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Transcranial Direct Current Stimulation and Its Effects on Upper Extremity Neurorehabilitative Training in Stroke: A Meta-Analysis

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Abstract

Objectives: To evaluate the efficacy of tDCS as an adjuvant to neuro-rehabilitative training in stroke patients with motor deficits by a meta-analysis and discuss the results critically in the view of the current literature.

Methods: In the current analyses, we included randomized controlled trials applying tDCS to primary motor areas (anodal, cathodal, bihemispheric) combined with motor training to improve upper extremity deficits in stroke patients. Two pooled effect size meta-analyses were performed to address immediate and longer-lasting effects of tDCS. A meta-regression model was performed to evaluate tDCS dose-response relationships and the influence of various moderator factors.

Results: A total of 35 studies were included. For both, the immediate and longer-lasting analyses, tDCS respectively demonstrated a significant impact on rehabilitative training with a moderate effect size of +0.52 ($p < 0.001$) and +0.69 ($p < 0.001$). A negative direct linear relationship was found between tDCS efficacy and the number of stimulation sessions. No significant relationships were found between tDCS efficacy and other moderator factors such as charge density, stimulation type, phase after stroke, time point of assessment, training type.

Conclusions: The current results support the therapeutic potential of tDCS as an adjuvant treatment strategy to enhance neurorehabilitative training in stroke patients with upper extremity deficits. Treatment effects are mixed between studies, which might be explained by a considerable amount of heterogeneity due to moderator factors that have to be identified in more detail. Understanding such moderator factors and their impact on the treatment effect will pave the way to precision medicine approaches for motor recovery based on tDCS to maximize the magnitude of neuro-rehabilitation in patients suffering from stroke.

Abbreviations

ES: Effect Size; BCI: Brain Computer Interface; RCT: Randomized Clinical Trial; SMD: Standardized Mean Difference; tDCS: Transcranial Direct Current Stimulation; UE-FM: Upper Extremity Fugl-Meyer score

Introduction

Stroke is a relevant health problem worldwide in terms of prevalence, mortality, long-term disability, quality of life and respective health care costs and societal impact [1,2]. Among the different deficits, motor impairment of the upper limb, alongside with aphasia and cognitive impairments, are the most common deficits with pronounced impact on re-integration into normal life [3,4]. At present, guideline-based treatment strategies lead to full recovery in only 15% of patients, leaving the larger part of patients with long-term disabilities [5]. Therefore, novel treatment strategies are constantly developed and evaluated [6,7]. In the last years, Non-Invasive Brain Stimulation (NIBS) techniques, e.g., Transcranial Direct Current Stimulation (tDCS), have shown promising effects in facilitating the learning of novel motor tasks in healthy subjects [8,9]. These

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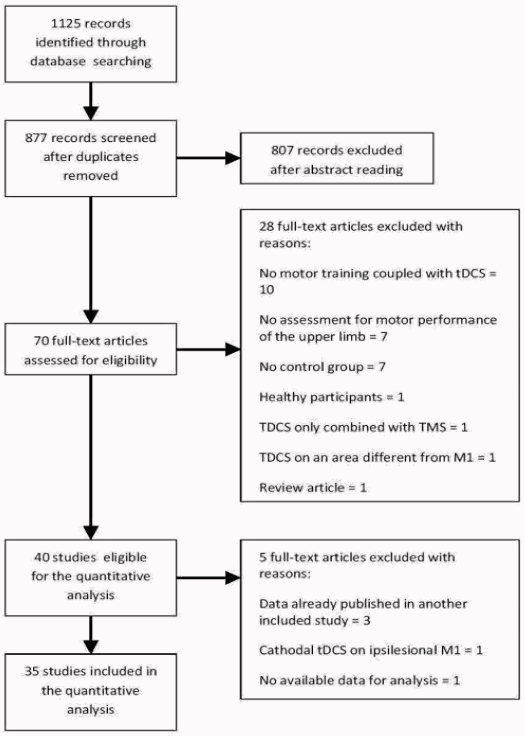

Figure 1: Study selection PRISMA flow chart.

promising results, combined with the opportunity to perform non-invasive, safe and cost-effective modulation of neural plastic processes and behavior, explain the large interest towards these techniques and their therapeutic application in motor rehabilitation for stroke patients [10-13]. In the present review, we will focus on the field of tDCS and neurorehabilitative motor training of the upper extremity to enhance functional recovery. We will provide a brief introduction in the field, present the methods and results for the meta-analyses, and discuss the findings in the view of the current literature. In the last part, we will provide a future outlook of the field. Research performed in the last decade, suggests that tDCS could possibly have a beneficial adjuvant effect in stroke rehabilitation. Despite this, a consistent significant impact of tDCS on the course of recovery is still not demonstrated, leaving many questions unanswered [14,15]. Evaluating the efficacy of tDCS is accompanied by relevant challenges. One of them is the lack of a detailed understanding of the pathophysiological phenomena underlying stroke recovery, and of the neurophysiological effects induced by tDCS, making the interpretation of the interaction between the two processes difficult [16]. Furthermore, NIBS-based interventions are applied in a 'one suits all, non-precision' way, independent of individual differences and clinical heterogeneity between patients. This might be due to the fact that NIBS-based interventional strategies are based on a model of "dysbalanced inter-hemispheric competition"[17], and to the fact that 'biomarkers' for treatments, tailored to the individual patients' characteristics, such as lesion site, time after stroke or white matter involvement, are still not fully available and used for patient stratification [18]. The adopted model is too simplistic to reflect the complexity of the mechanisms underlying stroke recovery. Driven by the growing need to define the factors influencing the responses to tDCS, several meta-analyses and clinical trials focused on specific variables and classes of patients [19-21]. Nevertheless the question related to the importance of "dose-response effects" in tDCS protocols for stroke rehabilitation has only marginally been investigated. The majority of clinical trials published to date focused on short-time (few days) stimulation varying between one to ten sessions of stimulation per patient [21]. Increasing the intensity of tDCS interventions might be a decisive factor in determining its efficacy and relevance for rehabilitative applications. At the same time, a direct linear relationship is far from being obvious. First, the definition of "dose of treatment" in the context of tDCS can be based on several factors, the modulation of which can differently affect the efficacy of the stimulation. For instance, doubling the intensity of the stimulation current does not have the same effect as doubling the number of stimulation sessions, even though they both can be considered as an increase of the dose of treatment. In addition, several factors might interact and hereby influence the dose-response relationship (e.g., time after stroke, lesion type and location). The main purpose of the present meta-analysis was to evaluate the efficacy of tDCS as an adjuvant to rehabilitative therapies for stroke patients and to investigate the dose-response relationships within this setting. As motor deficits represents one of the most frequent and most impairing symptoms, we focused on studies, where tDCS was administered before or during active motor training of the upper extremity [15,22]. To date only one other meta-analysis, from Chamber et al.[23], investigated the relationship between the intensity of the tDCS treatment and its resulting efficacy in improving recovery of upper extremity motor deficits after stroke, measured as increases from baseline of the Upper Extremity Fugal-Meyer (UE-FM) score. In this

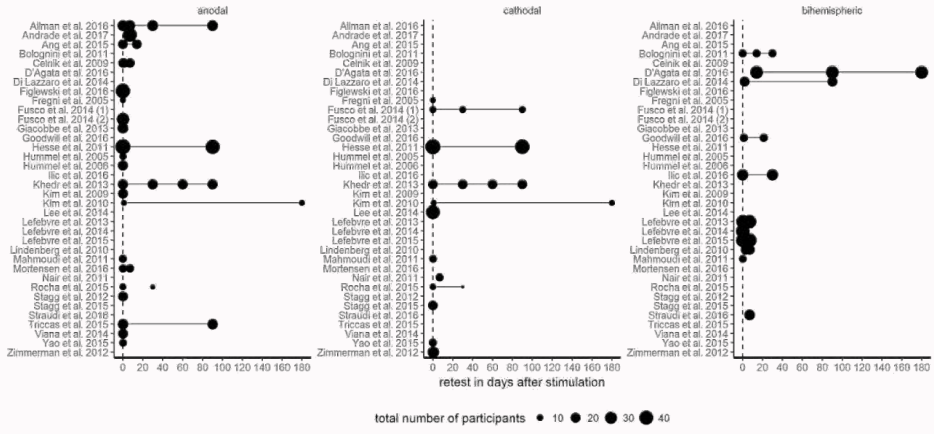

Figure 2: Time points of outcome assessments.

Figure 3: Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

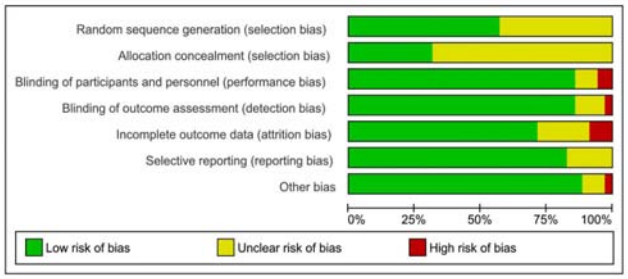

Figure 4: Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

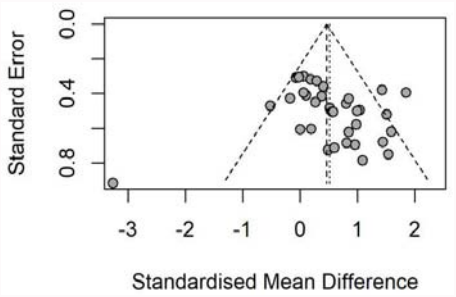

Figure 5a: Funnel plot: immediate tDCS effects.

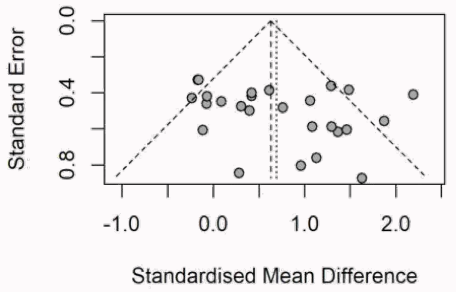

Figure 5b: Funnel plot: longer-lasting tDCS effects.

particular study, individual linear meta-regression analyses were performed for each of nine interrelated tDCS dose-related parameters, based on four stimulation variables (number of sessions, current intensity, electrode size, duration of a single stimulation session). A significant positive correlation between tDCS efficacy on motor recovery and "current density" and "charge density' was identified, while a negative one was found for "electrode size". Despite these interesting results, methodological aspects might represent a limitation of this study. The use of individual linear meta-regression analyses does not take into account the combined influence resulting from the interaction of the different parameters. Additionally, the choice of adopting highly selective eligibility criteria, despite partially reducing the amount of between studies heterogeneity, resulted in the inclusion of a relatively small amount of studies (8 studies for 10 comparison groups), thereby reducing the reliability of the results of the meta-analyses. In order to overcome these methodological limitations, a different analytical approach was adopted in the current work. The present analyses included studies, where any kind of outcome assessment of the upper extremity motor performance was used. The problem of comparing different outcome scores was addressed by performing a standardized mean difference calculation of the effect sizes of the studies [24]. Additionally, no limitations were defined concerning the number of tDCS sessions performed in each study. This approach made it possible to increase the number of included studies and, for the first time, to develop a complex meta-regression model applied to the evaluation of the dose-response relationships for tDCS in neurorehabilitative training of the upper extremity after stroke. The effect sizes of the different studies were included as dependent variable with various stimulation-dose-related, clinical and intervention factors as covariates. This model allows the simultaneous analysis of multiple moderator factors, taking into account possible confounding effects among them. Evaluating the combined influence of multiple covariates might offer a better explanation of heterogeneity encountered in the studies. In addition, two pooled effect size meta-analysis were performed to address the questions on tDCS efficacy for upper extremity motor learning in stroke patients at different time points. Here we differentiated between motor outcome evaluated right after the end of the last tDCS session, and the outcome evaluation starting from one week after the last session was administered. This allowed us to distinguish between immediate and longer-lasting effects of tDCS, with the latter being interpreted as a rough estimate of long-term tDCS efficacy. In sum, the article examines the efficacy of tDCS combined with motor training for improvement of motor functions of the upper extremity in post-stroke patients. In addition, we

Table 1: Overview of eligibility criteria.

	Inclusion	Exclusion
Participants	• Diagnosis of stroke (Ischemic or hemorrhagic, any location)	• Individuals under 18 years of age
Characteristics of stroke	• Any level of motor impairment of the upper limb at baseline	• Time after stroke onset <48h
Trial design	• Randomized controlled trials	• Non randomized trials, case reports and review articles
	• tDCS combined with motor training	• tDCS not combined with motor training
	• Comparison with sham + motor training or training alone	
Type of stimulation	• Anodal tDCS of ipsilesional M1	• Other TES techniques (tACS, tRNS, etc.)
	• Cathodal tDCS of contralesional M1	• tDCS on cortical areas other than M1
	• Dual tDCS of M1 bilaterally (anode on ipsilesional M1 and cathode on contra lateral M1)	
Type of motor training	• Active motor training commonly used in clinical settings or specific task oriented training	• Passive motor training • Non-invasive stimulation techniques for the peripheral nervous system and the locomotor apparatus
Intervention protocol	• tDCS administered before or during the motor training sessions	• tDCS administered after the motor training
	• Single or multiple sessions	
Outcome measure	• Any clinical scale and task oriented outcome measure for the assessment of upper limb motor performance	• Scores not specific for the upper limb motor performance

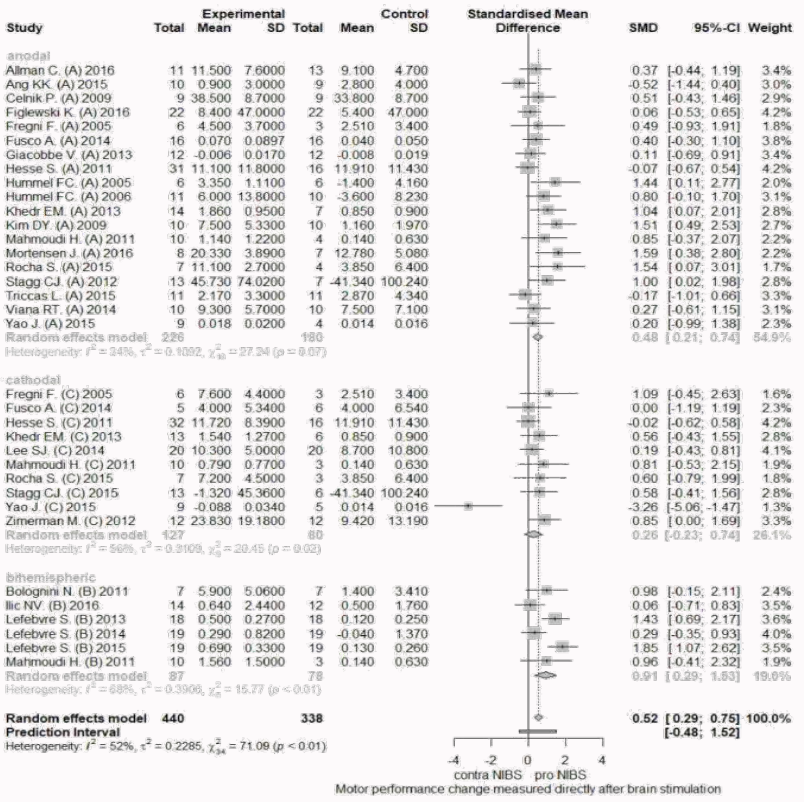

Figure 6: Forest plot: immediate effects.

evaluated the relationship between the intensity of tDCS and its effects on motor training. Furthermore, the influence of different moderator variables on tDCS efficacy was determined.

Methods

A systematic search (Prospero protocol registration: CRD42017058866) was performed in electronic databases "Pubmed" and "Ovid Medline" (search terms see Appendix). Only English articles published until February 2017 were considered. The software "Covidence" [25] assisted the screening process. After removal of duplicates, two independent reviewers (MA, WB) screened title and abstracts for inclusion and exclusion criteria. In case of doubt, the paper was included in the full text screening. Disagreement between the two reviewers was resolved by discussion and reaching a final consensus. Full text screening was also performed by two independent reviewers (MA, WB). A single researcher (MA) extracted the data, assessed the risk of bias for each article according to the Cochrane "Risk of Bias Assessment Tool" and contacted the authors in case of lacking information.

Eligibility criteria

Eligible studies included Randomized Controlled Trials (RCTs) applying tDCS to the motor cortex in combination with any kind of

active motor training of the upper limb (Table 1). The intervention, being tDCS directly before or during active motor training, had to be compared to either sham stimulation or the active motor training alone. Studies adopting any outcome assessment for the evaluation of motor performance of the upper limb, both in terms of global function and performance in a specific task were included. When multiple outcomes were published in a single study, the UE-FM was the first choice as it represented the most commonly adopted assessment, otherwise the primary outcome was selected. The patient populations comprised of adults at least two days post stroke, with both haemorrhagic and ischemic lesions.

Three of the most commonly applied electrode placement protocols targeting the primary motor area, without restrictions concerning the number of sessions and session duration, were evaluated:

1) Anodal stimulation: anode placement on the ipsilesional M1 and cathode on the contralateral supraorbital region.

2) Cathodal stimulation: cathode placement on the contralesional M1 and anode on the contralateral supraorbital region.

3) Bihemispheric stimulation: Anode on the ipsilesional M1 and cathode on the contralesional M1.

Active motor training was defined as training that involved the execution of a repetitive and consistent sequence of active movements or mental activation of motor areas. Task oriented training had to consist of more than two blocks of repetition of the same task performed before or during the stimulation. Research on Brain Computer Interface (BCI) treatment and motor imagery has shown a significant efficacy in improving motor performances in healthy subjects and in motor rehabilitation settings [20-22], thus these kinds of training were also included in the analysis. Outcome assessment such as box and block test or grip force production tasks were only considered as motor training, if they met the first criterion, being repeated for more than two times during or after the stimulation. As a consequence of this wide definition, motor training in the current study ranges from task assessment to therapeutic application. To address this issue all tasks were classified as either therapeutic training or task oriented training for the final meta-regression analysis.

Data analysis and synthesis

In order to estimate the efficacy of tDCS-based interventions, two distinct pooled effect size comparisons of tDCS versus the control groups were evaluated for the included studies. The first analysis focused on tDCS efficacy immediately after the last session of stimulation, which might still be relevantly influenced by the online effects of tDCS [26]. The focus of the second analysis was to study tDCS effects lasting for several days after the end of stimulation. Latter generating a basis for assumptions about its long term efficacy. For studies presenting multiple time points, the latest time point of retest available, per study, was include. Finally, including all studies at all time points, a meta-regression analysis was performed. Software for statistical analysis included "Revman 5.3" [27] and "R" (version 3.4.2) [28-35]. Pooled effect size comparisons based on the values of means and standard deviations of the outcome changes from baseline, Standardized Mean Differences (SMD) were computed using the Hedges' adjusted g and served as Effect Size (ES) measure. Changes from baseline were evaluated to removes between-person and between-study variability from the analysis [24]. In case of multiple experimental tDCS groups from a single study, these were compared independently against the common control group, per time point and with the sample size equally divided by the number of comparisons. Data from crossover trials were also included in the meta-analysis. The presence of carry-over effects and other potential biases related to this specific experimental design was evaluated in the risk of bias assessment. SMDs from all comparisons were used to compute a pooled ES value along with a 95% confidence interval. Global heterogeneity was assessed with Higgins I-squared and Chi-squared statistics. Given the intrinsic variability of the studies included, in terms of multiple factors (stimulation type and intensity, outcome assessment, clinical differences in sample populations, etc.) a random effect model was adopted for the analysis. The influence of the different types of tDCS (anodal, cathodal, bihemispheric) was hypothesized and is reflected in subgroup analyses. The pooled effect sizes were interpreted according to Cohen's convention of small (>0.2), moderate (>0.5), and large (>0.8) effects [36].

Meta-regression

The weighted values of SMD were used as dependent variables for the meta-regression, while dose-related parameters were used as continuous explanatory variables. Latter included four independent variables (current intensity (mA), electrode size (cm^2), number of sessions and duration of stimulation in a single session (h)). These variables are commonly pooled and reported as charge density or current density. Different models including these pooled variables were evaluated against another and the combination of the main effect 'charge density' (defined as current intensity (mA) x duration of stimulation in a single session (h) ÷ electrode size (cm^2)) and the main effect 'number of sessions' was chosen. A multivariate random effect model was created for the meta-regression, introducing the additional factors before step-wise backward elimination. These factors included; the type of stimulation (anodal, cathodal, bihemispheric), the phase after stroke (subacute, chronic (> 3 months)), the time point of outcome assessment (days after last stimulation) and the type of training (therapeutic training, task oriented training).

Results

Data extraction

Results of the screening process are shown in the flow chart (Figure 1). Five studies were excluded from the analysis. In three of them [37-39] data from one intervention group had been published previously in an article already included in the analysis. One study [40] had to be excluded because, after contacting the author, we found that the cathodal stimulation was applied to the ipsilesional M1, making the study not eligible for the meta-analysis. In one case [41] we were not able to obtain all the necessary data. A total of 35 studies [20,42-75] were available for the statistical analysis and nine among these presented multiple experimental tDCS groups. Results from 778 participants were included for the immediate post effects analysis and results from 571 participants could be included into the longer-lasting effects analysis.

Studies characteristics

A general overview of the characteristics of the included studies is summarized in (Table 2). Fourteen clinical trials had a cross-over design, 21 had a parallel group design. The patients were classified as being in a subacute phase after stroke in 9 studies and being in chronic phase in 26 studies. The mean age of patients from all included trials was 59.5 years. The great majority of strokes had an ischemic aetiology. Study participants included individuals ranging

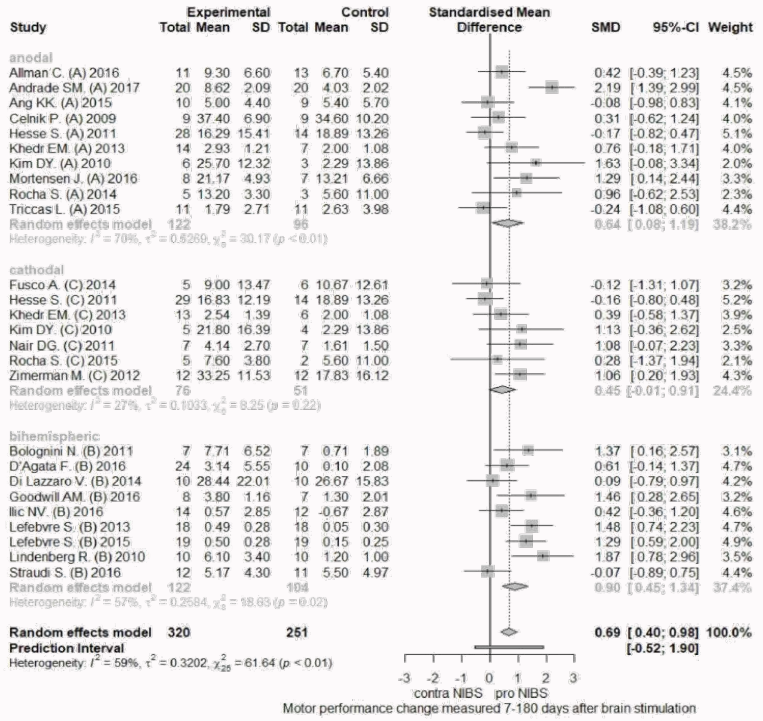

Figure 7: Forest plot: Longer-lasting effects.

from 3 days [48] to 1.85 months post stroke [43] in the subacute group, and from an average of 8.3 months [66] to more than 5 years (range of 5-17 years) [74] in the chronic group. Twenty-two studies presented a baseline impairment evaluation performed by means of the UE-FM assessment, with scores ranging from 8 to 64 points, thereby covering almost all degrees of severity. 21 studies performed anodal stimulation, 20 cathodal and 11 studies performed bihemispheric stimulation. The effect of stimulation combined with training was compared with that of sham stimulation in all studies but one [70], where the control group received motor training alone. Details on stimulation parameters and training interventions are listed in (Table 2). According to our classification, 21 training protocols were considered as "therapeutic training" and 14 as "task oriented". The latter group included: motor imagery practice, finger tapping, reaction time tasks with joystick movements, virtual reality visuomotor tasks with a mouse circuit, a visual target task with robot assisted wrist extensions, a reaching task with robot arm under load, pinch force production tasks, grip lift tasks, the Jebsen Taylor Test of hand function (JTT) or the Box and Block Test (BBT). Studies investigating the effect of one single session of intervention and up to a max of 30 sessions were included. A single session was performed in 14 clinical trials while multiple sessions were performed in the remaining 21 studies. Multiple different outcome assessments were adapted to measure motor skills, either specifically linked to the task executed (e.g. finger tapping sequence accuracy) or a clinical assessment (e.g., action research arm test). Nine outcome assessments belonged to the first group and 24 to the second with the most common outcome scale, the UE-FM, being used in 15 studies (Table. 2). For each study the time points for the assessment of the immediate or longer-lasting effects of tDCS are shown in the (Figure 2).

Risk of Bias assessment

The outcome of the Cochrane risk of bias assessment tool is reported in (Figure 3 and 4). The adoption of group randomization

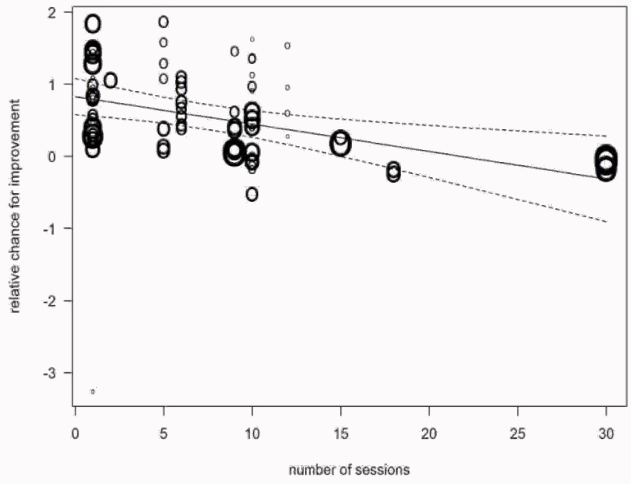

Figure 8: Model prediction; relative improvement after tDCS is inversely related to the number of tDCS sessions, when charge density is held constant at its mean. The point symbols refer to the experimental vs. control comparison with the size representing the weight of each comparison in the meta-regression.

was clearly stated in all the included studies, but a lack of published information regarding the details of randomization and allocation procedures was common. Consequently, for several studies it has not been possible to produce a reliable evaluation of the risks of bias, and a judgment of unclear risk was assigned. Sham stimulation was not performed in two studies which were, therefore, evaluated at high risk for the blinding of participants and personnel. High risk of incomplete outcome data because of exclusion or withdrawal of participants was reported in three studies. The main reasons for a judgment of high risk were a relatively high proportion of missing data on the total of participants, and an unbalance of distribution between the intervention groups due to events related to the severity

Table 2: Characteristics of the studies.

Study	Study design; blinding	Total sample size (n)	Mean age (years)	Phase after stroke	Mean Baseline impairment	Motor training	Outcome measure	N of sessions
Allman C. 2016(42)	Parallel group; DB	24	63.2	C	37.7 (UEFM)	PT	UEFM	9
Andrade S.M. 2017(43)	Parallel group; DB	40	55	S	20 (UEFM)	CIMT	UEFM	10
Ang K.K. 2015(44)	Parallel group; NA	19	54.1	C	34 (UEFM)	Motor imagery	UEFM	10
Bolognini N. 2011(45)	Parallel group; DB	14	46.7	C	26 (UEFM)	CIMT	UEFM	10
Celnik P. 2009(46)	Cross-over; DB	9	55.3	C	62 (UEFM)	Finger tapping sequence	Tapping sequence accuracy	1
D'Agata F. 2016(47)	Parallel group; DB	34	61	C	NA	Mirror box	ARAT	10
Di Lazzaro V. 2014(48)	Parallel group; DB	20	64.8	S	28/57 (ARAT)	CIMT	ARAT	5
Figlewski K. 2016(49)	Parallel group; DB	44	60.5	C	44.8/75 (WMFT)	CIMT	WMFT	9
Fregni F. 2005(50)	Cross-over; DB	6	53.7	C	63.5s (JTT)	JTT	JTT	1
Fusco A. 2014 (1)(51)	Parallel group; DB	11	58.4	S	24.7 (UEFM)	PT	UEFM	10
Fusco A. 2014 (2)(52)	Cross-over; DB	16	60.4	S	NA	PT	9-HPT	1
Giacobbe V. 2013(53)	Cross-over; DB	12	64	C	38.3 (UEFM)	Visual targeted robot wrist task	Lateral deviation from target	1
Goodwill A.M. 2016(54)	Parallel group; DB	15	56.9	C	6.1/18 (MMAS)	PT	MMAS	9
Hesse S. 2011(55)	Parallel group; DB	85	64.9	S	8 (UEFM)	Robot arm	UEFM	30
Hummel F.C. 2005(56)	Cross-over; DB	6	62.2	C	62.7 (UEFM)	JTT	JTT	1
Hummel F.C. 2006(57)	Cross-over; DB	10	57.1	C	59.9 (UEFM)	Pinch force production task	Pinch force	1
Ilić N.V. 2016(58)	Parallel group; DB	26	60	C	48.9 (UEFM)	OT	UEFM	10
Khedr E.M. 2013(59)	Parallel group; DB	40	58.3	S	10.7/42 (NIHSS)	PT	Hand grip force	6
Kim D.Y. 2009(60)	Cross-over; NA	10	62.8	S	36.3 (BBT)	BBT	BBT	1
Kim D.Y. 2010(61)	Parallel group; DB	18	57.2	S	38 (UEFM)	OT	UEFM	10
Lee S.J. 2014(20)	Parallel group; DB	40	61.9	S	36.7 (UEFM)	VR multitasks therapy	UEFM	15
Lefebvre S. 2013(62)	Cross-over; DB	18	61	C	7.1 (PPT)	VR visuomotor task	Accuracy-speed index	1
Lefebvre S. 2014(63)	Cross-over; DB	19	60	C	6.9 (PPT)	Grip lifts	Grip force/Lift force	1
Lefebvre S. 2015(64)	Cross-over; DB	19	65	C	7.4 (PPT)	VR visuomotor task	Accuracy-speed index	1
Lindenberg R. 2010(65)	Parallel group; DB	20	56.2	C	39 (UEFM)	PT	UEFM	5
Mahmoudi H. 2011(66)	Cross-over; DB	10	60.8	C	NA	JTT	JTT	1
Mortensen J. 2016(67)	Parallel group; DB	15	63.1	C	35.2 (BBT)	OT	JTT (Australian version)	5
Nair D.G. 2011(68)	Parallel group; DB	14	55.8	C	30.5 (UEFM)	OT	UEFM	5
Rocha S. 2015(69)	Parallel group; DB	21	58.4	C	49.6 (UEFM)	CIMT	UEFM	12
Stagg C.J. 2012(70)	Cross-over; SB	13	64	C	47.2 (UEFM)	RT task with joystick	RT	1
Straudi S. 2016(71)	Parallel group; DB	23	58.2	C	22.8 (UEFM)	Robot arm	UEFM	10
Triccas L. 2015(72)	Parallel group; DB	22	63.4	C	32.3 (UEFM)	Robot arm	UEFM	18
Viana R.T. 2014(73)	Parallel group; DB	20	55.5	C	40.3 (UEFM)	VR multitasks therapy	UEFM	15
Yao J. 2015(74)	Cross-over; SB	9	60	C	28.7 (UEFM)	Reaching task with SABD load	Reaching distance	1
Zimerman M. 2012(75)	Cross -over; SB	12	58.3	C	64 (UEFM)	Finger tapping sequence	N of correct sequences	1

9-HPT= nine hole peg test; ARAT= action reaction arm test; BBT= block and box test; C= chronic; CIMT= constrained induced movement therapy; DB= double blind; JTT= Jebsen Taylor hand function test; MMAS= modified motor assessment scale; NA= not available; NIHSS= national institute of health stroke scale; OT= occupational therapy; PT= physiotherapy; PTT= Purdue pegboard test (paretic hand); RT= reaction time; S= subacute; SABD= shoulder abduction; SB= single blind; UEFM= upper extremity Fugl Meyer; VR=virtual reality; WMFT = Wolf motor function test - functional activity scale

Table 3: Intervention parameters.

Study	tDCS protocol	Current intensity (mA)	Electrode size (cm^2)	Stimulation duration (min)	Charge density	N of sessions
Allman C. 2016(42)	A	1	35	20	0.01	9
Andrade S.M. 2017(43)	A	0.7	16	20	0.01	10
Ang K.K. 2015(44)	A	1	35	20	0.01	10
Bolognini N. 2011(45)	D	2	35	40	0.04	10
Celnik P. 2009(46)	A	1	58	20	0.01	1
D'Agata F. 2016(47)	D	1.5	25	20	0.01	10
Di Lazzaro V. 2014(48)	D	2	35	40	0.04	5
Figlewski K. 2016(49)	A	1.5	35	30	0.02	9
Fregni F. 2005(50)	A/C	1	35	20	0.01	1
Fusco A. 2014 (1)(51)	C	1.5	35	10	0.007	10
Fusco A. 2014 (2)(52)	A	1.5	35	15	0.01	1
Giacobbe V. 2013(53)	A	2	35	20	0.02	1
Goodwill A.M. 2016(54)	D	1.5	25	20	0.02	9
Hesse S. 2011(55)	A/C	2	35	20	0.02	30
Hummel F.C. 2005(56)	A	1	25	20	0.01	1
Hummel F.C. 2006(57)	A	1	25	20	0.01	1
Ilić N.V. 2016(58)	D	2	25	20	0.03	10
Khedr E.M. 2013(59)	A/C	2	35	25	0.02	6
Kim D.Y. 2009(60)	A	1	25	20	0.01	1
Kim D.Y. 2010(61)	A/C	2	25	20	0.03	10
Lee S.J. 2014(20)	C	2	25	20	0.03	15
Lefebvre S. 2013(62)	D	1	35	30	0.01	1
Lefebvre S. 2014(63)	D	1	35	20	0.01	1
Lefebvre S. 2015(64)	D	1	35	30	0.01	1
Lindenberg R. 2010(65)	D	1.5	16.3	30	0.05	5
Mahmoudi H. 2011(66)	A/C/D	1	35	20	0.01	1
Mortensen J. 2016(67)	A	1.5	35	20	0.01	5
Nair D.G. 2011(68)	C	1	25	30	0.02	5
Rocha S. 2015(69)	A/C	1	35	13A, 9C	0.03	12
Stagg C.J. 2012(70)	A/C	1	35	20	0.01	1
Straudi S. 2016(71)	D	1	35	30	0.01	10
Triccas L. 2015(72)	A	1	35	20	0.01	18
Viana R.T. 2014(73)	A	2	35	13	0.01	15
Yao J. 2015(74)	A/C	0.8	16	15	0.01	1
Zimerman M. 2012(75)	C	1	25	20	0.01	1

of clinical conditions. In the study from Hesse et al. [55], for instance, three out of the four drop-outs from the anodal group were caused by a case of pneumonia and two deceases, whereas only partial information were available for the patients' drop-outs in the cathodal (three) or sham group (four). A prevalent lack of information in the publication about incomplete outcome data was found in seven studies, to which an evaluation of unclear risk was assigned. A risk for selective reporting bias was consistently low, and an unclear risk was identified in six studies, where partial inconsistency between published outcome results and outcome measures pre-specified in the study protocol. A high risk of bias due to possible carry-over effects was identified in the cross-over study from Mahmoudi et al. [66] where four different stimulation protocols were evaluated with a minimum washout period of 96 hours between each of them. With regard to the results of the pooled effect size analysis of tDCS efficacy at immediate post intervention, the test for the funnel plot asymmetry revealed a significant risk for publication biases (p= 0.046) indicating that caution is needed in the interpretation (Figure 5a). On the other hand no significant risk for publication biases was found for the results of long term tDCS efficacy (p= 0.19) (Figure5b).

Statistical analyses

Immediate effects: The analysis included 35 comparisons of which 29 presented a positive ES. The resulting pooled ES was of 0.52 ($p < 0.001$; CI 0.29 to 0.75) in favor of tDCS combined with motor training compared to the control group, suggesting a moderate effect (Figure 6). A moderate to high heterogeneity between the studies was found ($x^2=71.09$, $p < 0.001$; $I2 = 52\%$). Ten comparisons for the

cathodal and six for the bihemispheric stimulation resulted in an ES of 0.26 (p =0.02; CI -0.23 to 0.74) and 0.91 (p <0.01; CI 0.29 to 1.53) respectively. Nineteen comparisons for the anodal subgroup showed a non significant ES of 0.48 (p =0.07; CI 0.21 to 0.74). However no statistically significant difference was found between the three types of stimulation (anodal, cathodal and bihemispheric) (Q =2.68; p =0.262).

Longer-lasting effects: The analysis included 26 comparisons with 20 of them resulting in a positive ES. The time point for the outcome assessment ranged from one week to six months after the last stimulation session (Figure 2). A pooled ES of 0.69 (p < 0.001; CI 0.40 to 0.98) is suggesting a moderate positive effect of tDCS (Figure 7). A moderate to high heterogeneity between the studies was found (x^2=61.64, p< 0.001; I2 = 59.4%). Ten comparisons for the anodal and nine for the bihemispheric stimulation resulted in an ES of 0.64 (p <0.01; CI 0.084 to 1.19) and 0.90 (p =0.02; CI 0.45 to 1.34) respectively. Seven comparisons for the cathodal subgroup showed a non significant ES of 0.45 (p= 0.22; CI -0.01 to 0.91). Also in this subgroup analysis, no statistically significant difference was found between the three types of stimulation (Q = 1.89; p =0.39).

Meta-regression: The best fitting model for our data was obtained including the single moderator factor "number of sessions", which significantly influenced the effectiveness of tDCS with an estimated value (expressed as natural log of the relative risk) of -0.04 (p =0.003; CI -0.06 to -0.01). This result indicates that increasing the number of sessions by 1 would correspond to a decrease of 0.04 units in terms of the average natural logarithm of the relative risk (Figure 8). The estimated amount of residual heterogeneity was equal to Tau^2 = 0.145, suggesting that 32.95 % of the total amount of heterogeneity can be accounted for by including the "number of sessions" moderator. The test for residual heterogeneity remained significant (Q-test =98.5; p >0.021) indicating that other moderators, not considered in the model were influencing the effect size. The other variables included in the meta-regression did not prove to be a significant enhancement to the model and were excluded during step-wise backwards regression.

Discussion

The current review and its meta-analyses were performed to address the question of the effects of tDCS applied to the motor cortex on upper extremity neurorehabilitative training in stroke patients. To this end, we addressed interventional efficacy, dose-response relationships and potential factors influencing the effects of tDCS in this setting significantly.

tDCS efficacy

tDCS showed a statistically significant, moderate effect on motor function, when evaluated both, immediately after the end of the interventional session and after a minimum delay of seven days after the intervention (longer-lasting). Eight other meta-analyses published in the last decade, investigating tDCS effects in various neurorehabilitative applications for motor deficits after stroke, overall demonstrated a small to moderate positive effect of tDCS without always reaching statistical significance [14,21,23,76-80]. In the light of these latter, it is interesting to note that, despite the fact that all the meta-analyses presented many differences in terms of outcomes, effects on learning *vs.* effects on functional recovery, eligibility criteria or statistical methods, a general tendency towards a positive effect was consistent among them. These results also reflect the fact that negative or null effects are considerably less frequently observed (or published) than positive ones at the level of the single clinical trial. A risk for publication bias towards positive effects might have to be taken into account when drawing conclusions. Within and over the included studies, there is significant heterogeneity in the response of individual patients to the intervention impacting on the overall effect size. Due to the lack of overarching factors or biomarkers allowing to predict treatment responses or to stratify patients into treatment strategies, to date clinical trials are characterized by one suits all treatment strategies [16,81]. Thus, we might most likely be far from exploiting the therapeutic potential of this technique [18]. It can be speculated that as soon as our understanding is extended towards factors allowing us to predict treatment responses and stratifying patients, the effect sizes might be much larger with a respective effect on recovery. Taken together, despite the relatively small effect sizes, the finding of positive effects of tDCS in a relatively large pool of studies, with few studies showing negative or no effects should not be underestimated. Based on these considerations, it seems not conclusive to deny the point that tDCS has the potential for enhancing rehabilitative approaches. Instead, the question at stake should be, do the effects observed from the application of tDCS in stroke rehabilitation represent already the magnitude limit of this treatment or can they be enhanced by patient-tailored, precision medicine-based approaches. Therefore, in the last decade the need to move towards an application of tDCS tailored to the patient had a growing consensus [18,82,83]. However, it will be difficult to find an answer to the previous question without systematically rethinking the way, how clinical research on this topic is performed. To expand our insights on which patients will respond or not and with which magnitude from tDCS, the understanding of the processes underlying functional recovery and NIBS has to be extended allowing to stratify patients. Nevertheless, it is also important to highlight the importance of standardization among clinical trials in regard to the stimulation protocols, outcome measures and training protocols to combine with tDCS.

Dose-response analysis

In the present study also a meta-regression analysis was performed to examine the relationship between tDCS efficacy for neurorehabilitation of motor deficits after stroke and two dose-related parameters (number of stimulations; charge density). Charge density, which was found to be the best variable to summarize three basic, interacting stimulation parameters (current intensity, electrode size, duration of stimulation in a single session), showed no statistically significant influence on tDCS effects. On the other hand, the factor "number of sessions" was found to significantly affect tDCS efficacy across the included studies. When using this model to predict the ES, an increase of the number of tDCS sessions by one would reduce the predicted ES by 0.04. Only one other study, from Chamber et al. [23], investigated the dose-response relationships for tDCS in neurorehabilitative motor training for stroke patients. By applying simple linear regression analyses for different stimulation parameters and number of sessions they found a positive correlation of charge density with tDCS efficacy, while no relationship was revealed with the number of sessions. It is unlikely that the inconsistency with the results of the present work might be ascribed to the presence of differences in the patient populations considered in the two meta-analyses. Indeed, a relevant overlap of the included studies between the meta-analyses is present, while on the other hand the methodological approach differed also concerning the selection of articles based on the number of sessions. Chamber et

al. limited their analysis to studies, where tDCS was applied for more than 4 sessions. A major fundamental aspect is that the application of simple linear regressions of individual factors does not account for modifying influence of others. In the present meta-regression, dose-related parameters were analyzed simultaneously to other modifiers associated to the heterogeneity of tDCS effect sizes. However, a substantial amount of heterogeneity remained unexplained also in the current analyses, making it probable that other relevant factors influenced the final result of the model. With regard to the charge density, findings from experimentation on healthy subjects generally support the results of the present meta-analysis, with no evidence of a simple linear relationship with tDCS efficacy demonstrated to date [84,85]. Even considering the modulation of the three independent stimulation parameters that compose the charge density (current intensity, stimulation duration, electrode size), a linear correlation has not been shown [86-88]. The negative association of number of session with tDCS efficacy is somehow unexpected at a first glance, however the way stimulation sessions were distributed in time might represent a crucial factor to be considered for the interpretation of results [89,90]. In the view of the importance of specific inter-stimulation intervals demonstrated in healthy humans, e.g., performing tDCS in consecutive days resulted in stronger excitation effects compared to stimulation applied every two days [91], one might have expected a different result. tDCS interventions for stroke rehabilitation are usually administered on the basis of the standard motor rehabilitation protocols that are applied for e.g., five consecutive sessions per week. However, when evaluating the influence of the two discussed parameters (charge density, number of sessions), it has to be admitted that effects determined in young healthy subjects cannot necessarily be directly translated to other populations (old healthy, neuropsychiatric disorders). Especially after stroke, patients present important and highly variable structural and functional brain alterations, which might result in different responsiveness to tDCS compared to healthy subjects [92]. In fact, crucial neural mechanisms normally involved in learning processes, like memory consolidation or homeostatic meta-plasticity, might show different responsiveness and time scales in stroke, making different inter-stimulation intervals more efficient compared to healthy subjects, a question which has to be addressed in upcoming studies.

Moderating factors

Four additional factors were included in the meta-regression model, they did not have an influence on tDCS efficacy. The type of application set-ups (anodal on ipsilesional M1; cathodal on contra-lesional M1; bihemispheric) had no significant influence on the efficacy of the intervention, thus they can be considered as equivalent approaches in terms of efficacy. However recent meta-analyses comparing the differences between these stimulation types reported mixed results [14,21,23]. An interesting hypothesis to test in future studies is that on an individual patient basis specific stimulation protocols tailored to the characteristics of the patient might lead to a clear difference in the efficacy of the stimulation compared to the standard applications. We also examined, whether the application of tDCS during different phases after stroke could represent a relevant factor for therapeutic success. Considering the time passed after stroke onset, patients were allocated to either the subacute or chronic group. The rationale behind this classification is based on the knowledge that during the first 3 months (subacute) following the stroke there are the largest reorganizational, neuroplastic changes in the course of functional recovery [81,93]. However, here no significant differences were found between patients in subacute and chronic stage. For the first time, the current analyses evaluated, whether the differences in motor performance observed between tDCS and control group would vary significantly, if measured at different times after the end of tDCS intervention. Interestingly, the results showed that motor outcomes immediately after the end of tDCS treatment did not differ from longer-term outcomes. The time points for the follow-ups ranged from one week to a maximum of six months (Figure 2). From a practical point of view these results suggest that the changes of motor performances induced by tDCS combined with motor training demonstrate a good retention and that they are likely to result from learning and plasticity mechanisms, which are stable at medium-long-term. A similar tendency was shown in healthy subjects [94] and the current results in stroke are in line with Triccas et al. [14]. A fourth categorical factor was used to investigate whether the effects were different when tDCS was combined with clinical therapeutic training or with task-specific training (sequence tapping, reaction time tasks, etc.). No significant difference was found, suggesting that tDCS is a valid adjuvant for both types of training.

Study limitations

The following limitations should be taken into account, when interpreting the results of the present meta-analyses. The definition of motor training adopted for the selection of eligible studies was not restricted to specific practices. Consequently, across the studies under analysis, tDCS was performed in combination with a large variety of motor training, including rehabilitation procedures and different task specific training. The related outcome assessments measured global changes in the motor function of the upper limb or variations in specific motor performances respectively. While the former assessments provide information about the functional and clinical recovery, the same cannot be said for the latter. Therefore, main conclusions resulting from the present meta-analysis should be referred to tDCS effects on motor learning in the context of upper extremity neurorehabilitative training of stroke patients.

Furthermore, while the choice of including studies with different outcome measures allowed us to increase the number of included studies and to make more general inferences about the efficacy of tDCS, it also increased the heterogeneity and could have partially affected the reliability of the estimate values. A considerable amount of heterogeneity (66.7%) presented remained unexplained. Additional variables, not examined in the current analysis, might have a relevant influence on the statistical model. Nevertheless, it must be considered that the use of a meta-regression method represents a better estimate compared to simple subgroup analyses, where each factor is analyzed without considering the influence of another.

Conclusions

The results of the current meta-analyses support the view that tDCS has the potential to adjuvant neurorehabilitative training in stroke patients and by this contribute significantly to the recovery of upper limb motor functions in these patients. The substantial lack of knowledge about how to apply this technology in a patient-tailored way, and which patients could benefit more or less from its effects probably limits the magnitude of tDCS efficacy currently. Factors (type of tDCS, phase of recovery, type of training) that are considered to be determinant for the variability observed in the response to therapy appear to have a rather limited influence. Indeed, a relevant part of heterogeneity is still not explained and most likely related to individual characteristics of the patients, such as lesions site or size,

beyond others. This work revealed for the first time that prolonging the tDCS treatment by simply increasing the number of stimulation sessions might not lead to an increase of the treatment effect but might even reduce it. To maximize tDCS effects for neuro-rehabilitation, it is mandatory to determine factors predicting treatment responses allowing the application of tDCS in precision medicine fashion, tailored to the individual patients, maximizing treatment effects with respective impact on functional recovery.

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