decrease of CSE with c-tDCS in the placebo arm (Table 4 and Table 5).

Insert Table 2 and Table 3 near here

Insert Table 4 and Table 5 near here

Pooled data analysis

Effects of a-tDCS over M1 on CSE

Effect of a-tDCS and its parameters on CSE

The combined results showed a-tDCS had a significant effect (SMD 0.67, 95% CI 0.49 to 0.86, $P < 0.001$), with high heterogeneity ($I^2 = 75\%$, $P < 0.001$), on CSE in healthy cohorts (Fig. 4).

Seven studies provided data on a-tDCS in their placebo arms (Nitsche et al., 2003; Nitsche et al., 2004; Nitsche et al., 2006; Grundey et al., 2012a; Batsikadze et al., 2015; Lugon et al., 2015; Kuo et al., 2016). Pooled data from these studies showed a significant effect on CSE (SMD 0.31, 95% CI 0.19 to 0.42, $P < 0.00001$), and non-significant heterogeneity ($I^2 = 2\%$, $P = 0.42$) (Fig. 5).

Insert Figure 4 and Figure 5 near here

Duration and intensity of current

Overall, 38 articles provided adequate data for analyses based on stimulus parameters (Fig. 6A – see Supplementary Fig. S2 for accompanying forest plot). The two data levels that applied a-tDCS with less than 1 mA intensity and less than 10 min duration measured non-significant effects on CSE (SMD 0.46, 95% CI -0.94 to 1.86, $P = 0.52$). However, the

heterogeneity remained significantly high ($I^2 = 82\%$, $P = 0.02$). Studies involving stimulus durations < 10 min and intensities ≥ 1 mA demonstrated a significant mean effect on CSE (SMD 0.60, 95% CI 0.34 to 0.87, $P < 0.001$), with no heterogeneity ($I^2 = 0\%$, $P = 0.46$).

Separating studies that delivered a-tDCS for ≥ 10 min with intensity < 1 mA ($I^2 = 84\%$, $P < 0.00001$) from those that delivered a-tDCS for ≥ 10 min with intensity ≥ 1 mA ($I^2 = 77\%$, $P < 0.00001$) did not affect heterogeneity substantially. Studies in both of these categories found significant effects on CSE ($P = 0.005$ and $P < 0.001$ respectively).

Duration and density of current

By restricting the analysis to the subcategory of ≥ 10 min duration and ≥ 0.029 mA/cm² density, the effect on CSE remained significant ($P < 0.001$) with high heterogeneity ($I^2 = 79\%$, $P < 0.0001$) (Fig. 6B— see Supplementary Fig. S3 for accompanying forest plot). For studies in the subcategory of ≥ 10 min duration and < 0.029 mA/cm² density, heterogeneity was substantial ($I^2 = 57\%$, $P = 0.05$), and the pooled effect was not significant (SMD 0.47, 95% CI -0.02 to 0.96, $P = 0.06$). Two datasets were pooled into the category of < 10 min and < 0.029 mA/cm², and analysis revealed a non-significant effect on CSE (SMD 0.46, 95% CI -0.94 to 1.86, $P = 0.52$). The studies in the subcategory of < 10 min duration and ≥ 0.029 mA/cm² density showed a significant effect on CSE (SMD 0.60, 95% CI 0.34 to 0.87, $P < 0.0001$) with no heterogeneity ($I^2 = 0\%$, $P = 0.46$).

Effects of non-dominant side M1 tDCS on CSE

Data from six studies were included in the analysis of tDCS effects (right M1 in right-handed individuals). Heterogeneity was high ($I^2 = 92\%$, $P < 0.001$), and a significant effect on CSE was observed (WMD 0.29, 95% CI 0.10 to 0.48, $P = 0.003$) (Fig.7).

Insert Figure 7 near here

After-effects of a-tDCS on CSE

Pooled after-effects of a-tDCS on CSE were non-significant (WMD -0.01, 95% CI -0.04 to 0.03, $P = 0.77$) with substantial heterogeneity ($I^2 = 77\%$, $P = 0.0002$). Restricting the analysis to studies of follow-up at “same day evening” demonstrated a non-significant effect on CSE

(WMD 0.01, 95% CI -0.03 to 0.06, $P = 0.56$) with high heterogeneity ($I^2 = 83\%$, $P = 0.0006$) (Fig. 8). Two studies of follow-up after 24 hours demonstrated a significant pooled effect – a significant reduction of CSE compared to baseline (WMD -0.05, 95% CI -0.08 to -0.01, $P = 0.006$) with non-significant heterogeneity ($I^2 = 6\%$, $P = 0.35$).

Insert Figure 8 near here

Effect of c-tDCS and its parameters on CSE

Fig. 9 summarizes the data from 22 studies. Pooled analysis revealed a significant decrease of CSE compared to baseline (SMD -0.59, 95% CI -0.78 to -0.39, $P < 0.001$) with substantial heterogeneity ($I^2 = 65\%$, $P < 0.001$).

Three studies that used c-tDCS in the placebo arm were pooled separately and showed a significant reduction of CSE compared to baseline (WMD -0.32, 95% CI -0.45 to -0.19, $P < 0.001$) with no heterogeneity ($I^2 = 65\%$, $P = 0.45$) (Fig. 10A- see Supplementary Fig.S4 for accompanying forest plot).

Duration and intensity of current

By restricting the analysis to the subcategory of ≤ 1 mA and ≤ 15 min of current, we demonstrated a significant mean effect on CSE (SMD -0.66, 95% CI -0.89 to -0.42, $P < 0.001$) with substantial heterogeneity ($I^2 = 68\%$, $P < 0.001$). For studies in the subcategory of > 1 mA and > 10 min of current, heterogeneity was zero ($I^2 = 0\%$, $P = 0.60$), and the pooled effect was not significant (SMD -0.19, 95% CI -0.59 to 0.21, $P = 0.35$) (Fig.10B-see Supplementary Fig, S5 for accompanying forest plot). Three datasets were pooled into the category of > 1 mA and ≤ 15 min and analysis revealed a significant effect on CSE (SMD -0.46, 95% CI -0.83 to -0.08, $P = 0.02$). The studies in the subcategory of ≤ 1 mA intensity and > 15 min duration of current showed a non-significant effect on CSE (SMD -0.65, 95% CI -2.93 to 1.49, $P = 0.55$) with high heterogeneity ($I^2 = 90\%$, $P = 0.002$).

Insert Figure 10 here

Effects of tACS, tRNS and tPCS on CSE

Effects of tACS on CSE

Data from four studies of tACS on CSE were pooled according to stimulation frequency, either ≥ 140 Hz or < 140 Hz (Fig. 11A). There was no significant heterogeneity ($I^2 = 0\%$, $P = 1.00$) and the pooled effect was statistically significant (SMD 0.44, 95% CI 0.19 to 0.69, $P = 0.0007$) for the frequency of ≥ 140 Hz but not for the frequency of < 140 Hz (SMD 0.02, 95% CI -0.34 to 0.39, $P = 0.90$, with no heterogeneity).

Effects of tRNS on CSE

Seven studies provided data on the effects of tRNS on CSE. Pooling of these studies, irrespective of their parameters, demonstrated a significant effect (SMD 0.31, 95% CI 0.10 to 0.51, $P = 0.003$) with non-significant heterogeneity ($I^2 = 0\%$, $P = 0.80$) (Fig. 11B).

Effects of tPCS on CSE

Fig. 11C summarizes the data from the two tPCS studies. Pooled analysis revealed a significant effect on CSE (SMD 0.90, 95% CI 0.26 to 1.55, $P = 0.006$) with substantial heterogeneity ($I^2 = 62\%$, $P = 0.03$).

Insert Figure 11A, B and C near here

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis providing a comprehensive evaluation of the effects of tES techniques, including a-tDCS, c-tDCS, tACS, tRNS and tPCS, on CSE in healthy individuals. The pooled analysis of tES techniques of a-tDCS, tACS, tRNS and tPCS separately revealed significant improvement in CSE following tES application. The effect of c-tDCS was a significant reduction in CSE. Importantly, the effects of stimulation parameters (duration, intensity and density) of a-tDCS and c-tDCS showed mixed results on CSE. In addition, the results showed a significant effect of a-tDCS on non-dominant M1, and also, in the placebo arm, on enhancement of CSE. The after-effects of a-tDCS on CSE were significantly reduced after 24 hours compared to the pre-stimulation state.

Potential bias

Publication bias

Five funnel plots were generated to examine the results of meta-analysis of a-tDCS, c-tDCS, tACS, tRNS and tPCS for evidence of publication bias. Funnel plots related to the effect of a-tDCS and tPCS were asymmetrical, indicating that studies with significant positive results are more likely to be published than studies lacking such results (Head et al., 2015). Since this publication bias influences the findings of this meta-analysis, caution should be taken when interpreting the results.

There are two types of publication bias: selection and inflation. Selection bias is also known as the file drawer effect, in which studies with non-significant results have lower publication rates. Simonsohn et al. (2014) highlighted that researchers may file only the subsets of analyses that produce non-significant results, rather than placing entire studies in the file drawer, which is referred to as inflation bias or p-hacking. Recently, John et al. (2012) showed that many researchers p-hack, but do not appreciate the extent to which this process is a form of scientific misconduct. Thus p-curve analysis can be used to assess whether the overall effect of the meta-analysis is due to p-hacking or true effect (Simonsohn et al. 2014). However, while the present study indicated a publication bias related to a-tDCS and tPCS, a p-curve analysis could not be applied to this literature because there was a lack of reported p values and test statistics in the original papers.

Other biases

Substantial variation exists between the included studies of tES in healthy individuals. This heterogeneity was reflected in the I^2 statistics for a-tDCS and tPCS. Heterogeneity would be due to the diversity of stimulation parameters used, the small numbers of included studies, variation in gender composition and range of ages of participants. In addition, several studies have allocated participants to more than one experiment (Lang et al., 2004a; Nitsche et al., 2005; Nitsche et al., 2007; Batsikadze et al., 2013; Bastani and Jaberzadeh, 2013; Horvath et al., 2016), which can increase the likelihood of enrichment of responders. One approach to minimize this risk is to identify participants who respond to the techniques and then randomize them to either an intervention or sham group in a double-blind fashion. Another strategy is to identify responders with an RCT and then enrol them into another RCT study of intervention vs sham (Straube et al., 2008). Thus, the results should be interpreted with these factors in mind.

a-tDCS and corticospinal excitability

The primary aims of this study were to investigate the effects of a-tDCS over M1 and its parameters on CSE. To date, one quantitative review (Bastani and Jaberzadeh, 2012) and one qualitative review (Horvath et al., 2015) have evaluated the effects of a-tDCS on CSE, the results of which are in line with the present review. Bastani and Jaberzadeh (2012) pooled data from studies exploring the effects of a-tDCS applied over the dominant side of M1 in healthy individuals, and reported a significant increase in CSE. In a recent qualitative review, Horvath et al. (2015) explored the effects of a-tDCS on CSE by reviewing a wide range of studies of healthy participants fitting broad inclusion criteria. They pooled studies irrespective of diversity of protocols and concluded that a-tDCS had a reliable effect on CSE. The present study extends the findings of the earlier reviews by taking protocol components (stimulation duration, intensity, electrode position) and anatomical/physiological differences (dominant vs. non-dominant stimulation side) into account. In addition, the present study included qualitative analysis of normalised data when the original data could not be extracted from published graphs or authors did not provide the raw data. Thus, this review incorporated a large number of studies into a comprehensive meta-analytic review.

The present meta-analysis highlighted the effect of a-tDCS on CSE using raw and normalized data. In both cases, a-tDCS demonstrated significant effects on CSE. The significant effect of a-tDCS appears to be due to the depolarization of the cortical neuron membranes (Batsikadze et al., 2013). In most studies, the participants were female; however, the authors did not comment on the possible effect of menstrual cycle on the CSE in females of reproductive age (Smith et al., 1999; Inghilleri et al., 2004; Zoghi et al., 2015).

The results of the current study show that applications of a-tDCS at current intensities of < 1 mA with durations > 10 min produce larger effects than higher intensities with either < 10 min or > 10 min duration. Moreover, the effect size with < 1 mA and < 10 min was not significant. Superficially, this finding supports a previously published quantitative analysis of a-tDCS (Bastani and Jaberzadeh, 2012), which found larger effects with longer stimulation duration. This finding highlights the effect of stimulation duration on CSE, which is probably due to more changes in neuronal membrane potentials occurring with larger amount of total charge under the stimulating electrode. However, Bastani and Jaberzadeh (2012) did not consider stimulation intensity when pooling the data, which limits direct comparison of effect sizes.

The current review demonstrated the greater effect of higher current density ($\geq 0.029 \text{ mA/cm}^2$) with either $<10 \text{ min}$ or $>10 \text{ min}$. It is more evidence of a correlation between CSE and current density. These findings largely agree with those of Bastani and Jaberzadeh (2012) and Horvath (2015). However, the previous reviews found significant effects on CSE with $< 0.029 \text{ mA/cm}^2$, which contradicts the finding of the current review. It is likely that this is due to the use of very low current intensities (e.g., 0.01 mA) by the studies in this category. Since larger current densities increase depth of magnetic field penetration, precautions should be taken when they are used in a clinical setup, as they will increase cutaneous pain sensation and may affect primary sensory neurons (Bastani and Jaberzadeh, 2012).

Several studies with pharmacological modulation have used a-tDCS in the placebo arm as an intervention group, and these studies were plotted separately due to the difference between this study design and those of other a-tDCS studies. These studies of a-tDCS of M1 also showed significant improvement in CSE in the present review. This effect could also be due to neuronal depolarization at the membrane level (Bastikadze et al., 2013).

The present study also showed significant increases in CSE after stimulation of M1 on the non-dominant side. Boggio et al. (2006) applied a-tDCS over the non-dominant M1 in right-handed individuals and reported a significant improvement in motor function, which the authors suggested was due to a ceiling effect and under-use of the non-dominant hand. The findings of the present review provide another explanation for Boggio et al.'s results in relation to the effect of CSE improvement.

Our findings of non-significant after-effects at same day evening, and the significant reduction of offline after-effects 24 hours from stimulation, are important. The studies that assessed after-effects used longer stimulation durations than studies which did not assess them. The results, therefore, provide support for a linear relationship between stimulation duration and after-effects (M. A. Nitsche and Paulus, 2000; Fricke et al., 2011). The offline after-effects could be based on two mechanisms: changes in synaptic strength involving the modulation of GABAergic and glutamatergic activity (M. Nitsche et al., 2003; Stagg and Nitsche, 2011), and/or the amount of calcium influx the a-tDCS induces. It has been shown that large post-synaptic calcium level increases long-term potentiation (LTP), which produces after-effects lasting for several hours (Cho et al., 2001; Lisman, 2001). This finding lends support to reducing washing-out periods from seven days to two days to prevent carry-over effects in crossover trials.

c-tDCS and CSE

Overall, with respect to the second aim of the study, we found a significant decrease of CSE with c-tDCS using both raw and normalized data. Moreover, the results showed a significant decrease of CSE from baseline in the placebo arm. A possible explanation for this effect is that c-tDCS hyperpolarizes the neuronal membrane, which decreases neuronal function (Batsikadze et al., 2013).

The results also highlighted that c-tDCS intensities of ≤ 1 mA with duration ≤ 15 min produce larger effects than >1 mA and ≤ 15 min. Moreover, the effect sizes with ≤ 1 mA with >15 min and >1 mA with >15 min were not significant. Recent evidence suggests that the opposing directions of plasticity with c-tDCS are no longer warranted with higher intensities for longer durations (e.g. 2 mA for 20 min) (Batsikadze et al., 2013). Importantly, other studies applying different plasticity-inducing stimulation have shown a non-linear association between stimulation intensities and the direction of effects (Doeltgen and Ridding, 2010; Moliadze et al., 2012). However, the current meta-analysis shows a non-significant effect with higher intensities and longer durations, and a significant effect with lower intensities and longer durations. This does not fully support the findings of individual studies. The possible reversed effects of c-tDCS with higher intensities for longer durations could be due to the dependency of the direction of plasticity on the amount of neuronal calcium influx resulting from the respective stimulation protocol (Batsikadze et al., 2013). Thus, c-tDCS with higher intensities and longer durations might increase calcium to a level that induces LTP-like plasticity, whereas lower intensities and shorter duration result in lower calcium levels that can cause long-term depression-like plasticity (LTD) (Batsikadze et al., 2013). Another explanation for this reversed effect is that increasing intensity with c-tDCS may induce de- and hyperpolarization via hyperpolarizing the soma and depolarizing dendrites. Increasing the intensity could increase the dendritic depolarization to a level which has an impact on neuronal excitability, or polarize structures with different neuronal orientation, to produce plasticity that differs from that at low intensities (Batsikadze et al., 2013). Modelling and imaging studies have found that current application by conventional tDCS can affect several non-targeted brain regions and change the functional connectivity between them (Datta et al., 2009; Polania et al., 2011a,b). Accordingly, recruitment of other non-targeted areas with higher intensities might change the direction of plasticity in the target regions (Batsikadze et al., 2013). However, to make a firm conclusion on the reversed effect of c-tDCS with higher intensities and longer current durations, more research is needed. The current explanations for

the reversed effects of c-tDCS are hypothetical, and there is no meta-analysis of CSE for c-tDCS to allow for direct comparison of effect sizes.

tACS, tRNS, tPCS and CSE

The results of the present meta-analysis showed a significant increase in CSE following tACS. However, this effect of tACS was limited to stimulus frequencies of ≥ 140 Hz. Those studies that used stimulus frequencies of < 140 Hz did not show a consistent effect on CSE. Unlike tDCS, which induces positive NDCC, tACS produces zero NDCC due to the nature of its alternating current. Whether or not this disparity affects CSE is an open question. While speculative, previous evidence suggests that rapidly alternating current use in tACS temporarily modifies the synapses via alteration of associated biochemical mechanisms, leading to short-term synaptic plasticity (Citri and Malenka, 2008; Chaieb et al., 2011a). Specifically, the frequency of 140 Hz, which is at the mid-range of 80–200 Hz, appears to have a pronounced effect on CSE (Moliadze et al., 2010b). No systematic review or meta-analysis to date has directly compared the effects of these two frequencies. Research involving different frequencies would allow for more systematic comparisons.

High-frequency stimulation was used in all the tRNS studies included in this review, and they all demonstrated a significant increase in CSE. The exact mechanism for this is unclear, but it has been proposed that tRNS induces temporal summation which can interact with the engaged neurons (Moliadze et al., 2014). Another possible explanation for the effect is that tRNS promotes the activity of the sodium channels (Terney et al., 2008).

The results also suggest that tPCS raises CSE. The observed tonic effect of NDCC and phasic effect of the on/off nature of pulsative current could facilitate the effects of tPCS on CSE. Nevertheless, the substantial heterogeneity between these two studies and the small number of studies that applied this technique limits the generalization of its effects.

tES and CSE

The present review confirms that tES paradigms of a-tDCS, tACS, tRNS and tPCS – can significantly increase CSE, while c-tDCS produces a significant decrease in the CSE in healthy individuals. Interestingly, the greatest effect size was observed with a-tDCS, suggesting that a-tDCS is more effective in modulating CSE than tACS, tRNS and tPCS. However, the number of a-tDCS studies pooled for analysis is larger than those for other tES paradigms, so caution should be taken when comparing effect sizes. Therefore, more research with tACS, tRNS and tPCS on CSE is required to draw stronger conclusions. Recent studies

have used these techniques to target non-motor areas, with promising results (Giglia et al., 2014; Groen and Wenderoth, 2016). Any firm conclusions on the effect of these techniques on CSE will shed light on the underlying mechanisms.

Quality of evidence

Some of the included studies did not clearly report the status of assessor blinding, which can affect homogeneity and the effect size. In an epidemiological study, incomplete blinding in controlled trials may exaggerate the effect size by 25% (Wood et al., 2008). O'Connell et al. (2012) reported that proper blinding could not be achieved when using current intensity of 2 mA or more. Even though this was challenged by Russo et al. (2013) and Palm et al. (2013) in their subsequent experiments, the implication is that the overall quality of the evidence for the effect of tES on CSE should be considered moderate.

Another important aspect is the sample size of the included studies. Most studies found mixed effects, either significant or non-significant, in a few very small samples (e.g. 5-12 participants). Thus, studies that show mixed effects in very small samples might over- or underestimate efficacy in this meta-analysis. When developing a study with healthy individuals, it is suggested to make an assumption of small to intermediate effect sizes (between $d = 0.4$ and $d = 0.5$) to perform a priori power analysis (Cohen, 1988; Minarik et al., 2016).

The PEDro scale and the Downs and Black scale scores showed the included studies are of good to medium quality. This reflects that the included studies have substantial methodological quality and internal validity (de Morton, 2009).

Limitations of the study

The findings of this meta-analysis should be interpreted in the context of the following limitations. The review was limited to peer-reviewed English language articles, which possibly reduced the number of studies to pool in the analysis. Another critical point is the small number of studies on some of the tES techniques, especially tPCS, which prevented subgroup analysis to investigate the effects of stimulation parameters. In addition, the number of studies included in each subgroup varied, which may have affected overall statistical significance. It should be noted that a putative publication bias indicated by the meta-analysis could not be further appraised through the application of p-curve analysis, due to lack of reported statistics in the original papers. Finally, although the size of active and return electrodes is a critical component that could have an effect on the modulation of CSE, this

was not directly considered in the meta-analysis as it was already covered under the current density.

Suggestions for future research

To date, few researchers have investigated the effects of tACS, tRNS or tPCS on CSE in healthy individuals, or the long-term offline effects of tES techniques – specifically tPCS. More carefully planned RCTs with sufficient sample size, proper blinding and inclusion of participants lacking experience with the method need to be considered when assessing the efficacy of these techniques on modulation of CSE, to reduce the odds of enrichment of responders and improve study quality. In addition, it will be important to investigate the effect of multiple-session tES applications and combinations of tES techniques that may be more effective in increasing CSE. Moreover, the researcher performing data analysis should be blinded to reduce p-hacking and improve the quality of evidence.

This systematic review and meta-analysis showed that a-tDCS increases CSE among healthy individuals. Since the p-curve analysis related to the a-tDCS could not be applied due to lack of reported p-values and test statistics in the original papers, future studies should made data sets publicly available to aid meta-analysis and make accurate conclusions from it. The results also highlighted that the stimulating parameters (e.g. intensity, duration, current density and electrode montage) affect the level of CSE after a-tDCS application. Based on the limited available evidence, other tES techniques, including tACS, tRNS and tPCS, also increase CSE following stimulation. In contrast, c-tDCS decreases CSE by emphasizing the effect of stimulation parameters (e.g. intensity and duration).

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Author contribution

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This study was designed by TDD and SJ. TDD, SJ, MZ, MJF and GFE did the data extraction and analysis. The manuscript was written by TDD. All authors commented on the manuscript.

Abbreviations

a-tDCS – anodal transcranial direct current stimulation, c-tDCS- cathodal transcranial direct current stimulation, CSE – corticospinal excitability, LTP – long term potentiation, LTD- long term depression, MEP – motor evoked potential, NDCC – net direct current component, RCT – randomized controlled trials, SD – standard deviation, SE – standard error, SMD - standard mean difference, tACS – transcranial alternating current stimulation, tES - transcranial electrical stimulation, tRNS – transcranial random noise stimulation, tPCS – transcranial pulsed current stimulation, TMS – transcranial magnetic stimulation, M1 – primary motor cortex

References

- Alonzo, A., Brassil, J., Taylor, J.L., Martin, D., Loo, C.K.(2012). Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimul.* **5** (3), 208-213.
- Ambrus, G.G., Antal, A., Paulus, W.(2011). Comparing cutaneous perception induced by electrical stimulation using rectangular and round shaped electrodes. *ClinNeurophysiol.* **122** (4), 803-807.
- Amadi, U., Allman, C., Johansen-Berg, H., Stagg, C.J.(2015).The Homeostatic Interaction Between Anodal Transcranial Direct Current Stimulation and Motor Learning in Humans is Related to GABAA Activity. *Brain Stimul.* **8** (5), 898-905.

- Antal, A., Boros, K., Poreisz, C., Chaieb, L., Terney, D., Paulus, W.(2008). Comparatively weak after-effects of transcranial alternating current stimulation (tACS) on cortical excitability in humans. *Brain Stimul.* **1** (2), 97-105.
- Antal, A., Paulus, W.(2013). Transcranial alternating current stimulation (tACS). *Front Hum Neurosci.***7**, 1-4.
- Antal, A., Terney, D., Poreisz, C., Paulus, W.(2007). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *Eur J Neurosci.* **26** (9), 2687-2691.
- Bastani, A., Jaberzadeh, S.(2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: A systematic review and metaanalysis.*ClinicalNeurophysiology.***123** (4), 644-657.
- Bastani, A., Jaberzadeh, S.(2013).a-tDCS Differential Modulation of Corticospinal Excitability: The Effects of Electrode Size. *Brain Stimul.***6** (6), 932-937.
- Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M.F., Nitsche, M.A. (2013).Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol.* **591**, 1987-2000.
- Batsikadze, G., Paulus, W., Grundey, J., Kuo, M.F., Nitsche, M.A. (2015). Effect of the Nicotinic alpha4beta2-receptor Partial Agonist Varenicline on Non-invasive Brain Stimulation-Induced Neuroplasticity in the Human Motor Cortex. *Cereb Cortex.* **25** (9), 3249-3259.
- Boggio, P.S., Castro, L.O., Savagim, E.A., Braite, R., Cruz, V.C., Rocha, R.R., Rigonatti, S.P., Silva, M.T., Fregni, F.(2006). Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. *Neurosci Lett.* **404** (1-2), 232-236.
- Brunoni, A.R., Nitsche, M.A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D.J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P.S., Fregni, F.(2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.***5** (3), 175-195.
- Butler, A.J., Shuster, M., O'Hara, E., Hurley, K., Middlebrooks, D., Guilkey, K. (2013). A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *Journal of hand therapy: official journal of the American Society of Hand Therapists.* **26** (2), 162-70

- Chaieb, L., Antal, A., Paulus, W.(2011a).Transcranial alternating current stimulation in the low kHz range increases motor cortex excitability.*RestorNeurolNeurosci.* **29** (3), 167-175.
- Chaieb, L., Paulus, W., Antal, A.(2011b).Evaluating aftereffects of short-duration transcranial random noise stimulation on cortical excitability. *Neural Plast.* 1-5.
- Chew, T., Ho, K.A., Loo, C.K. (2015). Inter- and Intra-individual Variability in Response to Transcranial Direct Current Stimulation (tDCS) at Varying Current Intensities. *Brain Stimul.* **8** (6), 1130-1137.
- Chib, V.S., Yun, K., Takahashi, H., Shimojo, S.(2013).Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. *Transl Psychiatry.* 3 e268.
- Cho, K., Aggleton, J.P., Brown, M.W., Bashir, Z.I.(2001). An experimental test of the role of postsynaptic calcium levels in determining synaptic strength using perirhinalcortex of rat. *J Physiol.* **532**, 459-466.
- Chung, S.W., Hill, A.T., Rogasch, N.C., Hoy, K.E., Fitzgerald, P.B. (2016). Use of theta-burst stimulation in changing excitability of motor cortex: A systematic review and meta-analysis. *Neuroscience and biobehavioral reviews.* 63, 43-64
- Citri, A., Malenka, R.C.(2008).Synaptic plasticity: multiple forms, functions, and mechanisms.*Neuropsychopharmacology.* **33** (1), 18-41.
- Cohen J. (1988). Statistical power analysis for the behavioural sciences. 2 ed. New Jersey: Lawrence Erlbaum Publishers.
- Datta A, Bansal V, Diaz J, Patel J, Reato D & Bikson M (2009). Gyri-precise head model of transcranial DC stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul***2**, 201–207.
- Davidson, T.W., Bolic, M., Tremblay, F.(2016). Predicting Modulation in Corticomotor Excitability and in Transcallosal Inhibition in Response to Anodal Transcranial Direct Current Stimulation. *Front Hum Neurosci.***10**, 1-10.
- Deeks, J., Higgins, J., (2010). Statistical algorithms in Revman Manager 5. Cochrane Collaboration [Internet].
- de Morton NA. (2009). The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother.***55**, 129–33.
- Doeltgen, S.H., Ridding, M.C. (2010). Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks. *Clin Neurophysiol.***122**, 1411–1416.

- Downs, S.H., Black, N.(1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. **52** (6), 377-384.
- Dyke, K., Kim, S., Jackson, G.M., Jackson, S.R.(2016). Intra-Subject Consistency and Reliability of Response Following 2 mA Transcranial Direct Current Stimulation. *Brain Stimul*. **9**, 819-825.
- Egger, M., Davey, Smith, G., Schneider, M., Minder, C.(1997).Bias in meta-analysis detected by a simple, graphical test. *Bmj*. **315** (7109), 629-634.
- Fresnoza, S., Stiksrud, E., Klinker, F., Liebetanz, D., Paulus, W., Kuo, M.F., Nitsche, M.A.(2014b).Dosage-Dependent Effect of Dopamine D2 Receptor Activation on Motor Cortex Plasticity in Humans. *The Journal of Neuroscience*. **34** (32), 10701-10709.
- Fresnoza, S., Paulus, W., Nitsche, M.A., Kuo, M.F.(2014a). Nonlinear dose-dependent impact of D1 receptor activation on motor cortex plasticity in humans. *J Neurosci*. **34** (7), 2744-2753.
- Fricke, K., Seeber, A.A., Thirugnanasambandam, N., Paulus, W., Nitsche, M.A., Rothwell, J.C.(2011). Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex. *J Neurophysiol*.**105** (3), 1141-1149.
- Furubayashi, T., Terao, Y., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., Hamada, M., Yugeta, A., Inomata-Terada, S., Ugawa, Y.(2008). Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Exp Brain Res*.**185** (2), 279-286.
- Galvez, V., Alonzo, A., Martin, D., Loo, C.K.(2013). Transcranial direct current stimulation treatment protocols: should stimulus intensity be constant or incremental over multiple sessions? *Int J Neuropsychopharmacol*. **16** (1), 13-21.
- Giglia, G., Brighina, F., Rizzo, S., Puma, A., Indovino, S., Maccora, S., Baschi, R., Cosentino, G., Fierro, B. (2014). Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex enhances memory-guided responses in a visuospatial working memory task. *Funct Neurol*. **29**(3), 189-93.
- Groen, O.V.D., Wenderoth, N. (2016). Transcranial random noise stimulation of visual cortex: stochastic resonance enhances central mechanisms of perception. *The journal of neuroscience*. **36**(19), 5289-5298.

- Groppa, S., Bergmann, T.O., Siems, C., Molle, M., Marshall, L., Siebner, H.R.(2010).Slow-oscillatory transcranial direct current stimulation can induce bidirectional shifts in motor cortical excitability in awake humans. *Neuroscience*. **166** (4), 1219-1225.
- Grundey, J., Thirugnanasambandam, N., Kaminsky, K., Drees, A., Skwirba, A.C., Lang, N., Paulu, W., Nitsche, M.A. (2012a). Neuroplasticity in Cigarette Smokers Is Altered under Withdrawal and Partially Restituted by Nicotine Exposition. *Journal of Neuroscience*. **32**(12), 4156-4162.
- Grundey, J., Thirugnanasambandam, N., Kaminsky, K., Drees, A., Skwirba, A.C., Lang, N., Paulu, W., Nitsche, M.A. (2012b). Rapid effect of nicotine intake on neuroplasticity in non-smoking humans. *Frontiers in Pharmacology*. **3**, 1-9.
- Hasan, A., Aborowa, R., Nitsche, M. A., Marshall, L., Schmitt, A., Gruber, O., Falkai, P. &Wobrock, T. (2012). Abnormal bihemispheric responses in schizophrenia patients following cathodal transcranial direct stimulation. *Eur Arch Psychiatry Clin Neurosci*, **262** (5), 415-423
- Hasan, A., Misewitsch, K., Nitsche, M. A., Gruber, O., Padberg, F., Falkai, P. &Wobrock, T. (2013). Impaired motor cortex responses in non-psychotic first-degree relatives of schizophrenia patients: a cathodal tDCS pilot study. *Brain Stimul*, **6** (5), 821-829.
- Head, M.L., Holman, L., Lanfear, R., Kahn, A.T., Jennions, M.D. (2015). The extent and consequences of p-hacking in science. *PLoS biology*. **13**(3), e1002106.
- Higgins, J.P., Green, S.(2008). *Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration*. Wiley.
- Hill, A.T., Fitzgerald, P.B., Hoy, K.E. (2016). Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations. *Brain stimulation*. **9** (2), 197-208.
- Ho, K.A., Taylor, J.L., Loo, C.K.(2015). Comparison of the effects of transcranial random noise stimulation and transcranial direct current stimulation on motor cortical excitability. *J ect*. **31** (1), 67-72.
- Horvath, J.C., Forte, J.D., Carter, O.(2015). Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia*.**66**, 213-236.
- Horvath, J.C., Vogrin, S.J., Carter, O., Cook, M.J., Forte, J.D.(2016). Effects of a common transcranial direct current stimulation (tDCS) protocol on motor evoked potentials

- found to be highly variable within individuals over 9 testing sessions. *Exp Brain Res.* **234** (9), 2629-2642.
- Inghilleri, M., Conte, A., Curra, A., Frasca, V., Lorenzano, C., Berardelli, A. (2004). Ovarian hormones and cortical excitability. An rTMS study in humans. *Clin Neurophysiol.* **115** (5), 1063-1068.
- Inukai, Y., Saito, K., Sasaki, R., Tsuiki, S., Miyaguchi, S., Kojima, s., Masaki, M., Otsuru, N., Onishi, H. (2016). Comparison of Three Non-Invasive Transcranial Electrical Stimulation Methods for Increasing Cortical Excitability. *Frontiers in Human Neuroscience.* **10**, 1-7.
- Jaberzadeh, S., Bastani, A., Zoghi, M. (2014). Anodal transcranial pulsed current stimulation: A novel technique to enhance corticospinal excitability. *Clin Neurophysiol.* **125** (2), 344-351.
- Jaberzadeh, S., Bastani, A., Zoghi, M., Morgan, P., Fitzgerald, P.B. (2015). Anodal Transcranial Pulsed Current Stimulation: The Effects of Pulse Duration on Corticospinal Excitability. *PLoS One.* **10** (7), 1-14.
- Jamil, A., Batsikadze, G., Kuo, H. I., Labruna, L., Hasan, A., Paulus, W. & Nitsche, M. A. (2016). Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *J Physiol*, 1-16.
- Jelicic Kadic, A., Vucic, K., Dosenovic, S., Sapunar, D., Puljak, L. (2016). Extracting data from figures with software was faster, with higher interrater reliability than manual extraction. *Journal of clinical epidemiology.* **74**:119-23
- John LK, Loewenstein G, Prelec D (2012). Measuring the prevalence of questionable research practices with incentives for truth telling. *Psychol Sci* **23**: 524–532
- Joseph A. (2010). Plot Digitizer 2.4.1 [Internet], open source software available at <http://plotdigitizer.sourceforge.net/>.
- Kidgell, D.J., daly, R.M., Young, K., Lum, J., Tooley, G., Jaberzadeh, S., Zoghi, M., Pearce, A.J. (2013a). Different current intensities of anodal transcranial direct current stimulation do not differently modulate motor cortex plasticity. *Neural Plasticity.* 1-9.
- Kidgell, D.J., Goodwill, A.M., Frazer, A.K., Daly, R.M. (2013b). Induction of cortical plasticity and improved motor performance following unilateral and bilateral transcranial direct current stimulation of the primary motor cortex. *BMC Neurosci.* **14** (64), 1-12.

- Kim, G.W., Ko, M.H.(2013). Facilitation of corticospinal tract excitability by transcranial direct current stimulation combined with voluntary grip exercise. *Neurosci Lett.* **548**,181-184.
- Krause, B., Cohen, K.R.(2013).Can transcranial electrical stimulation improve learning difficulties in atypical brain development? A future possibility for cognitive training. *Dev Cogn Neurosci.***6**, 176-194.
- Kuo, H.I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M.F., Nitsche, M.A.(2013).Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. *Brain Stimul.* **6** (4), 644-648.
- Kuo, M.F., Grosch, J., Fregni, F., Paulus, W., Nitsche, M.A.(2007). Focusing effect of acetylcholine on neuroplasticity in the human motor cortex. *J Neurosci.* **27** (52), 14442-14447.
- Kuo, H.I., Paulus, W., Bastikadze, G., Kuo, M-F., Nitsche, M.A. (2016). Acute and chronic effects of noradrenergic enhancement on transcranial direct current stimulation-induced neuroplasticity in humans. *The journal of Physiology.* 1-10.
- Kuo, M.F., Paulus, W., Nitsche, M.A.(2008).Boosting focally-induced brain plasticity by dopamine. *Cereb Cortex.* **18** (3), 648-651.
- Labruna, L., Jamil, A., Fresnoza, S., Batsikadze, G., Kuo, M.F., Vanderschelden, B., Ivry, R.B., Nitsche, M.A.(2016). Efficacy of Anodal Transcranial Direct Current Stimulation is Related to Sensitivity to Transcranial Magnetic Stimulation. *Brain Stimul.***9** (1), 8-15.
- Lang, N., Siebner, H.R., Ernst, D., Nitsche, M.A., Paulus, W., Lemon, R.N., Rothwell, J.C.(2004a)Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. *Biol Psychiatry.* **56** (9), 634-639.
- Lang, N., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N.(2004b). Effects of transcranial direct current stimulation over the human motor cortex on corticospinal and transcallosal excitability. *Exp Brain Res.* **156** (4), 439-443.
- Lee, M., Kim, Y.H., Im, C.H., Kim, J.H., Park, C.H., Chang, W.H., Lee, A.(2015). What is the optimal anodal electrode position for inducing corticomotor excitability changes in transcranial direct current stimulation? *Neurosci Lett.***584**, 347-350.
- Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W.(2002).Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain.* **125** (Pt 10), 2238-2247.

- Lisman, J.E. (2001). Three Ca²⁺ levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. *J Physiol.* **532** (Pt 2), 285.
- López-Alonso, V., Cheeran, B., Fernández-del-Olmo, M.(2015).Relationship Between Non-invasive Brain Stimulation-induced Plasticity and Capacity for Motor Learning. *Brain Stimul.* **8**(6), 1209-1219.
- Lopez-Alonso, V., Cheeran, B., Rio-Rodriguez, D., Fernandez-Del-Olmo, M.(2014). Inter-individual variability in response to non-invasive brain stimulation paradigms. *Brain Stimul.***7** (3), 372-380.
- Lugon, M.D.M.V., Batsikadze, G., Fresnoza, S., Grundey, J., Kuo, M-F., Paulus, W., Nakamura-Palacios, E.M., Nitsche, M.A. (2015). Mechanisms of Nicotinic Modulation of Glutamatergic Neuroplasticity in Humans. *Cerebral cortex.*1-10.
- Maher, C.G., Sherrington, C., Herbert, R.D., Moseley, A.M., Elkins, M.(2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther.* **83** (8), 713-721.
- Minarik T., Berger B., Althaus L., Bader V., Biebl B., Brotzeller F., et al. (2016). The importance of sample size for reproducibility of tDCS effects. *Front. Hum. Neurosci.* **10**, 453
- Moliadze, V., Antal, A., Paulus, W.(2010a).Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes. *ClinNeurophysiol.* **121** (12), 2165-2171.
- Moliadze, V., Antal, A., Paulus, W.(2010b). Boosting brain excitability by transcranial high frequency stimulation in the ripple range. *J Physiol.***588** (Pt 24), 4891-4904.
- Moliadze, V., Atalay, D., Antal, A., Paulus, W.(2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimul.* **5** (4), 505-511.
- Moliadze, V., Fritzsche, G., Antal, A.(2014). Comparing the efficacy of excitatory transcranial stimulation methods measuring motor evoked potentials. *Neural Plast.* 1-6.
- Moliadze, V., Schmanke, T., Andreas, S., Lyzhko, E., Freitag, C.M., Siniatchkin, M.(2015). Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. *Clinical Neurophysiology.* **126** (7), 1392-1399.
- Mondino, M., Bennabi, D., Poulet, E., Galvao, F., Brunelin, J., Haffen, E.(2014). Can transcranial direct current stimulation (tDCS) alleviate symptoms and improve cognition in psychiatric disorders?*World J Biol Psychiatry.* **15** (4), 261-275.

- Monte-Silva, K., Kuo, M.F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., Nitsche, M.A.(2013).Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul.* **6** (3), 424-432.
- Monte-Silva, K., Kuo, M.F., Thirugnanasambandam, N., Liebetanz, D., Paulus, W., Nitsche, M.A.(2009). Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. *J Neurosci.* **29** (19), 6124-6131.
- Monte-Silva, K., Liebetanz, D., Grundey, J., Paulus, W., Nitsche, M.A.(2010).Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity. *J Physiol.* **588** (Pt 18), 3415-3424.
- Morales-Quezada, L., Cosmo, C., Carvalho, S., Leite, J., Castillo-Saavedra, L., Rozisky, J.R., Fregni, F.(2015).Cognitive effects and autonomic responses to transcranial pulsed current stimulation. *Exp Brain Res.* **233** (3), 701-709.
- Mordillo-Mateos, L., Turpin-Fenoll, L., Millán-Pascual, J., Núñez-Pérez, N., Panyavin, I., Gómez-Argüelles, J.M., Botia-Paniagua, E., Foffani, G., Lang, N., Oliviero, A.(2012).Effects of simultaneous bilateral tDCS of the human motor cortex. *Brain Stimul.* **5** (3), 214-222.
- Moseley, A.M., Herbert, R.D., Sherrington, C., Maher, C.G.(2002). Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). *Aust J Physiother.* **48** (1), 43-49.
- Munneke, M. A., Stegeman, D. F., Hengeveld, Y. A., Rongen, J. J., Schelhaas, H. J. &Zwarts, M. J. (2011). Transcranial direct current stimulation does not modulate motor cortex excitability in patients with amyotrophic lateral sclerosis. *Muscle Nerve*, **44** (1), 109-114.
- Nitsche, M.A., Doemkes, S., Karakose, T., Antal, A., Liebetanz, D., Lang, N., Tergau, F., Paulus, W.(2007).Shaping the effects of transcranial direct current stimulation of the human motor cortex. *J Neurophysiol.* **97** (4), 3109-3117.
- Nitsche, M.A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., Paulus, W.(2003).Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol.* **553** (Pt 1), 293-301.
- Nitsche, M.A., Paulus, W.(2000).Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*, **527** (3), 633-639.

- Nitsche, M., Paulus, W.(2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurolog.* 1989-1901.
- Nitsche, M.A., Grundev, J., Liebetanz, D., Lang, N., Tergau, F., Paulus, W.(2004).Catecholaminergic consolidation of motor cortical neuroplasticity in humans. *Cereb Cortex.* **14** (11), 1240-1245.
- Nitsche, M.A., Kuo, M.F., Karrasch, R., Wachter, B., Liebetanz, D., Paulus, W.(2009).Serotonin affects transcranial direct current-induced neuroplasticity in humans. *Biol Psychiatry.***66** (5), 503-508.
- Nitsche, M.A., Lampe, C., Antal, A., Liebetanz, D., Lang, N., Tergau, F., Paulus, W.(2006). Dopaminergic modulation of long-lasting direct current-induced cortical excitability changes in the human motor cortex. *Eur J Neurosci.* **23** (6), 1651-1657.
- Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W., Tergau, F.(2005).Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J Physiol.* **568** (Pt 1), 291-303.
- Palm U, Reisinger E, Keeser D, Kuo MF, Pogarell O, Leicht G, et al. (2013). Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain Stimul.* **6**, 690–695.
- Pellicciari, M.C., Brignani, D., Miniussi, C.(2013).Excitability modulation of the motor system induced by transcranial direct current stimulation: a multimodal approach. *Neuroimage.***83**, 569-580.
- Polan'ia R, Paulus W, Antal A & Nitsche MA (2011a). Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. *Neuroimage***54**, 2287–2296.
- Polan'ia R, PaulusW& Nitsche MA (2011b). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Hum Brain Mapp***32**, 1236–1249.
- Power, H.A., Norton, J.A., Porter, C.L., Doyle, Z., Hui, I., Chan, K.M.(2006). Transcranial direct current stimulation of the primary motor cortex affects cortical drive to human musculature as assessed by intermuscular coherence. *J Physiol.***577**(3), 795-803.
- Pisegna, J.M., Kaneoka, A., Pearson, W.G., Jr., Kumar, S., Langmore, S.E. (2016). Effects of non-invasive brain stimulation on post-stroke dysphagia: A systematic review and meta-analysis of randomized controlled trials. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology.* **127**(1), 956-68

- Quartarone, A., Morgante, F., Bagnato, S., Rizzo, V., Sant'Angelo, A., Aiello, E., Reggio, E., Battaglia, F., Messina, C., Girlanda, P.(2004).Long lasting effects of transcranial direct current stimulation on motor imagery. *Neuroreport*.**15** (8), 1287-1291.
- Rizzo, V., Terranova, C., Crupi, D., Sant'angelo, A., Girlanda, P., Quartarone, A.(2014).Increased Transcranial Direct Current Stimulation After Effects During Concurrent Peripheral Electrical Nerve Stimulation. *Brain Stimul*.**7** (1), 113-121.
- Rosenthal R. (1979). The file drawer problem and tolerance for null results. *Psychol Bull*.**86**, 638–641
- Russo R, Wallace D, Fitzgerald PB, Cooper NR. (2013). Perception of comfort during active and sham transcranial direct current stimulation: a double blind study. *Brain Stimul*.**6**, 946–951.
- Santaracchi, E., Feurra, M., Barneschi, F., Acampa, M., Bianco, G., Cioncoloni, D., Rossi, A., Rossi, S.(2014).Time Course of Corticospinal Excitability and Autonomic Function Interplay during and Following Monopolar tDCS. *Front Psychiatry*. **5** (86), 1-11.
- Sasaki, R., Miyaguchi, S., Kotan, S., Kojima, S., Kirimoto, H. &Onishi, H. (2016). Modulation of Cortical Inhibitory Circuits after Cathodal Transcranial Direct Current Stimulation over the Primary Motor Cortex. *Front Hum Neurosci*, **10**, 30, 1-8.
- Scelzo, E., Giannicola, G., Rosa, M., Ciocca, M., Ardolino, G., Cogiamanian, F., Ferrucci, R., Fumagalli, M., Mameli, F., Barbieri, S., Priori, A.(2011).Increased short latency afferent inhibition after anodal transcranial direct current stimulation. *Neurosci Lett*. **498** (2), 167-170.
- Schabrun, S.M., Chipchase, L.S., Zipf, N., Thickbroom, G.W., Hodges, P.W.(2013). Interaction between simultaneously applied neuromodulatory interventions in humans. *Brain Stimul*. **6** (4), 624-630.
- Schade, S., Moliadze, V., Paulus, W., Antal, A.(2012). Modulating neuronal excitability in the motor cortex with tDCS shows moderate hemispheric asymmetry due to subjects' handedness: a pilot study. *RestorNeurolNeurosci*. **30** (3), 191-198.
- Siebner, H.R., Lang, N., Rizzo, V., Nitsche, M.A., Paulus, W., Lemon, R.N., Rothwell, J.C.(2004).Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex. *J Neurosci*. **24** (13), 3379-3385.
- Simis, M., Adeyemo, B.O., Medeiros, L.F., Miraval, F., Gagliardi, R.J., Fregni, F.(2013). Motor cortex-induced plasticity by noninvasive brain stimulation: a comparison

- between transcranial direct current stimulation and transcranial magnetic stimulation. *Neuroreport*. **24** (17), 973-975.
- Simonsohn U, Nelson LD, Simmons JP. (2014a) P-curve: A key to the file drawer. *J Exp Psychol Gen*. **143**, 534–547
- Smith, M.J., Keel, J.C., Greenberg, B.D., Adams, L.F., Schmidt, P.J., Rubinow, D.A., Wassermann, E.M.(1999). Menstrual cycle effects on cortical excitability. *Neurology*. **53** (9), 2069-2072.
- Stagg, C.J., Nitsche, M.A.(2011).Physiological basis of transcranial direct current stimulation. *Neuroscientist*. **17** (1), 37-53.
- Sterne, J.A., Egger, M., Smith, G.D.(2001). Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *Bmj*. **323** (7304), 101-105.
- Straube S, Derry S, McQuay HJ, Moore RA. (2008). Enrichedenrollment: definition and effects of enrichment and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review. *Br J ClinPharmacol*. **66** (2), 266-275.
- Strube, W., Bunse, T., Nitsche, M.A., Nikolaeva, A., Palm, U., Padberg, F., Falkai, P., Hasan, A.(2016). Bidirectional variability in motor cortex excitability modulation following 1 mA transcranial direct current stimulation in healthy participants. *Physiol Rep*. **4** (15),
- Suzuki, K., Fujiwara, T., Tanaka, N., Tsuji, T., Masakado, Y., Hase, K., Kimura, A., Liu, M.(2012). Comparison of the after-effects of transcranial direct current stimulation over the motor cortex in patients with stroke and healthy volunteers. *Int J Neurosci*. **122** (11), 675-681.
- Terney, D., Chaieb, L., Moliadze, V., Antal, A., Paulus, W.(2008). Increasing Human Brain Excitability by Transcranial High-Frequency Random Noise Stimulation. *Journal of Neuroscience*. **28** (52), 14147-14155.
- Thirugnanasambandam, N., Grundey, J., Adam, K., Drees, A., Skwirba, A.C., Lang, N., Paulus, W., Nitsche, M.A.(2011a).Nicotinic impact on focal and non-focal neuroplasticity induced by non-invasive brain stimulation in non-smoking humans.*Neuropsychopharmacology*. **36** (4), 879-886.
- Tremblay, S., Beaulé, V., Lepage, J.F., Theoret, H.(2013). Anodal transcranial direct current stimulation modulates GABA_B-related intracortical inhibition in the M1 of healthy individuals. *Neuroreport*. **24** (1), 46-50.
- Uy, J., Ridding, M.C.(2003). Increased cortical excitability induced by transcranial DC and peripheral nerve stimulation. *J Neurosci Methods*. **127** (2), 193-197.

- Vaseghi, B., Zoghi, M., Jaberzadeh, S.(2015). The effects of anodal-tDCS on corticospinal excitability enhancement and its after-effects: Conventional vs. unihemispheric concurrent dual-site stimulation. *Front Hum Neurosci.***9**, 1-13.
- Wiethoff, S., Hamada, M., Rothwell, J.C.(2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimul.* **7** (3), 468-475.
- Williams, P.S., Hoffman, R.L., Clark, B.C.(2013). Preliminary evidence that anodal transcranial direct current stimulation enhances time to task failure of a sustained submaximal contraction. *PLoS One.* **8** (12), e81418.
- Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. 2008. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *Bmj.* **336**: 601–605.
- Zaghi, S., de Freitas Rezende, L., de Oliveira, L.M., El-Nazer, R., Menning, S., Tadini, L., Fregni, F.(2010).Inhibition of motor cortex excitability with 15 Hz transcranial alternating current stimulation (tACS). *Neurosci Lett.***479** (3), 211-214.
- Zoghi, M., Vaseghi, B., Bastani, A., Jaberzadeh, S., Galea, M. (2015).The effects of sex hormonal fluctuations during menstrual cycle on corticospinal excitability and manual dexterity (a pilot study). *PLoS One.* 1-14.

Figure legends

Figure1. Flow diagram of included studies (n = number of articles)

Figure 2. Risk of bias of the included studies

Figure 3. Funnel plots for tES on MEPs amplitude (A) a-tDCS, (B) c-tDCS, (C) tACS, (D) tRNS and (E) tPCS

Figure 4. Forest plot for effect of a-tDCS on MEPs amplitude, Current intensity, *; TMS intensity, ‡; resting motor threshold, †; reference electrode size, ‡; stimulated muscle, *; ADM, abductor digiti minimi; APB, abductor pollicis brevis; FDI, first dorsal interosseous; experiment, Exp

Figure 5. Forest plot for effect of a-tDCS in placebo arm on MEPs amplitude, Experiment, Exp; Flunarizine, FLU; Other drug, Othr

Figure 6A. Forest plot for effect of a-tDCS on MEPs amplitude related to parameters of stimulation duration and current intensity, Current intensity, *; TMS intensity, ‡; resting motor threshold, †; reference electrode size, ‡; stimulated muscle, *; ADM, abductor digiti minimi; APB, abductor pollicis brevis; FDI, first dorsal interosseous; experiment, Exp

Figure 6B. Forest plot for effect of a-tDCS on MEPs amplitude related to parameters of stimulation duration and current density, Current intensity, *; TMS intensity, ‡; resting motor threshold, †; reference electrode size, ‡; stimulated muscle, *; ADM, abductor digiti minimi; APB, abductor pollicis brevis; FDI, first dorsal interosseous; experiment, Exp

Figure 7. Forest plot for effects of non-dominant side M1 stimulation on MEPs amplitude, Resting motor threshold, †

Figure 8. Forest plot for after effects of a-tDCS on MEPs amplitude, TMS intensity, ‡

Figure 9. Forest plots for effect of c-tDCS on MEPs amplitude, Current intensity, *; Frequency, #; Current intensity, *; Duration, ‡; Pulse duration, ‡; Inter-pulse interval, ^; experiment, Exp

Figure 10A. Forest plot for effect of c-tDCS in placebo arm on MEPs amplitude

Figure 10B. Forest plot for effect of c-tDCS on MEPs amplitude related to parameters of current intensity and duration, Current intensity, *; Frequency, #; Current intensity, *; Duration, ‡; Pulse duration, ‡; Inter-pulse interval, ^; experiment, Exp

Figure 11. Forest plots for effect of tACS, tRNS and tPCS on MEPs amplitude, (A) tACS, (B) tRNS, (C) tPCS, Current intensity, *; Frequency, #; Current intensity, *; Duration, ‡; Pulse duration, ‡; Inter-pulse interval, ^; experiment, Exp

Supplementary materials

S1: Details of search strategies

S2: Figure 6A: Forest plot for a-tDCS sub analysis according to current intensity and duration

S3: Figure 6B: Forest plot for a-tDCS sub analysis according to current density and duration

S4: Figure 10A: Forest plot for c-tDCS in placebo arm on MEPs amplitude

S5: Figure 10B: Forest plot for c-tDCS sub analysis according to current intensity and duration

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Tables

Table 1. Characteristics of the included studies

Included study	Sample size (n)	tES	Trial design	Muscle	Intensity (mA)	Time (min)	Stimulation site (active/return electrode size cm ²)
Nitsche et al., 2000	19	a-tDCS	SBSCS	ADM	1	5	M1(35/35)
	19	c-tDCS	SBSCS	ADM	1	5	M1(35/35)
	12	a-tDCS	SBSCS	ADM	1	1-5	M1(35/35)
	12	a-tDCS	SBSCS	ADM	0.2,0.4,0.6,0.8,1	5	M1(35/35)
Nitsche et al., 2001	12	a-tDCS	SBRCS	ADM	1	5,7,9,11,15	M1(35/35)
Liebetanz et al., 2002	8	a-tDCS	DBRPCS	ADM	1	5	M1(35/35)
	8	c-tDCS	DBRPCS	ADM	1	5	M1(35/35)
Uy and Ridding, 2003	10	a-tDCS	PP	FDI	1	10	M1(25/25)
Nitsche et al., 2003	14	a-tDCS	DBRPCS	ADM	1	11	M1(35/35)
	10	a-tDCS	DBRPCS	ADM	1	13	M1(35/35)
Quartarone et al., 2004	7	a-tDCS	RSC	FDI	1	5	M1(35/35)
	21	c-tDCS	RSC	FDI	1	5	M1(35/35)
Seibner et al., 2004	8	a-tDCS	RCS	FDI	1	10	M1(35/35)
	8	c-tDCS	RCS	FDI	1	10	M1(35/35)
	5	a-tDCS	RCS	FDI	1	10	M1(35/35)
	5	c-tDCS	RCS	FDI	1	10	M1(35/35)
	9	a-tDCS	DBRPCS	ADM	1	13	M1(35/35)
Nitsche et al., 2004	12	a-tDCS	DBRPCS	ADM	1	13	M1(35/35)
	6	a-tDCS	DBRPCS	ADM	1	7	M1(35/35)
	5	a-tDCS	SBSCS	FDI	1	10	M1(35/35)
	5	c-tDCS	SBSCS	FDI	1	10	M1(35/35)
Lang et al., 2004a	10	a-tDCS	SBSCS	FDI	1	10	M1(35/35)
	10	c-tDCS	SBSCS	FDI	1	10	M1(35/35)
	8	a-tDCS	PP	FDI	1	10	M1(35/35)
	8	c-tDCS	PP	FDI	1	10	M1(35/35)
Nitsche et al., 2005	12	a-tDCS	PP	ADM	1	13	M1(35/35)
	12	c-tDCS	PP	ADM	1	9	M1(35/35)
	13	a-tDCS	PP	ADM	1	7	M1(35/35)
	13	c-tDCS	PP	ADM	1	7	M1(35/35)
Power et al., 2006	10	a-tDCS	SBRCS	FDI	1	10	M1(35/35)
	10	c-tDCS	SBRCS	FDI	1	10	M1(35/35)
	5	a-tDCS	SBRCS	EDC	1	10	M1(35/35)
	5	c-tDCS	SBRCS	EDC	1	10	M1(35/35)

Nitsche et al., 2006	12	a-tDCS	DBRPCS	ADM	2	13	M1(35/35)
Nitsche et al., 2007	12	a-tDCS	PP	FDI	1	7	M1(35/35)
	12	c-tDCS	PP	FDI	1	7	M1(35/35)
	12	a-tDCS	PP	FDI	0.1	7	M1(3.5/35)
	12	c-tDCS	PP	FDI	0.1	7	M1(3.5/35)
	12	a-tDCS	PP	ADM	1	7	M1(35/35)
	12	c-tDCS	PP	ADM	1	7	M1(35/35)
	12	a-tDCS	PP	ADM	0.1	7	M1(3.5/35)
	12	c-tDCS	PP	ADM	0.1	7	M1(3.5/35)
	12	a-tDCS	PP	ADM	1	10	M1(35/35)
	12	c-tDCS	PP	ADM	1	9	M1(35/35)
	12	a-tDCS	PP	ADM	0.01	10	M1(35/100)
	12	c-tDCS	PP	ADM	0.01	10	M1(35/100)
Antal et al., 2007	12	a-tDCS	PP	FDI	1	10	M1(35/35)
	12	c-tDCS	PP	FDI	1	10	M1(35/35)
Kuo et al., 2007	12	a-tDCS	SBRPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	SBRPCS	ADM	1	9	M1(35/35)

Table 1 continued

Included study	Sample size (n)	tES	Trial design	Muscle	Intensity (mA)	Time (min)	Stimulation site (active/return electrode size cm ²)
Kuo et al., 2008	11	a-tDCS	RPCS	ADM	1	13	M1(35/35)
	11	c-tDCS	RPCS	ADM	1	9	M1(35/35)
Furubayashi et al., 2008	8	a-tDCS	PP	FDI	1	10	M1(15/15)
	8	c-tDCS	PP	FDI	1	10	M1(15/15)
Nische et al., 2009	12	a-tDCS	SBRCS	ADM	2	13	M1(35/35)
	12	c-tDCS	SBRCS	ADM	2	9	M1(35/35)
Monte-Silva et al., 2009	12	a-tDCS	SBRPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	SBRPCS	ADM	1	9	M1(35/35)
Moliadze et al., 2010a	9	a-tDCS	PP	FDI	2	10	M1(16/64)
Groppa et al., 2010	10	a-tDCS	PP	FDI	0.75	10	M1(12/12)
Monte-Silva et al., 2010	12	a-tDCS	SBRPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	SBRPCS	ADM	1	9	M1(35/35)
Thiiruganasamban et al., 2011	12	a-tDCS	RPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	RPCS	ADM	1	9	M1(35/35)
Scelzo et al., 2011	12	a-tDCS	PP	FDI	1	13	M1(35/35)
Fricke et al., 2011	8	a-tDCS	PP	FDI	1	5	M1(35/35)
	8	c-tDCS	PP	FDI	1	5	M1(35/35)
	12	a-tDCS	PP	FDI	1	7	M1(35/35)

	12	c-tDCS	PP	FDI	1	7	M1(35/35)
Munneke et al., 2011	10	c-tDCS	PP	ADM	1	7	M1 (35/35)
	10	c-tDCS	PP	ADM	1	11	M1 (35/35)
	10	c-tDCS	PP	ADM	1	15	M1 (35/35)
Mordillo-Mateos et al., 2012	13	a-tDCS	RSCS	FDI	2	20	M1(35/35)
	13	c-tDCS	RSCS	FDI	2	5	M1(35/35)
Suzuki et al., 2012	9	a-tDCS	SBRSCS	FDI	1	10	M1(35/35)
Schade et al., 2012	8	a-tDCS	DBRSCS	FDI	1	5	M1(35/35)
	8	c-tDCS	DBRSCS	FDI	1	5	M1(35/35)
Hasan et al., 2012	18	c-tDCS	PP	FDI	1	9	M1 (35/35)
Alonzo et al., 2012	12	a-tDCS	PP	FDI	2	20	M1(35/35)
Grundey et al., 2012a	12	a-tDCS	RPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	RPCS	ADM	1	9	M1(35/35)
Grundey et al., 2012b	12	a-tDCS	RPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	RPCS	ADM	1	9	M1(35/35)
Tremblay et al., 2013	10	a-tDCS	PP	FDI	1.5	20	M1(25/35)
Galvez et al., 2013	11	a-tDCS	PP	FDI	2	20	M1(35/35)
Schabrun et al., 2013	21	a-tDCS	SBRSCS	APB	1	20	M1(35/35)
	9	c-tDCS	SBRSCS	APB	1	20	M1 (35/35)
Pellicciari et al., 2013	16	a-tDCS	PP	FDI	1	13	M1(25/25)
	16	c-tDCS	PP	FDI	1	9	M1(25/25)
Hasan et al., 2013	20	c-tDCS	PP	FDI	1	9	M1 (35/35)
Batsikadze et al., 2013	14	a-tDCS	SBRSCS	FDI	2	20	M1(35/100)
	14	c-tDCS	SBRSCS	FDI	2	20	M1(35/100)
	9	c-tDCS	SBRSCS	FDI	1	20	M1(35/100)
Kuo et al., 2013	14	a-tDCS	PP	ADM	2	10	M1(35/100)
	14	c-tDCS	PP	ADM	2	10	M1 (35/100)
Bastani and Jaberzadeh, 2013	12	a-tDCS	PP	ECR	0.3	10	M1(12/35)
	12	a-tDCS	PP	ECR	0.7	10	M1(24/35)
	12	a-tDCS	PP	ECR	1	10	M1(35/35)
Kim and Ko, 2013	11	a-tDCS	SBRSCS	FDI	2	20	M1(25/25)
Williams et al., 2013	4	a-tDCS	DBRSCS	BB	1.5	20	M1(35/35)
Simis et al., 2013	11	a-tDCS	DBRSCS	FDI	1	20	M1(35/35)
Kidgell et al., 2013	11	a-tDCS	DBRSCS	ECRL	1	13	M1(25/25)
Kidgell et al., 2013	14	a-tDCS	PP	ECRL	0.8,1,1.2	10	M1(25/25)
Monte-Silva et al., 2013	15	a-tDCS	PP	ADM	1	13	M1(35/35)
Wiethoff et al., 2014	53	a-tDCS	PP	FDI	2	10	M1(35/64)

Table 1 continued

Included study	Sample size (n)	tES	Trial design	Muscle	Intensity (mA)	Time (min)	Stimulation site (active/return)
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							electrode size cm ²)
Rizzo et al., 2014	10	a-tDCS	SBRSCS	APB	1	5	M1(35/35)
	10	c-tDCS	SBRSCS	APB	1	5	M1(35/35)
Santarnechchi et al., 2014	10	a-tDCS	RCS	FDI	1	15	M1(35/35)
	10	c-tDCS	RCS	FDI	1	15	M1(35/35)
Fresnoza et al., 2014a	12	a-tDCS	DBRPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	DBRPCS	ADM	1	9	M1(35/35)
Fresnoza et al., 2014b	12	a-tDCS	DBRPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	DBRPCS	ADM	1	9	M1(35/35)
Jaberzadeh et al., 2014	12	a-tDCS	SBRSCS	ECR	0.7	10	M1(35/35)
Lopez-Alonso et al., 2014	56	a-tDCS	PP	FDI	1	13	M1(35/35)
Moliadze et al., 2014	12	a-tDCS	DBRSCS	FDI	1	10	M1(16/84)
Jaberzadeh et al., 2015	11	a-tDCS	SBRSCS	FDI	0.7	10	M1(24/35)
Lopez-Alonso et al., 2015	45	a-tDCS	PP	FDI	1	13	M1(35/35)
Bastikadze et al., 2015	12	a-tDCS	SBRPCS	ADM	1	13	M1(35/35)
	12	c-tDCS	SBRSCS	ADM	1	9	M1(35/35)
Vaseghi et al., 2015	12	a-tDCS	SBRSCS	FDI	0.3	20	M1(3/12)
Lugon et al., 2015	13	a-tDCS	RPCS	ADM	1	13	M1(35/35)
Chew et al., 2015	29	a-tDCS	DBRCS	FDI	0.2,0.5,1,2	10	M116/35)
Lee et al., 2015	16	a-tDCS	SBRSCS	FDI	1	20	M1(18.49/18.49)
Ho et al., 2015	15	a-tDCS	SBRSCS	FDI	1,2	10	M1(35/35)
Amadi et al., 2015	13	a-tDCS	RCS	FDI	1	20	M1(35/35)
Davidson et al., 2016	19	a-tDCS	PP	FDI	2	20	M1(35/100)
Kuo et al., 2016	16	a-tDCS	RPCS	ADM	1	13	M1(35/35)
	16	a-tDCS	RPCS	ADM	1	9	M1(35/35)
Labruna et al., 2016	34	a-tDCS	PP	ADM	1	13	M1(35/35)
	34	c-tDCS	PP	ADM	1	9	M1(35/35)
Dyke et al., 2016	10	a-tDCS	SBRSCS	FDI	2	20	M1(35/35)
	10	c-tDCS	SBRSCS	FDI	2	20	M1(35/35)
Horvath et al., 2016	14	a-tDCS	SBRSCS	FDI	1	10	M1(35/35)
	14	c-tDCS	SBRSCS	FDI	1	10	M1(35/35)
Jamil et al., 2016	20	a-tDCS	SBRSCS	ADM	0.5,1,1.5,2	15	M1(35/100)
	18	c-tDCS	SBRSCS	ADM	0.5,1,1.5,2	15	M1(35/100)
Strube et al., 2016	59	a-tDCS	DBRSCS	FDI	1	13	M1(35/35)
	59	c-tDCS	DBRSCS	FDI	1	9	M1 (35/35)
Inukai et al., 2016	15	a-tDCS	PP	FDI	1	10	M1 (35/35)
Jaberzadeh et al., 2014	12	tPCS	SBRSCS	ECR	1.5	10,5	M1(35/35)
Jaberzadeh et al., 2015	11	tPCS	SBRSCS	FDI	1.5	20,10,5	M1(24/35)
Antal et al., 2008	10	tACS	DBRSCS	FDI	0.4	5	M1(16/50)

Moliadze et al., 2010b	12,8	tACS	SBRSCS	FDI	1	10	M1(16/84)
Chaieb et al., 2011a	11	tACS	RSCS	FDI	1	10	M1(48/48)
Moliadze et al., 2012	11	tACS	SBRSCS	FDI	0.2,0.4,0.6,0.8,1	10	M1(16/84)
Inukai et al., 2016	15	tACS	PP	FDI	1	10	M1(35/35)
		tRNS	PP	FDI	1	10	M1(35/35)
Terney et al., 2008	17,12	tRNS	SBRSCS	FDI	1	10	M1(16/84)
Moliadze et al., 2010a	11	tRNS	PP	FDI	1	10	M1(16/84)
Chaeib et al., 2011b	10,12	tRNS	SBRSCS	FDI	1	4-6	M1(16/84)
Ho et al., 2015	15	tRNS	SBRSCS	FDI	2	10	M1(35/35)
Moliadze et al., 2012	14	tRNS	SBRSCS	FDI	0.2,0.4,0.6,0.8,1	10	M1(16/84)
Moliadze et al., 2014	12	tRNS	DBRSCS	FDI	1	10	M1(16/84)

SBRSCS, Single-blinded randomized sham controlled study; SBRCS, single-blinded randomized controlled study; DBRPCS, double-blinded randomized placebo controlled study; RSCS, randomized sham controlled study; PP, pre-post; RCS, randomized controlled study; SBRPCS, single-blinded randomized placebo controlled study; RPCS, randomized placebo controlled study; DBRCS, double-blinded randomized sham controlled study; DBRCS, double-blinded randomized controlled study; ADM, abductor digit minimi; FDI, first dorsal interosseous; ECR, extensor carpi radialis; BB, biceps brachi; FCR, flexor carpi radialis; ECRL, extensor carpi radialislongus; APB, abductor pollicisbrevis; EDC, extensor digitorumcommunis; M1, primary motor cortex; a-tDCS, anodal transcranial direct current stimulation; tPCS, transcranial pulsed current stimulation; tACS, transcranial alternating current stimulation; tRNS, transcranial random noise stimulation.

Table 2. Analysis of normalized data for the effect of a-tDCS on MEPs amplitude (peak to peak, mV)

Study	Intervention	Sample size (n)	Baseline normalized (mV)	Post intervention (mV)
Nitche et al., 2000	a-tDCS	12 (1min)	1.00	0.93
	a-tDCS	12(2 min)	1.00	1.05
	a-tDCS	12(3 min)	1.00	1.31
	a-tDCS	12(4 min)	1.00	1.39
	a-tDCS	12(5 min)	1.00	1.43
	a-tDCS	12 (0.2 mA)	1.00	0.97
	a-tDCS	12(0.4 mA)	1.00	1.12

	a-tDCS	12(0.6 mA)	1.00	1.33
	a-tDCS	12(0.8 mA)	1.00	1.44
	a-tDCS	12(1 mA)	1.00	1.46
Nitsche et al., 2001	a-tDCS	12 (5min)	1.00	1.50
	a-tDCS	12(7min)	1.00	1.53
	a-tDCS	12(9 min)	1.00	1.51
	a-tDCS	12(11 min)	1.00	1.56
	a-tDCS	12(13 min)	1.00	1.52
Siebner et al., 2004	a-tDCS	8	1.00	1.23
	a-tDCS	5	1.00	1.19
Lang et al., 2004b	a-tDCS	8	1.00	1.31
Power et al., 2006	a-tDCS	10 (FDI)	1.00	1.13
	a-tDCS	5 (EDC)	1.00	1.18
Fricke et al., 2011	a-tDCS	8 (5 min)	1.00	2.04
	a-tDCS	12 (7 min)	1.00	1.18
Alonzo et al., 2012	a-tDCS	12	1.00	1.19
Galvez et al., 2013	a-tDCS	11	1.00	1.00
Santarnechchi et al., 2014	a-tDCS	10	1.00	1.04
Lopez-Alonso et al., 2014	a-tDCS	56	1.00	1.06
Lopez-Alonso et al., 2015	a-tDCS	45	1.00	1.11
	Average		1.00	1.28

Table 3. Analysis of normalized data for the effect of c-tDCS on MEPs amplitude (peak to peak, mV)

Study	Intervention	Sample size (n)	Baseline normalized (mV)	Post intervention (mV)
Siebner et al., 2004	c-tDCS	8	1.00	0.84
	c-tDCS	5	1.00	0.71

Lang et al., 2004b	c-tDCS	8	1.00	0.71
Power et al., 2006	c-tDCS	10 (FDI)	1.00	0.69
	c-tDCS	5 (EDC)	1.00	0.67
Fricke et al., 2011	c-tDCS	8 (5 min)	1.00	0.73
	c-tDCS	12 (7 min)	1.00	1.17
Santarnechchi et al., 2014	c-tDCS	10	1.00	0.93
Average			1.00	0.80

Table 4. Analysis of normalized data for the effect of a-tDCS on MEPs amplitude in placebo arm

Study	Intervention	Sample size (n)	Pre Mean	Post Mean
Libetanz et al., 2002	a-tDCS	8	1.00	1.31
Kuo et al., 2007	a-tDCS	12	1.00	1.30
Kuo et al., 2008	a-tDCS	11	1.00	1.40
Monte-Silva et al., 2009	a-tDCS	12	1.00	1.45
Nitsche et al., 2009	a-tDCS	12	1.00	1.20
Monte-Silva et al., 2010	a-tDCS	12	1.00	1.24
Thirugnasaddam et al., 2011	a-tDCS	12	1.00	1.13
Grundey et al., 2012b	a-tDCS	12	1.00	1.22
Fresnoza et al., 2014a	a-tDCS	12	1.00	1.38
Fresnoza et al., 2014b	a-tDCS	12	1.00	1.45
Average			1.00	1.30

Table 5. Analysis of normalized data for the effect of c-tDCS on MEPs amplitude in placebo arm

Study	Intervention	Sample size (n)	Pre Mean	Post Mean
Libetanz et al., 2002	c-tDCS	8	1.00	0.72
Kuo et al., 2007	c-tDCS	12	1.00	0.80
Kuo et al., 2008	c-tDCS	12	1.00	0.76
Monte-Silva et al., 2009	c-tDCS	12	1.00	0.86
Nitsche et al., 2009	c-tDCS	12	1.00	0.88
Monte-Silva et al., 2010	c-tDCS	12	1.00	0.80
Thirugnasaddam et al., 2011	c-tDCS	12	1.00	0.81
Grundey et al., 2012b	c-tDCS	12	1.00	0.84
Fresnoza et al., 2014a	c-tDCS	12	1.00	0.78
Fresnoza et al., 2014b	c-tDCS	12	1.00	0.69
Average			1.00	0.79

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