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Transcranial Direct Current Stimulation Post-Stroke Upper Extremity Motor Recovery Studies Exhibit a Dose–Response Relationship

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Abstract

Background and purpose—Transcranial direct current stimulation (tDCS) has shown mixed results in post-stroke motor recovery, possibly because of tDCS dose differences. The purpose of this meta-analysis was to explore whether the outcome has a dose–response relationship with various dose-related parameters.

Methods—The literature was searched for double-blind, randomized, sham-controlled clinical trials investigating the role of tDCS (5 sessions) in post-stroke motor recovery as measured by the Fugl-Meyer Upper Extremity (FM-UE) scale. Improvements in FM-UE scores were compared between active and sham groups by calculating standardized mean differences (Hedge’s g) to derive a summary effect size. Inverse-variance-weighted linear meta-regression across individual studies was performed between various tDCS parameters and Hedge’s g to test for dose–response relationships.

Results—Eight studies with total of 213 stroke subjects were included. Summary Hedge’s g was statistically significant in favor of the active group (Hedge’s $g = 0.61$, $p = 0.02$) suggesting moderate effect. Specifically, studies that used bihemispheric tDCS montage (Hedge’s $g = 1.30$, $p = 0.08$) or that recruited chronic stroke patients (Hedge’s $g = 1.23$, $p = 0.02$) showed large improvements in the active group. A positive dose–response relationship was found with current density ($p = 0.017$) and charge density ($p = 0.004$), but not with current amplitude. Moreover, a

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negative dose–response relationship was found with electrode size ($p < 0.001$, smaller electrodes were more effective).

Conclusions—Our meta-analysis and meta-regression results suggest superior motor recovery in the active group when compared to the sham group and dose–response relationships relating to electrode size, charge density and current density. These results need to be confirmed in future dedicated studies.

Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that can modulate (up- or down-regulate) cortical excitability of targeted brain regions. Recently, researchers have investigated the potential benefits of tDCS in various diseases, including post-stroke motor recovery. The common theoretical model upon which non-invasive brain stimulation is based for stroke patients takes into consideration: (1) interhemispheric inhibition of human motor cortex; and (2) the imbalance of such interhemispheric motor interactions after stroke with decreased motor activity in the lesional hemisphere and increased activity in the contralesional hemisphere [1,2]. Therefore, the approach for applying tDCS generally has been to either up-regulate the lesional hemisphere with excitatory anodal stimulation, or down-regulate the contralesional hemisphere with inhibitory cathodal stimulation, or use bihemispheric stimulation with anode on the lesional side and cathode on the contralesional side simultaneously [3].

Over a dozen clinical trials have been published to investigate the potential efficacy of transcranial direct current stimulation (tDCS) in post-stroke motor recovery using sham-controlled designs in quasi-randomized or randomized fashion. Different studies have used various current levels (1–2 mA), electrode size (16–35 cm²), session duration (7–40 minutes) and number of sessions (1–30 sessions), with mixed results in term of improving motor outcomes. However, there have been no dedicated dose/current comparison studies investigating the dose–response relationship in either stroke or other disease populations. It remains unclear whether higher doses of tDCS, as determined by the tDCS parameters we outlined, would be more effective in enhancing treatment efficacy while remaining safe and tolerable to stroke patients. tDCS does not necessarily follow simple dose–response relationship rules [4–6]. Therefore, knowledge of the optimal tDCS dosage to use in treating stroke recovery remains limited.

Several stimulation parameters have been tested experimentally primarily to determine the safety profile of stimulation [7]. Systemic reviews and meta-analyses have hinted on the overall efficacy of tDCS in post-stroke motor recovery [8–10]. The present meta-analysis aims to investigate the dose–response relationship by pooling the published studies in post-stroke upper extremity motor recovery. In order to compare across studies, we derived secondary stimulation parameters, namely, current density, charge, charge density, total charge and total charge density.

Methods

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement [11]. We systematically searched PubMed, EMBASE, and the clinical trial registry maintained at clinicaltrials.gov from 1980 to January 2014. The search terms are described in the study selection flow diagram (Fig. 1). A study was selected only if it met the inclusion and exclusion criteria (Table 1). Two investigators independently abstracted all data from any eligible publication, according to the standard protocol. Discrepancies were resolved by discussion between the two investigators. Authors were contacted in cases where we were unable to extract the data needed to calculate relevant statistics and most authors courteously provided us with the requested data. We used PEDro [12] and Jadad [13] scores to report risk of publication bias.

We adopted statistical methods used in Review Manager 5.3 (Cochrane IKMD – Copenhagen, Denmark; Freiburg, Germany; London, UK; USA) [14]. Briefly, we derived effect size as a standardized mean difference (Hedge's g) [15] of change scores [16] in Fugl-Meyer Upper Extremity Scale (FM-UE) [17] between active and sham stimulation groups. Change score is defined as the difference in FM-UE score between after and before the tDCS treatment (active or sham). Hedge's g is a context-independent measure of comparison across two groups. Conventionally, Hedge's g values of <0.2 , ~ 0.5 and >0.8 are considered as mild, moderate and strong effect, respectively. We defined Hedge's less-biased estimator $\hat{g}_i$ for an individual study i as [18],

$$\hat{g}_i = J(n_{i,tDCS} + n_{i,sham} - 2) \frac{\bar{d}_{(post-pre)i,tDCS} - \bar{d}_{(post-pre)i,sham}}{s_i} \quad (1)$$

where $\bar{d}_{(post-pre)i,tDCS}$ (or $\bar{d}_{(post-pre)i,sham}$) are mean change scores [19] (difference in the FM-UE score between before (pre-) and after (post-) active (or sham) stimulation) for a given study i . Likewise, $n_{i,tDCS}$ and $n_{i,sham}$ are the number of subjects in tDCS and sham groups, respectively, for a given study i . s_i is the pooled standard deviation for a given study i and is described as,

$$s_i = \sqrt{\frac{(n_{i,tDCS} - 1)s_{(post-pre)i,tDCS}^2 + (n_{i,sham} - 1)s_{(post-pre)i,sham}^2}{n_{i,tDCS} + n_{i,sham} - 2}} \quad (2)$$

where $s_{(post-pre)i,tDCS}$ and $s_{(post-pre)i,sham}$ are standard deviations of change scores of active and sham stimulation, respectively, for a given study i . Correction factor $J(\cdot)$ involves the gamma function [20] (Γ) and is described as,

$$J(a) = \frac{\Gamma\left(\frac{a}{2}\right)}{\sqrt{\frac{a}{2}}\Gamma\left(\frac{a-1}{2}\right)} \quad (3)$$

a simpler approximation of which is typically used in the majority of statistical software that we also used for consistency is,

$$J(n_{i,tDCS} + n_{i,sham} - 2) \approx 1 - \frac{3}{4(n_{i,tDCS} + n_{i,sham}) - 9} \quad (4)$$

The standard error of Hedge's g ($\sigma(\hat{g}_i)$) is calculated as,

$$\sigma(\hat{g}_i) = \sqrt{\frac{1}{n_{i,tDCS}} + \frac{1}{n_{i,sham}} + \frac{\hat{g}_i^2}{2(n_{i,tDCS} + n_{i,sham} - 3.94)}} \quad (5)$$

While the majority of studies reported mean and standard deviations of pre-tDCS and post-tDCS FM-UE scores, only a few studies reported the mean and standard deviations of the change scores. Therefore, we contacted the corresponding authors of publications that lacked the mean and standard deviations of the change scores for additional information. We successfully received values necessary to calculate Hedge's g from all but one study that met our inclusion criteria [21].

We combined results across studies using inverse-variance weighted pooling of Hedge's g . The summary estimate of Hedge's g , $\hat{g}_{IV}$, and its standard error, $\sigma(\hat{g}_{IV})$, are defined as,

$$\hat{g}_{IV} = \frac{\sum w_i \hat{g}_i}{\sum w_i} \quad (6)$$

$$\sigma(\hat{g}_{IV}) = \frac{1}{\sqrt{\sum w_i}} \quad (7)$$

where $\hat{g}_i$ is Hedge's unbiased estimator for a given study i and w_i is the weight assigned to that study which is calculated as,

$$w_i = \frac{1}{\sigma^2(\hat{g}_i)} \quad (8)$$

These weights can offer an unfair advantage to certain studies if the distribution of included studies is heterogeneous. We tested heterogeneity using the statistic Q_{IV} described as,

$$Q_{IV} = \sum w_i (\hat{g}_i - \hat{g}_{IV})^2 \quad (9)$$

from which heterogeneity index, I^2 , was calculated as,

$$I^2 = \max \left\{ 100\% \times \frac{Q_{IV} - (n-1)}{Q_{IV}}, 0 \right\} \quad (10)$$

where n is the number of individual studies included in the meta-analysis. We consider I^2 value of $>25\%$ as a presence of heterogeneity in the data, in which we assume that the effect sizes have a distribution

$$g \sim N(0, \tau^2) \quad (11)$$

where estimate of heterogeneity index, τ^2 , is given by

$$\hat{\tau}^2 = \max \left\{ \frac{Q_{IV} - (n-1)}{\sum w_i - (\sum w_i^2) / \sum w_i}, 0 \right\} \quad (12)$$

This estimate then was added when calculating the weight $w_{i,h}$ of the given study.

$$w_{i,h} = \frac{1}{\sigma^2(\hat{g}_i) + \hat{\tau}^2} \quad (13)$$

The summary estimate of Hedge's g given the heterogeneity, $\hat{g}_{IV,h}$, and its standard error, $\sigma(\hat{g}_{IV,h})$, are defined as,

$$\hat{g}_{IV,h} = \frac{\sum w_{i,h} \hat{g}_i}{\sum w_{i,h}} \quad (14)$$

$$\sigma(\hat{g}_{IV,h}) = \frac{1}{\sqrt{\sum w_{i,h}}} \quad (15)$$

The $100(1-\alpha)\%$ confidence interval for $\hat{g}_{IV,h}$ can be given by

$$\left(\hat{g}_{IV,h} - \sigma(\hat{g}_{IV,h}) \Phi \left(1 - \frac{\alpha}{2} \right), \hat{g}_{IV,h} + \sigma(\hat{g}_{IV,h}) \Phi \left(1 - \frac{\alpha}{2} \right) \right) \quad (16)$$

where Φ is the standard normal deviate. The Z-statistic can be calculated for significance as,

$$Z = \frac{\hat{g}_{IV,h}}{\sigma(\hat{g}_{IV,h})} \quad (17)$$

Note that Equations 13, 14 and 15 give the same results as Equations 8, 6 and 7, respectively, if I^2 value is 0 or, in other words, if Q_{IV} is less than the degrees of freedom ($n-1$).

tDCS studies typically list applied current (mA), electrode size (cm^2), tDCS duration (minutes) and number of tDCS sessions. Toward finding the appropriate tDCS dosage parameter most correlated with the outcome Hedge's g , we derived the following tDCS parameters by calculations (units in parenthesis) [7]:

$$\text{Current Density (mA/cm}^2\text{)} = \text{Current (mA)} \div \text{electrode size (cm}^2\text{)} \quad (18)$$

$$\text{Charge (mAh)} = \text{Current (mA)} \times \text{tDCS duration (minutes)} \div 60 \quad (19)$$

$$\text{Charge Density (mAh/cm}^2\text{)} = \text{Charge (mAh)} \div \text{electrode size (cm}^2\text{)} \quad (20)$$

$$\text{Total Charge (mAh)} = \text{Charge (mAh)} \times \text{tDCS sessions} \quad (21)$$

$$\text{Total Charge Density (mAh/cm}^2\text{)} = \text{Charge Density (mAh/cm}^2\text{)} \times \text{tDCS sessions} \quad (22)$$

We performed inverse-variance-weighted linear meta-regression by plotting Hedge's g against each of the dose parameters and obtained a linear fit using regress function of MATLAB (Mathworks, Natick, MA). Weighted least squares technique was implemented by multiplying weights W_i so that the sum below is minimized:

$$\sum_i W_i (\hat{g}_i - (b_0 + b_1 x_i)) \quad (23)$$

where $\hat{g}_i$ and W_i are Hedge's g and the weight (inverse of variance of Hedge's g) assigned to the study i (w_i if study population is deemed homogeneous or $w_{i,h}$ if heterogeneous). x_i is any of the dose variable, reported or derived, as described above. b_0 and b_1 represent y-intercept and slope, respectively.

Results

We included eight studies with a total of 213 stroke subjects in the final analysis (Fig. 1, Table 2) [22–29]. We found no concerns on risk of a publication bias in the included studies based on either PEDro [12] (Table 3) or Jadad [13] scores (Table 4). Inverse-variance-weighted linear meta-analysis of standardized mean difference (Hedge's g) on these studies revealed a medium effect size (summary Hedge's g) of 0.61 favoring tDCS (95% CI = [0.08, 1.13], $p = 0.02$, Fig. 2). Two studies in our meta-analysis had three groups (anodal, cathodal, sham) and reported outcome measures on both anodal and cathodal tDCS montages [24, 25]. Considering these two studies with 3 treatment groups, we had 10 data points in the meta-analysis with 252 subjects (instead of 8 data points with 213 subjects, because of duplication of subjects in the sham group of these two studies). We used random-effects model to account for this duplication (between-study variance $\tau^2 = 0.46$; heterogeneity index $I^2 = 71\%$). We grouped individual studies based on tDCS montage as anodal [24, 25, 28], cathodal [23–25, 27] or bihemispheric [22, 26, 29] (Fig. 2A) as well as based on the mean post-stroke duration as acute stroke [23–25, 28] or chronic stroke [22, 26, 27, 29] (mean time post-stroke 1 month or 2.5 years, respectively; Fig. 2B). A relatively large effect size was found with bihemispheric tDCS montage (Hedge's $g = 1.30$, 95% CI = [−0.14, 2.75], $p = 0.08$), but mild to moderate effect size was found with anodal

(Hedge's $g = 0.21$, 95% CI = $[-0.72, 1.14]$, $p = 0.65$) and cathodal (Hedge's $g = 0.43$, 95% CI = $[-0.23, 1.08]$, $p = 0.20$) montages. Studies that recruited subjects with chronic stroke showed larger effect size (Hedge's $g = 1.23$, 95% CI = $[0.20, 2.25]$, $p = 0.02$) while those with acute stroke subjects showed smaller effect size (Hedge's $g = 0.18$, 95% CI = $[-0.30, 0.66]$, $p = 0.07$). Inverse-variance-weighted linear meta-regression analysis of Hedge's g against tDCS dosage parameters revealed a positive dose–response relationship with current density ($R^2 = 0.45$, $p = 0.017$; Fig. 3C) and charge density ($R^2 = 0.60$, $p = 0.004$; Fig. 3B) as well as a negative dose–response relationship with electrode size ($R^2 = 0.79$, $p < 0.001$; Fig. 3A). No dose–response relationship was revealed in the other dose-related parameters including the conventional parameter – current amplitude (Fig. 3D–G).

Discussion

Study selection and data synthesis considerations

Previous tDCS meta-analyses regarding the efficacy of tDCS for post-stroke recovery have not been consistent [8–10]. This might be attributed to the study selection and data synthesis methodology as both can contribute significantly to the results and interpretation [16]. Since the goal is to evaluate the efficacy of tDCS (compared to Sham) treatment, we used mean and standard deviations of change scores [19] (post – pre difference of the outcome measure) for calculation of effect size (Hedge's g) in this meta-analysis.

Use of post-active treatment (or post-sham treatment) outcome values with an assumption of comparable pre-treatment baseline values can potentially lead to incorrect findings (Figs. 4 and 5). Three factors contribute to these incorrect findings. First, baseline (pre-treatment) outcome values in tDCS can be different although not being proven statistically. This is because the studies are not typically designed or powered to show that baseline outcome values of the two groups are comparable. Second, post-treatment outcome values already incorporate baseline differences across the groups and therefore offer a relatively noisy dataset to answer a question on tDCS efficacy across groups. Third, variance of post-treatment (tDCS or Sham) outcome values are different from change scores (post – pre difference) of the outcome. Since the value of standardized mean difference (e.g., Hedge's g as used here) depends heavily on variance of the outcome, selection of suboptimal outcome leads to inaccurate conclusions.

Different outcome measures have different scoring systems with different dispersion patterns. A normalized score of one outcome does not necessarily translate into a normalized score of another outcome. Extracting the same outcome measure across studies also prevents the confounding issue induced by different reference ranges of individual outcomes and the subsequent normalization. Due to this, we used only one outcome variable that is commonly available in the published tDCS literature namely the Fugl-Meyer Upper Extremity scale (FM-UE).

Stroke rehabilitation therapy is generally offered in more than 5 sessions. Additionally, it is less likely to observe changes on outcome measures, such as FM-UE, with single session tDCS. This premise led us to choose the clinical trial that is close to real world practice with 5 sessions.

With considerations above, we decided to include a few highly selective trials based on the selection criteria (Table 1). We present meta-analysis and meta-regression results from 8 studies with 213 stroke subjects (Fig. 1, Table 2).

Montage and time since stroke

Bihemispheric montage appears to offer superior recovery when compared with anodal or cathodal montages (Fig. 2A). As mentioned in the Introduction, bihemispheric montage may prove advantageous by simultaneously down-regulating neural activity on the non-lesioned hemisphere through cathodal stimulation and up-regulating neural activity on the lesioned hemisphere through anodal stimulation [1,2]. We also observed superior recovery among chronic stroke patients when compared with acute stroke patients (Fig. 2B). Several factors may explain this difference during the acute phase: patients included in the acute phase are more severely affected; the DCS effect may be masked by spontaneous motor recovery; and too many confounders in the acute phase may make it difficult to detect the tDCS treatment effect. Regardless, more data are needed to determine whether bihemispheric tDCS montage or chronic stroke state or both offer an advantage in post-stroke motor recovery. While we are confident on the overall effect of tDCS in post-stroke upper extremity motor recovery, we note that sub-comparisons on tDCS montage and time since stroke have 5 data points. Therefore, we caution against over-interpreting these results that should be viewed as mere trends rather than definite results. A confirmatory study is required.

Dose–response relationship

Using inverse-variance-based linear meta-regression, we demonstrate the dose–response relationships of current density, charge density and pad size with tDCS-related improvement (Fig. 3). Our findings suggest that proper selection of tDCS current amplitude, electrode and duration of stimulation might play an important role in maximizing therapeutic efficacy of tDCS in post-stroke motor recovery. Furthermore, these findings are consistent with tDCS studies in healthy subjects that demonstrated a similar dose–response relationship (response is defined as Transcranial Magnetic Stimulation (TMS)-induced Motor Evoked Potential (MEP), a measurement of cortical excitability) with electrode size [5] as well as with current density [31]. Our analysis did not find statistically significant dose–response relationships for many stimulus parameters (applied current, duration of stimulation, number of sessions) and derived parameters (charge, total charge, total charge density). However, we cannot exclude the importance of these dose-related parameters due to the small number of studies and the relatively small sample size of included patients in this meta-analysis. Therefore, we again underscore the need for more studies to confidently identify the stimulus parameters responsible in tDCS-related post-stroke upper extremity motor recovery.

Our study, for the first time, reveals a dose–response relationship in tDCS response in stroke upper extremity studies. Specifically, higher tDCS current with appropriate electrode size, i.e., higher current density, may lead to better motor recovery. Two prior studies have hinted such response in healthy controls [5,31]. The majority of human studies have capped the current amplitude at 2 mA (i.e. current density 0.03–0.09 mA/cm²). It remains unknown whether such dose–response relationship observed in this meta-analysis would extend to the range beyond 0.09 mA/cm². Question also rises whether higher dosage is safe to humans,

especially to stroke patients. In animal studies, at least two orders of magnitude higher current density (up to 14.29 mA/cm²) than the one typically generated with 1–2 mA current in human tDCS studies have been administered without risking brain injury [32,33]. In general, the present tDCS study protocol has been well tolerated by stroke patients as well as subjects with other disease conditions. Out of the included 8 studies, only one had two subjects discontinue because of possible tDCS-related headache (anodal) or dizziness (cathodal) [25]. The remaining subjects tolerated tDCS well without safety concerns. However, we did note that safety was not the primary focus of the included studies. A recent tDCS safety study raised a concern of possible negative impact on cerebral autoregulation in stroke patients with carotid stenosis demanding careful safety evaluation in this vulnerable population [34]. In 1964, a case with drastic but reversible changes in brain function following 3 mA current applied bitemporally was reported with potential brainstem involvement combined with higher electric fields generated during tDCS application [35]. However, no clear description of the physical attributes of the used electrodes (size, the current density) was provided on this reported case. Safety concerns with higher charge density [7,32] align with the positive dose–response relationship results presented here. Skin is the first barrier encountered by penetrating current, making it prone to injury [36–39], that may not necessarily be linked with brain injury. Skin/scalp injury can be a critical safety issue in addition to the safety to the brain tissue. Given the variability of skin resistance across species [40] and human races [41], skin injury can be minimized in clinical trials by skin preparation to decrease the resistance of skin, e.g., hydration [42], moisturization [43], or other skin pre-treatment [44].

Limitations

Different studies offer various amounts and types of physical therapy along with the tDCS stimulation (active or sham). For example, Constraint-Induced Movement Therapy was offered for up to 4 hours per day with simultaneous tDCS for 10 sessions in one study while Robot Arm Assisted Training along with tDCS was used for 20 minutes for 6 weeks in another study. Detailed dosage or method of administration of such therapies was not typically provided, limiting the inclusion of such information for quantitative analysis. Number of sessions and duration of therapy only provide crude but poor estimation of the amount of therapy. This is a major limitation of our study.

Caution should be exercised when generalizing the results presented here in motor outcomes other than FM-UE, stroke recovery in non-motor domains, e.g., language or vision, other disease conditions or healthy population. Complementary meta-analyses can fill this gap, e.g., a recently accepted abstract suggests higher current density (at 0.13 mA/cm²) for tDCS produces greater changes in cortical excitability in healthy subjects [45]. However, such findings in healthy subjects (without brain lesion) cannot always serve as a surrogate for stroke patients (with brain lesion). Finally, extrapolating the dose–response relationship into the domain of higher amplitude tDCS stimulation (i.e., >2 mA) should be done with caution as well.

Conclusion

Meta-analysis of tDCS upper extremity motor recovery studies reveals a dose–response relationship with electrode size, charge density and current density – a higher charge or current density or smaller electrode size is associated with greater efficacy on post-stroke upper extremity motor recovery. A relatively larger effect size of tDCS is observed in subjects with chronic stroke or in subjects undergoing bihemispheric montage. Future dedicated studies are required to formally test the tDCS dose–response relationship and to determine the optimal dosage before launching further clinical trials in post-stroke motor recovery.

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References

1. Ferbert A, Priori A, Rothwell JC, Day BL, Colebatch JG, Marsden CD. Interhemispheric inhibition of the human motor cortex. *J Physiol.* 1992; 453:525–46. [PubMed: 1464843]
2. Di Lazzaro V, Oliviero A, Profice P, Insola A, Mazzone P, Tonali P, et al. Direct demonstration of interhemispheric inhibition of the human motor cortex produced by transcranial magnetic stimulation. *Exp Brain Res.* 1999; 124:520–4. [PubMed: 10090664]
3. Schlaug G, Renga V. Transcranial direct current stimulation: a noninvasive tool to facilitate stroke recovery. *Expert Rev Med Devices.* 2008; 5:759–68. [PubMed: 19025351]
4. Kuo HI, Bikson M, Datta A, Minhas P, Paulus W, Kuo MF, et al. Comparing cortical plasticity induced by conventional and high-definition 4×1 ring tDCS: a neurophysiological study. *Brain Stimul.* 2013; 6:644–8. [PubMed: 23149292]
5. Bastani A, Jaberzadeh S. A-tDCS differential modulation of corticospinal excitability: the effects of electrode size. *Brain Stimul.* 2013; 6:932–7. [PubMed: 23664681]
6. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* 2012; 5:175–95. [PubMed: 22037126]
7. Nitsche MA, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W. Safety criteria for transcranial direct current stimulation (tDCS) in humans. *Clin Neurophysiol.* 2003; 114:2220–2. author reply 2222–2223. [PubMed: 14580622]
8. Bastani A, Jaberzadeh S. 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 meta-analysis. *Clin Neurophysiol.* 2012; 123:644–57. [PubMed: 21978654]
9. Butler AJ, Shuster M, O'Hara E, Hurley K, Middlebrooks D, Guilkey K. A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors. *J Hand Ther.* 2013; 26:162–70. quiz 171. [PubMed: 22964028]
10. Marquez J, van Vliet P, McElduff P, Lagopoulos J, Parsons M. Transcranial direct current stimulation (tDCS): does it have merit in stroke rehabilitation? A systematic review. *Int J Stroke.* 2015; 10(3):306–16. [PubMed: 24148111]

11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *BMJ*. 2009; 339:b2535. [PubMed: 19622551]
12. Blobaum P. Physiotherapy evidence database (pedro). *J Med Libr Assoc*. 2006; 94:477–8.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996; 17:1–12. [PubMed: 8721797]
14. Review manager (revman) version 5.3; 2014.
15. Hedges LV. Distribution theory for glass's estimator of effect size and related estimators. *J Educ Behav Stat*. 1981; 6:107–28.
16. Chhatbar PY, Feng W. Data synthesis in meta-analysis may conclude differently on cognitive effect from transcranial direct current stimulation. *Brain Stimul*. 201510.1016/j.brs.2015.06.001.
17. Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med*. 1975; 7:13–31. [PubMed: 1135616]
18. Hedges, LV.; Olkin, I. Statistical method for meta-analysis. Academic press; 2014.
19. Allison PD. Change scores as dependent variables in regression analysis. *Sociol Methodol*. 1990; 20:93–114.
20. Rainville, ED. Special functions. New York: 1960.
21. Rossi C, Sallustio F, Di Legge S, Stanzione P, Koch G. Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients. *Eur J Neurol*. 2013; 20:202–4. [PubMed: 22448901]
22. Bolognini N, Vallar G, Casati C, Latif LA, El-Nazer R, Williams J, et al. Neurophysiological and behavioral effects of tdcS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair*. 2011; 25:819–29. [PubMed: 21803933]
23. Fusco A, Assenza F, Iosa M, Izzo S, Altavilla R, Paolucci S, et al. The ineffective role of cathodal tdcS in enhancing the functional motor outcomes in early phase of stroke rehabilitation: an experimental trial. *Biomed Res Int*. 2014; 2014:547290. [PubMed: 24895588]
24. Hesse S, Waldner A, Mehrholz J, Tomelleri C, Pohl M, Werner C. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized multicenter trial. *Neurorehabil Neural Repair*. 2011; 25:838–46. [PubMed: 21825004]
25. Kim DY, Lim JY, Kang EK, You DS, Oh MK, Oh BM, et al. Effect of transcranial direct current stimulation on motor recovery in patients with subacute stroke. *Am J Phys Med Rehabil*. 2010; 89:879–86. [PubMed: 20962598]
26. Lindenberg R, Renga V, Zhu LL, Nair D, Schlaug G. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology*. 2010; 75:2176–84. [PubMed: 21068427]
27. Nair DG, Renga V, Lindenberg R, Zhu L, Schlaug G. Optimizing recovery potential through simultaneous occupational therapy and non-invasive brain-stimulation using tdcS. *Restor Neurol Neurosci*. 2011; 29:411–20. [PubMed: 22124031]
28. Sattler V, Acket B, Raposo N, Albucher JF, Thalamas C, Loubinoux I, et al. Anodal tdcS combined with radial nerve stimulation promotes hand motor recovery in the acute phase after ischemic stroke. *Neurorehabil Neural Repair*. 2015; 29(8):743–54. [PubMed: 25567120]
29. Viana RT, Laurentino GE, Souza RJ, Fonseca JB, Silva Filho EM, Dias SN, et al. Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: a pilot randomized controlled trial. *Neurorehabilitation*. 2014; 34:437–46. [PubMed: 24473248]
30. Di Lazzaro V, Dileone M, Capone F, Pellegrino G, Ranieri F, Musumeci G, et al. Immediate and late modulation of interhemispheric imbalance with bilateral transcranial direct current stimulation in acute stroke. *Brain Stimul*. 2014; 7:841–8. [PubMed: 25458712]
31. Bastani A, Jaberzadeh S. Differential modulation of corticospinal excitability by different current densities of anodal transcranial direct current stimulation. *PLoS ONE*. 2013; 8:e72254. [PubMed: 23991076]
32. Liebetanz D, Koch R, Mayenfels S, Konig F, Paulus W, Nitsche MA. Safety limits of cathodal transcranial direct current stimulation in rats. *Clin Neurophysiol*. 2009; 120:1161–7. [PubMed: 19403329]

33. McCreery DB, Agnew WF, Yuen TG, Bullara L. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *IEEE Trans Biomed Eng.* 1990; 37:996–1001. [PubMed: 2249872]
34. List J, Lesemann A, Kubke JC, Kulzow N, Schreiber SJ, Floel A. Impact of tdcS on cerebral autoregulation in aging and in patients with cerebrovascular diseases. *Neurology.* 2015; 84:626–8. [PubMed: 25576632]
35. Lippold OC, Redfearn JW. Mental changes resulting from the passage of small direct currents through the human brain. *Br J Psychiatry.* 1964; 110:768–72. [PubMed: 14211693]
36. Palm U, Keeser D, Schiller C, Fintescu Z, Nitsche M, Reisinger E, et al. Skin lesions after treatment with transcranial direct current stimulation (tdcs). *Brain Stimul.* 2008; 1:386–7. [PubMed: 20633396]
37. Frank E, Wilfurth S, Landgrebe M, Eichhammer P, Hajak G, Langguth B. Anodal skin lesions after treatment with transcranial direct current stimulation. *Brain Stimul.* 2010; 3:58–9. [PubMed: 20633432]
38. Wang J, Wei Y, Wen J, Li X. Skin burn after single session of transcranial direct current stimulation (tdcs). *Brain Stimul.* 2015; 8:165–6. [PubMed: 25468075]
39. Riedel P, Kabisch S, Ragert P, von Kriegstein K. Contact dermatitis after transcranial direct current stimulation. *Brain Stimul.* 2012; 5:432–4. [PubMed: 21986238]
40. Davies DJ, Ward RJ, Heylings JR. Multi-species assessment of electrical resistance as a skin integrity marker for in vitro percutaneous absorption studies. *Toxicol in Vitro.* 2004; 18:351–8. [PubMed: 15046783]
41. Wesley NO, Maibach HI. Racial (ethnic) differences in skin properties: the objective data. *Am J Clin Dermatol.* 2003; 4:843–60. [PubMed: 14640777]
42. Rim JH, Jo SJ, Park JY, Park BD, Youn JI. Electrical measurement of moisturizing effect on skin hydration and barrier function in psoriasis patients. *Clin Exp Dermatol.* 2005; 30:409–13. [PubMed: 15953083]
43. Clar E, Her C, Sturelle C. Skin impedance and moisturization. *J Soc Cosmet Chem.* 1975; 26:337–53.
44. Lecomte MM, Atkinson KR, Kay DP, Simons JL, Ingram JR. A modified method using the sonoprep ultrasonic skin permeation system for sampling human interstitial fluid is compatible with proteomic techniques. *Skin Res Technol.* 2013; 19:27–34. [PubMed: 22697890]
45. Ho K-A, Taylor JL, Chew T, Galvez V, Alonzo A, Loo CK. Higher current densities for transcranial direct current stimulation produce greater changes in cortical excitability – evidence from a pooled data study. *Brain Stimul.* 2015; 8:350.

Figure 1.
Flow chart depicting selection algorithm and numbers of included and excluded studies.

Figure 2.

tDCS shows moderate effect in post-stroke upper extremity motor recovery, with strong subgroup effect in case of bihemispheric tDCS montage applied on subjects with chronic stroke. Meta-analysis of improvement in Fugl Meyer Upper Extremity (FM-UE) scores in subjects with stroke after application of tDCS when compared with sham suggests superior effect with bihemispheric tDCS montage in subjects with chronic stroke. Individual studies are segregated by tDCS montage (A) and by stage of stroke (B). Effect sizes were calculated as Standardized Mean Difference (Hedge's g). Forest plots on the right of the panels show individual studies with weights represented as the size of the square and 95% confidence intervals as whiskers. Summary Hedge's g is shown at the bottom of the group as a black filled diamond with the width covering 95% confidence interval. Overall summary Hedge's g across groups is shown at the bottom of the panel. Note that all the studies that applied bihemispheric tDCS montage (A) happened to recruit subjects that were in chronic stage

(B). Similarly, the majority of studies that applied anodal or cathodal tDCS montage (A) happened to recruit subjects that were in acute stage (average time since stroke = 1 month, B). Colored signs next to individual studies represent subjects with acute (red) or chronic (blue) stroke that are offered anodal (circle), cathodal (diamond) or bihemispheric (square) tDCS montage. Colors and shapes of the signs next to individual studies match those used in Fig. 3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Figure 3.

Dose-response relationship. Plots showing that the improvement in FM-UE scores after tDCS active stimulation group when compared with sham group (Hedge's g) is positively correlated with current density and charge density, and negatively correlated with electrode size. Inverse-variance-weighted linear meta-regression of Hedge's g against dose-related parameters revealed statistical significance for pad size (A), charge density (B) and current density (C) as shown by solid black regression line with coefficient of determination (R^2), significance value (p) and equation shown next to the line (A–C). However, we did not find statistical significance for any other derived (D–F) or primary (G–I) dose-related parameters, as shown by dashed regression line.

Figure 4.

Suboptimal synthesis of data may lead to misleading results. Meta-analysis of Fugl-Meyer Upper Extremity (FM-UE) scores in patients with stroke after application of active or sham treatment is shown. Note that here Hedge's g (noted in the figure as Standardized Mean Difference) are calculated from mean and standard deviation of FM-UE scores after tDCS or sham treatments in individual studies ("Post" column in Table 2), which are different from Hedge's g calculated from the change scores ("Change" column in Table 2). Compare with Fig. 2.

Figure 5.

Use of change scores may lead to different estimates of effect size when compared with using post-treatment scores. (A–C) Data from three publications are shown in individual panels as groups of subjects were offered a given intervention (tDCS stimulation – Bihemispheric, Anodal, Cathodal – or sham stimulation). Pre-treatment (white dots) and post-treatment (red dots) outcome values for a given subject are joined by a line and the change scores (difference between the two, green dots) are shown separately. Confidence interval bars and values are shown as well (mean $\pm$ SD). Note that individual subjects have different Post-, Pre- and Change scores in a given study in a given group. More importantly, range of standard deviation of Pre- or Post-treatment can be different from change scores. For example, change scores SD are larger in case of tDCS groups but smaller in case of sham groups in Di Lazzaro (2014) [30] (A), marginally smaller in Hesse (2011) [24] (B) and much smaller than Post-values in Lindenberg (2010) [26] (C) study. Therefore using Post-treatment values to calculate Hedge's g and its distribution (variance), and in turn weights assigned to them in case of inverse-variance model (D), can be very different from when change scores are used (E). Specifically, smaller SD of change scores relative to post scores led to marked increase in the effect size in Lindenberg (2010) study (2.86 versus 0.22). Signs of mean values are changed for Di Lazzaro (2014) study to keep the effect directionality consistent with rest of the two studies. D and E are generated for demonstration purposes only. We recommend avoid mixing different outcome measures

during data synthesis (see Discussion section). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1

Inclusion and exclusion criteria for included clinical trials.

Criteria	Inclusion	Exclusion
Participants	<ul style="list-style-type: none"> Individuals over 18 years of age Diagnosis of stroke 	<ul style="list-style-type: none"> Non-human subjects Healthy subjects Subjects with no stroke
Intervention	<ul style="list-style-type: none"> Ipsilesional anodal tDCS (C3/C4–FP2/FP1) montage Contralesional cathodal tDCS (FP2/FP1–C3/C4) montage Bihemispheric tDCS (C3/C4–C4/C3) montage with anodal on ipsilesional side At least 5 sessions of intervention (tDCS or sham) 	<ul style="list-style-type: none"> Ipsilesional cathodal tDCS (FP1/FP2–C4/C3) montage Extracerebral tDCS (reference or cathodal lead on shoulder or part of the body other than head) montage Less than 5 sessions of intervention (tDCS or sham)
Comparison	<ul style="list-style-type: none"> Studies with comparison of interest to “sham tDCS” 	<ul style="list-style-type: none"> Lack of “Sham tDCS” as a comparison group
Outcome	<ul style="list-style-type: none"> Studies with Fugl-Meyer Upper Extremity (FM-UE) as a reported outcome variable 	<ul style="list-style-type: none"> Other types of outcome measures including behavioral outcomes (NIHSS, WMFT etc.) or electrophysiological outcomes (MEPs as measured from TMS, paired TMS, rTMS, fMRI) without reporting FM-UE
Trial design	<ul style="list-style-type: none"> Randomized controlled trials with double blinding 	<ul style="list-style-type: none"> Non-blinded or single-blinded trials Non-randomized trials Case reports Review articles
Data reported	<ul style="list-style-type: none"> Data that enables analysis of effect of tDCS on FM-UE must be reported or obtained from authors 	
Type of publication	<ul style="list-style-type: none"> Articles of English language published in a peer-reviewed journal 	<ul style="list-style-type: none"> Non-English articles Non-peer-reviewed articles

NIHSS: National Institute of Health Stroke Scale; WMFT: Wolfe Motor Function Test; MEP: motor-evoked potential; TMS: transcranial magnetic stimulation; rTMS: repetitive TMS; fMRI: functional magnetic resonance imaging.

Table 2

Extracted and synthesized data from the included studies.

Study	Publication Year	PEDro Score	Jardad Score	Time since Stroke (months)	Group	Stim parameters				Derived parameters					tDCS group						Sham group						Effect size (Hedges's g)	SD(g)		
						Current (mA)	Pul Size (cm ²)	Duration (min)	Sessions	Current Density (mA/cm ²)	Charge (mAh)	Charge Density (mAh/cm ²)	Total Charge (mAh)	Total Charge Density (mAh/cm ²)	Mean			SD			Subjects	Mean			SD				Subjects	
															Pre	Post	Change	Pre	Post	Change		Pre	Post	Change	Pre	Post				Change
Bolognini	2011	8	3	35.21	Bi-S	2.00	35.00	40	10	0.06	1.33	0.04	13.33	0.38	25.43	31.74	5.90	10.85	13.14	5.06	7	27.57	29.00	1.40	18.18	20.37	3.41	7	0.98	0.58
Fusco	2014	8	5	1.00	C-S	1.50	35.00	10	10	0.04	0.25	0.01	2.50	0.07	29.79	33.71	4.00	28.49	29.36	5.00	5	20.44	24.57	4.00	21.42	22.72	7.00	6	0.00	0.61
Hesse	2011	10	5	0.84	A-S	2.00	35.00	20	30	0.06	0.67	0.02	20.00	0.57	7.63	18.38	10.75	3.76	14.39	11.77	32	8.81	20.72	11.91	4.50	15.12	11.43	32	-0.10	0.25
Hesse	2011	10	5	0.89	C-S	2.00	35.00	20	30	0.06	0.67	0.02	20.00	0.57	7.97	19.69	11.72	3.36	10.59	8.39	32	8.81	20.72	11.91	4.50	15.12	11.43	32	-0.02	0.25
Kim	2010	11	5	0.93	A-S	2.00	25.00	20	10	0.08	0.67	0.03	6.67	0.27	30.92	45.47	25.67	10.92	12.36	12.32	6	41.01	49.27	2.29	13.18	12.14	13.86	7	1.65	0.68
Kim	2010	11	5	0.71	C-S	2.00	25.00	20	10	0.08	0.67	0.03	6.67	0.27	39.18	52.94	21.80	19.05	18.91	16.39	5	41.01	49.27	2.29	13.18	12.14	13.86	7	1.21	0.66
Lindenber	2010	8	4	35.40	Bi-S	1.50	16.30	30	5	0.09	0.75	0.05	3.75	0.23	38.20	43.80	5.60	13.57	13.00	1.93	10	39.75	40.90	1.15	11.54	11.85	0.85	10	2.87	0.68
Nair	2011	8	3	30.50	C-S	1.00	25.00	30	5	0.04	0.50	0.02	2.50	0.10	29.60	33.70	4.14	11.40	12.90	2.70	7	30.60	32.30	1.61	10.20	9.80	1.50	7	1.08	0.59
Saiter	2015	10	5	0.18	A-S	1.20	35.00	13	5	0.03	0.26	0.01	1.30	0.04	-	-	6.60	-	-	4.20	10	-	-	-	9.00	-	6.20	10	-0.43	0.45
Yuan	2014	11	5	33.45	Bi-S	2.00	35.00	13	15	0.06	0.43	0.01	6.50	0.19	41.30	39.40	9.30	16.20	17.40	5.70	10	50.60	46.90	7.50	13.40	12.40	7.10	10	0.27	0.45

Each column or group of columns is color-coded for easy quantification of the values.

Table 3

PEDro score of included studies.

PEDro score	Bolognini	Fusco	Hesse	Kim	Lindenberg	Nair	Sattler	Viana
1. Eligibility criteria were specified	1	1	1	1	1	1	1	1
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	1	1	1	1	1	1	1	1
3. Allocation was concealed	0	0	0	1	0	0	0	1
4. The groups were similar at baseline regarding the most important prognostic indicators	1	1	1	1	1	1	1	1
5. There was blinding of all subjects	1	1	1	1	1	1	1	1
6. There was blinding of all therapists who administered the therapy	1	0	1	1	1	1	1	1
7. There was blinding of all assessors who measured at least one key outcome	1	1	1	1	1	1	1	1
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	0	0	1	1	0	0	1	1
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	0	1	1	1	0	0	1	1
10. The results of between-group statistical comparisons are reported for at least one key outcome	1	1	1	1	1	1	1	1
11. The study provides both point measures and measures of variability for at least one key outcome	1	1	1	1	1	1	1	1
TOTAL	8	8	10	11	8	8	10	11

Table 4

Jadad score of included studies.

Jadad score	Bolognini	Fusco	Hesse	Kim	Lindenberg	Nair	Sattler	Viana
1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	1	1	1	1	1	1	1	1
2. Was the study described as double blind?	1	1	1	1	1	1	1	1
3. Was there a description of withdrawals and dropouts?	0	1	1	1	0	0	1	1
Give 1 additional point if: For question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.) and/or: If for question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)	0	1	1	1	1	0	1	1
Deduct 1 point if: For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) and/or: For question 2, the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)	1	1	1	1	1	1	1	1
TOTAL	3	5	5	5	4	3	5	5