

REVIEW ARTICLE

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR IMPROVING SPASTICITY AFTER STROKE: A SYSTEMATIC REVIEW WITH META-ANALYSIS

Bernhard Elsner, PhD^{1,2}, Joachim Kugler, MD¹, Marcus Pohl, MD³ and Jan Mehrholz, PhD^{1,4}

From the ¹Department of Public Health, Dresden Medical School, Technical University Dresden, Dresden, ²Professorship of Physiotherapy, SRH University of Applied Health Sciences Gera, Gera, ³Neurological Rehabilitation, Helios Klinik Schloss Pulsnitz, Pulsnitz and ⁴Wissenschaftliches Institut, Private Europäische Medizinische Akademie der Klinik Bavaria in Kreischa GmbH, Kreischa, Germany

Objective: To evaluate the evidence regarding transcranial direct current stimulation (tDCS) and to assess its impact on spasticity after stroke.

Data sources: The following databases were searched up to 6 January 2016: Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library, latest issue), MEDLINE (from 1948), EMBASE (from 1980), CINAHL (from 1982), AMED (from 1985), Science Citation Index (from 1900).

Study selection: One author screened titles and abstracts and eliminated obviously irrelevant studies. Two authors retrieved the full text of the remaining studies and checked them for inclusion.

Data extraction: Two authors independently extracted data from the studies using predefined data extraction sheets. In case an author of being involved in an included trial, another author extracted data.

Data synthesis: Five trials were included, with a total of 315 participants. There was moderate-to-low quality of evidence for no effect of tDCS on improving spasticity at the end of the intervention period. There were no studies examining the effect of tDCS on improving spasticity at long-term follow-up.

Conclusion: There is moderate-to-low quality evidence for no effect of tDCS on improving spasticity in people with stroke.

Key words: stroke; rehabilitation; transcranial direct current stimulation; muscle spasticity.

J Rehabil Med 2016; 48: 565–570

Correspondence address: Jan Mehrholz, Wissenschaftliches Institut, Private Europäische Medizinische Akademie der Klinik Bavaria in Kreischa GmbH, Kreischa, Germany. E-mail: jan.mehrholz@klinik-bavaria.de

Accepted Mar 18, 2016; Epub ahead of print May 12, 2016

INTRODUCTION

Stroke affects activities of daily living and quality of life (1). Three out of 4 patients experience impaired function at hospital admission (2) and 6 months after stroke 2 out of 3 patients have not regained normal neurological functioning of the af-

ected arm (3). A common result of stroke is spasticity, often defined as a “velocity-dependent increase in muscle tone with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex”. Nearly every second person with stroke with initially impaired arm function experiences upper limb spasticity at 12 months after stroke (4), and 1 out of 3 stroke survivors has lower limb spasticity (5). Upper limb spasticity contributes to chronic post-stroke disability (6). Severe spasticity at 12 months post-stroke can be predicted with substantial accuracy at 4 weeks (7). Effective rehabilitation strategies for reducing upper and lower extremity spasticity, and thus increasing function, are needed to reduce the burden of stroke (5, 8, 9), particularly for the high-risk population likely to develop severe spasticity.

Regardless of today’s probably most commonly used intervention for focal spasticity after stroke, intramuscular botulinum toxin (10, 11), new rehabilitation strategies have emerged in recent years. These include non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS), which can alter cortical excitability and hence improve rehabilitation outcome (12–15). For example, tDCS is relatively safe, easy to administer and inexpensive (16). tDCS works by applying a direct current to the brain, usually transmitted by surface electrodes (16–18). The current, usually with a value of 0.5–2 mA, is generated by a direct current stimulator. Three different types of application can be distinguished: (i) the anodal electrode (+) is placed over the presumed brain area of interest and the cathodal electrode (–) is placed as a reference electrode, either on the contralateral orbit or on the contralateral arm (anodal stimulation, A-tDCS); (ii) the electrodes are placed the other way round (cathodal stimulation, C-tDCS); or (iii) they are placed as a combination of (i) and (ii) simultaneously (bihemispheric tDCS/dual-tDCS).

tDCS might be a promising tool for reducing spasticity and increasing function and activities after stroke. A recent randomized control trial (RCT) suggests that tDCS may improve spasticity after stroke and may also improve arm function and activities (19). However, other RCTs have not shown any beneficial effects of tDCS on improving spasticity (20–22).

There is a need for a comprehensive systematic review of RCTs with meta-analysis, taking into account different application techniques and describing the quality level of the evidence. The aim of the present study was therefore to provide an up-to-date systematic overview of the current evidence of randomized trials of tDCS for improving spasticity after stroke.

METHODS

This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (23) as well as Methodological Expectations of Cochrane Intervention Reviews (MECIR) (24).

Inclusion criteria

Only genuine randomized controlled trials (RCTs) or genuine randomized crossover trials, which evaluated tDCS vs sham and/or any other therapy for improving upper limb and lower limb spasticity (regardless of the outcome measure used) after stroke, were included. Stroke was defined according to the World Health Organization's (WHO) criteria. Subjects in the trials had to be 18 years of age or older. Quasi-randomized trials were excluded from the review. tDCS was defined as the long-lasting application of a direct current to the scalp (>1 min). Sham-tDCS was defined as the application of electrodes to the scalp, either only short-term (<1 min) or with no direct current applied (this is approximately the time it takes to fade in and fade out the current to produce perceivable sensations similar to the active condition) (25). In case of more than one active or sham group in an included trial, experimental and control groups were combined in order to minimize the number of comparisons. No restrictions were applied due to the language of studies.

Data sources

The following databases were searched up to 6 January 2016: Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library, latest issue), MEDLINE (from 1948), EMBASE (from 1980), CINAHL (from 1982), AMED (from 1985), Science Citation Index (from 1900). Our MEDLINE search strategy (shown in Appendix I) was modified for the search in all other databases. In addition, we hand-searched relevant conference proceedings and screened reference lists of relevant studies in order to identify further publications.

Study selection

One author screened titles and abstracts and eliminated obviously irrelevant studies. Two authors retrieved the full text of the remaining studies and ranked them as "relevant", "possibly relevant" or "irrelevant", according to our inclusion criteria. Two authors then examined whether the "possibly relevant" and "relevant" publications fitted the PICOS (population, intervention, comparison, outcome, study type) strategy of our study design. Disagreements were resolved by discussion with all authors.

Data extraction

Two authors independently extracted data from the studies using predefined data extraction sheets. In cases where an author was involved in an included trial, another author extracted data.

As primary outcome measures spasticity was defined at the end of the intervention. As secondary outcome we defined spasticity at long-term follow-up, which we defined as more than 6 months after the end of intervention. We used the Cochrane Risk of Bias Tool for rating the methodological quality of included studies (26). For statistical pooling the appropriate outcome measures for spasticity were used, as reported in the studies. The quality of evidence among studies was rated by the GRADE approach (27), using the software GRADEpro, Version 3.2 (28). Data were extracted regarding the effect of tDCS on improving

spasticity at the end of the study and at long-term follow-up, which is more than 6 months after study end.

Statistical analysis

For all continuous data, means and standard deviations were entered. A pooled estimate of the mean difference (MD) with 95% confidence intervals (95% CI) was then calculated. If studies did not use the same measure for an outcome standardized mean differences (SMD) were calculated instead of MD. Heterogeneity was assessed across the included studies by using I^2 statistics. A random-effects model was used regardless of the level of heterogeneity. RevMan 5.3 was used for all statistical comparisons (29).

RESULTS

The abstracts and titles of 5,283 unique records were screened for inclusion, 154 full-text articles were screened for eligibility, and 5 trials with 315 participants were included in the quantitative analysis. A flow chart for the study search process is shown in Fig. 1.

Five studies, with a total of 315 participants, evaluated the effect of tDCS on improving spasticity. All trials were RCTs. There was no trial examining the effect of tDCS on improving spasticity at long-term follow-up.

Included studies varied regarding study design, sample size, age of participants, time post-stroke, and initial severity of impairment, as well as treatment modalities and location of stimulation. Table I provides an overview of the demographics of included studies. Table II provides an overview of the study characteristics.

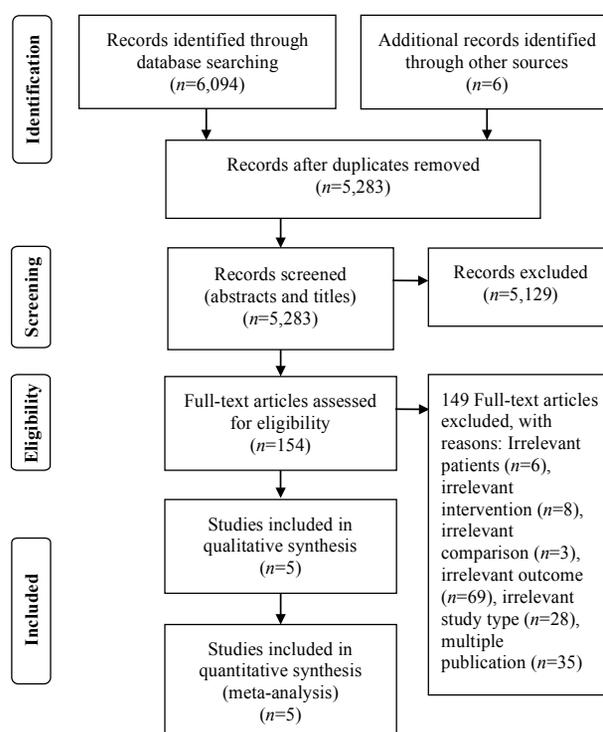


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Table I. Demographics of included studies

	Studies examining the effects of tDCS on improving spasticity after stroke	
	Experimental group	Control group
Total, <i>n</i>	183	132
Age, years, mean (SD)	56 (14)	55 (15)
Time post-stroke, months, mean (SD)	4 (8)	5 (10)
Males, %	68	71
Right-sided paresis, %	50	68
Severity (MAS), mean (SD)	2.1 (2.3)	2.3 (1.8)

SD: standard deviation; MAS: Modified Ashworth Scale; tDCS: transcranial direct current stimulation. Table shows pooled values (SD) from included studies, *n* describes the (pooled) number of subjects in the different groups.

Comparison 1: active vs sham tDCS for improving spasticity at the end of the intervention phase

Three studies, with a total of 206 participants, examining the effect of active vs sham tDCS for improving spasticity

(19, 20, 22, 30) were found, thus allowing statistical pooling. The difference in absolute values between active and sham groups at the end of the intervention phase was not statistically significant when using an inverse variance method with a random-effects model (SMD -0.61; 95% CI -1.51 to 0.30, *p*=0.19) (Fig. 2). The risk of bias of studies was low (Fig. 2). The quality level of evidence for this comparison is moderate according to the GRADE approach.

Comparison 2: active tDCS vs active control for improving spasticity at the end of the intervention phase

Two trials, with a total of 109 participants, evaluated the effect of active tDCS vs active control (physical therapy or virtual reality) for improving spasticity at the end of the intervention phase (21, 30). There was no statistically significant difference in spasticity (SMD -0.01; 95% CI -0.40 to 0.38, *p*=0.51; inverse variance method with random-effects model) (Fig. 2). The risk of bias of studies was low to high (Fig. 2). The quality level of evidence for this comparison is low according to the GRADE approach.

Table II. Characteristics of included studies

Study	Method of randomization	Number of subjects	Mean age, years	Time since stroke	Severity	Outcome measures for spasticity	Type and location of stimulation	Additional therapy	Treatment regime
Hesse et al., 2011 (22)	An independent person drew lots out of an envelope, indicating A, B or C	96	65	4 weeks	MAS sum score for wrist, elbow, shoulder 3	MAS sum score for wrist, elbow, shoulder	A-tDCS (2 mA for 20 min) over the lesioned M1, C-tDCS (2 mA for 20 min) over non-lesioned M1, S-tDCS (0 mA for 20 min). Electrode size: 35 cm ²	Robot-assisted arm training (20 min) 5 days a week for 6 consecutive weeks	Robot-assisted arm training plus A-tDCS, C-tDCS or S-tDCS
Lee & Chun, 2014 (21)	Random number table	59	61	17 days	MAS 0.5	MAS	C-tDCS (2 mA; 20 min) over hand area of M1 of the non-lesioned hemisphere. Electrode size: 25 cm ²	VR or OT for 30 min per day, 5 times per week for 3 weeks	tDCS plus VR, tDCS plus OT or VR alone
Qu et al., 2009 (30)	Unclear	50	45	5 months	MAS 2	MAS	C-tDCS (0.5 mA; 20 min) over non-lesioned M1 once a day for 5 consecutive days for 4 weeks. Electrode size: 18 cm ²	PT according to the Bobath, Brunnstrom and Rood approaches 40 min twice a day) for 5 consecutive days for 4 weeks	tDCS+PT or PT only
Viana et al., 2014 (20)	Sealed opaque envelopes with lots	20	56	33 months	MAS 2	MAS	A-tDCS (2 mA; 13 min) placed over M1 of the lesioned hemisphere or S-tDCS (2 mA; 30 s) 3 times a week for 5 weeks. Electrode size: 35 cm ²	VR (60 min per session), passive stretching before VR session, 3 days a week for 5 weeks	A-tDCS plus VR or S-tDCS plus VR
Wu et al., 2013 (19)	Computer-generated randomization scheme	90	48	5 months	MAS 2	MAS	C-tDCS (1.2 mA; 20 min) over non-lesioned M1 and S-tDCS (1.2 mA; 30 s) 5 days a week for 4 weeks	PT twice daily for 30 min, 5 days a week for 4 weeks	C-tDCS plus PT or S-tDCS plus PT

A-tDCS: anodal transcranial direct current stimulation; C-tDCS: cathodal transcranial direct current stimulation; MAS: Modified Ashworth Scale; M1: primary motor cortex; OT: occupational therapy; PT: physical therapy; S-tDCS: sham transcranial direct current stimulation; VR: virtual reality.

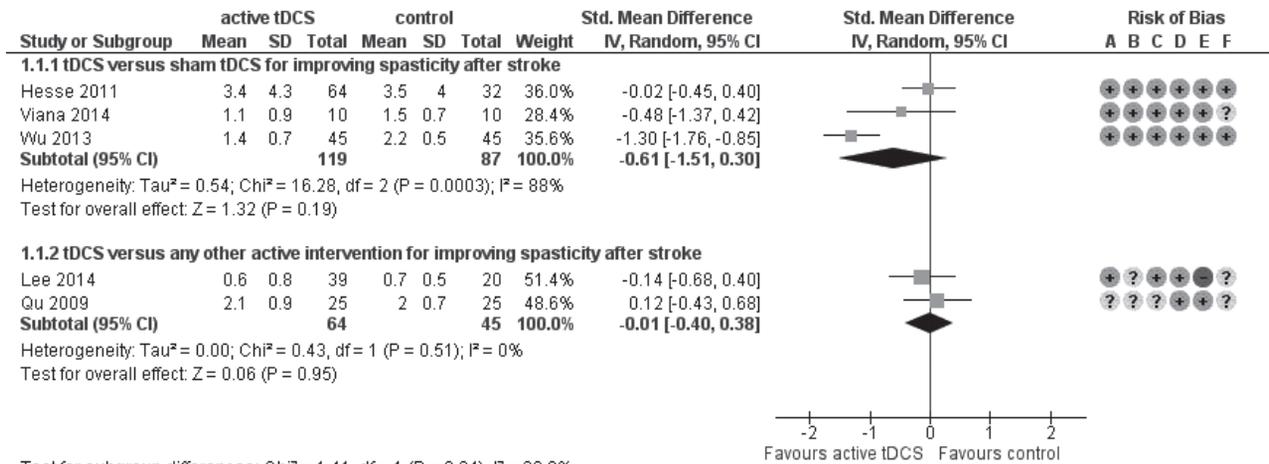


Fig. 2. Forest plot of comparison 1 and 2; active transcranial direct current stimulation (tDCS) vs sham tDCS and active tDCS vs any other active control intervention.

Test for subgroup differences: Chi² = 1.41, df = 1 (P = 0.24), I² = 29.0%

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

DISCUSSION

This systematic review describes all randomized studies published to date of the effects of tDCS on improving spasticity. Five trials, with a total of 315 participants, were included and outcome data analysed with combined intervention and control groups, respectively. No evidence was found for an effect that tDCS improves spasticity.

There are several published systematic reviews of the effects of tDCS on function and motor learning (31–37). However, none have focused on spasticity as an outcome and, to our knowledge, there is no similar systematic review of the effects of tDCS on spasticity.

The results of the present review appear to be quite generalizable to the population of stroke patients. It could be argued, however, that the applicability of our results is limited because only spasticity of the upper limbs was investigated, whereas spasticity in the lower limbs was not.

In general, the reasons for downgrading the quality level of evidence for our analysis according to the GRADE approach are concerns regarding risk of bias in included studies and imprecision of effect estimation. In detail, we found heterogeneity between trials regarding design (2 vs 3 study arms, single centre vs multicentre), study sample size and patient characteristics (e.g. age, severity of impairment and time post-stroke) as well as stimulation parameters (location of and type of stimulation, number and duration of treatment sessions, dosage of electrical charge) and base treatment. Despite the absence of unexplained or statistically significant heterogeneity in our analysis, this might have influenced our results.

We used a clinical definition of spasticity as our primary outcome measure. The clinical measurement of spasticity is, however, discussed very controversially and questions the Modified Ashworth Scale (MAS) as the gold standard for as-

sessing spasticity in clinical practice and research. There are concerns regarding the MAS as a reliable, valid and sensitive outcome measure for spasticity (38) and other scales, such as the modified Tardieu Scale, have been suggested by some (39). The MAS is, however, widely used in many clinical studies (40). For instance, all our eligible and included studies used the modified Ashworth Scale to measure spasticity clinically. Eventually our results might therefore be limited by the described limitation of the assessment of spasticity.

All of the 5 included studies aimed at rebalancing interhemispheric inhibition and thus improving rehabilitation outcome. However, recently doubts have emerged that the rationale of these comparisons, the interhemispheric competition model, may be oversimplified or even incorrect (41). Moreover, the optimal tDCS paradigm regarding polarization, electrode location, amount of direct current applied and time administered still has to be established (16). Despite the individualized approach of mapping M1 with transcranial magnetic stimulation prior to stimulation, further improvements may be achieved by involving functional imaging techniques during tDCS to identify other target areas of potential interest (42). Further research into individualized stimulation protocols is therefore warranted.

One could argue that further potentially relevant studies may have been missed by our literature search. However, by searching common databases using a comprehensive and sensitive search strategy and by making an additional hand-search, this possibility should have been avoided. Furthermore, one could argue that the results might be prone to publication bias. However, by visual inspection of funnel plots (not figured here) we were not able to identify funnel plot asymmetry as a possible marker of publication bias.

In conclusion, when comparing active with sham tDCS, there is moderate-quality evidence for no effect of tDCS on

improving spasticity. There is low-quality evidence for no effect of tDCS on improving spasticity compared with any other active control intervention.

Future research should aim at conducting further multicentre RCTs in a parallel group design in order to examine the impact of tDCS on spasticity together with function and activities. It is likely that more accurate measures of spasticity, perhaps including neurophysiological measures, would strengthen further studies in this area.

At present, there is insufficient evidence to support or refute the use of tDCS as an intervention for improving spasticity after stroke in daily routine practice.

REFERENCES

- Pohl M, Berger K, Ketter G, Krusch C, Pause M, Puschendorf W, et al. Langzeitverlauf von Patienten der neurologischen Rehabilitation Phase B. Ergebnisse der 6-Jahres-Nachuntersuchung einer Multicenterstudie. *Nervenarzt* 2011; 82: 753–763.
- Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Recovery of walking function in stroke patients: the Copenhagen Stroke Study. *Arch Phys Med Rehabil* 1995; 76: 27–32.
- Kwakkel G, Kollen BJ, van der Grond J, Prevo AJ. Probability of regaining dexterity in the flaccid upper limb: impact of severity of paresis and time since onset in acute stroke. *Stroke* 2003; 34: 2181–2186.
- Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Upper-limb spasticity during the first year after stroke: stroke arm longitudinal study at the University of Gothenburg. *Am J Phys Med Rehabil* 2014; 93: 884–896.
- Martin A, Abogunrin S, Kurth H, Dinot J. Epidemiological, humanistic, and economic burden of illness of lower limb spasticity in adults: a systematic review. *Neuropsychiatr Dis Treat* 2014; 10: 111–122.
- Sommerfeld DK, Eek EU, Svensson AK, Holmqvist LW, von Arbin MH. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. *Stroke* 2004; 35: 134–139.
- Opheim A, Danielsson A, Alt Murphy M, Persson HC, Sunnerhagen KS. Early prediction of long-term upper limb spasticity after stroke: part of the SALGOT study. *Neurology* 2015; 85: 873–880.
- Brainin M, Norrving B, Sunnerhagen KS, Goldstein LB, Cramer SC, Donnan GA, et al. Poststroke chronic disease management: towards improved identification and interventions for poststroke spasticity-related complications. *Int J Stroke* 2011; 6: 42–46.
- Pollock A, St George B, Fenton M, Firkins L. Top ten research priorities relating to life after stroke. *Lancet Neurol* 2012; 11: 209.
- Kwakkel G, Meskers CG. Botulinum toxin A for upper limb spasticity. *Lancet Neurol* 2015; 14: 969–971.
- Gracies JM, Brashear A, Jech R, McAllister P, Banach M, Valkovic P, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. *Lancet Neurol* 2015; 14: 992–1001.
- Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J Physiol* 1964; 172: 369–382.
- Purpura DP, McMurtry JG. Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol* 1965; 28: 166–185.
- Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 2001; 57: 1899–1901.
- Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet* 1985; 1: 1106–1107.
- Floel A. tDCS-enhanced motor and cognitive function in neurological diseases. *Neuroimage* 2014; 85 Pt 3: 934–947.
- Nowak DA, Grefkes C, Ameli M, Fink GR. Interhemispheric competition after stroke: brain stimulation to enhance recovery of function of the affected hand. *Neurorehabilitation & Neural Repair* 2009; 23: 641–656.
- Lang N, Siebner HR, Ward NS, Lee L, Nitsche MA, Paulus W, et al. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur J Neurosci* 2005; 22: 495–504.
- Wu D, Qian L, Zorowitz RD, Zhang L, Qu Y, Yuan Y. Effects on decreasing upper-limb poststroke muscle tone using transcranial direct current stimulation: a randomized sham-controlled study. *Arch Phys Med Rehabil* 2013; 94: 1–8.
- 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: 437–446.
- Lee SJ, Chun MH. Combination transcranial direct current stimulation and virtual reality therapy for upper extremity training in patients with subacute stroke. *Arch Phys Med Rehabil* 2014; 95: 431–438.
- 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. *NeuroRehabilitation & Neural Repair* 2011; 25: 838–846.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
- The Cochrane Collaboration. Cochrane Editorial Unit. 2013 Jul 23 [cited 2013 Sep 19]. Available from: <http://www.editorial-unit.cochrane.org/mecir>.
- Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol* 2006; 117: 845–850.
- Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Altman D, Sterne J, editors. *Cochrane handbook for systematic reviews of interventions* version 5.10 (updated March 2011): The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org.
- Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is “quality of evidence” and why is it important to clinicians? *BMJ* 2008; 336: 995–998.
- Brozek J, Oxman A, Schünemann H. GRADEpro [computer program]. Version 3.6 for Windows. GRADE working group: 2008.
- The Nordic Cochrane Centre. Review Manager (RevMan). 2014; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
- Qu YP, Wu DY, Tu XQ, Qian L, Yang YB, Geng H. Effect of transcranial direct current stimulation on relieving upper-limb spasticity after stroke (in Chinese). *Chin J Cerebrovasc Dis* 2009; 6: 586–589.
- Adeyemo BO, Simis M, Macea D, Fregni F. Systematic review of parameters of stimulation: clinical trial design characteristics and motor outcomes in noninvasive brain stimulation in stroke. *Front Psychiatry* 2012; 3: 88.
- Tedesco Triccas L, Burridge JH, Hughes AM, Pickering RM, Desikan M, Rothwell JC, et al. Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: a review and meta-analysis. *Clin Neurophysiol* 2015; 127: 946–955.
- Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. *Cochrane Database Syst Rev* 2016; 3: CD009645.
- 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: 162–171.
35. 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: 644–657.
 36. 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: 306–316.
 37. Kang N, Summers JJ, Cauraugh JH. Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016; 87: 345–355.
 38. Pandyan AD, Johnson GR, Price CI, Curless RH, Barnes MP, Rodgers H. A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity. *Clin Rehabil* 1999; 13: 373–383.
 39. Mehrholz J, Wagner K, Meissner D, Grundmann K, Zange C, Koch R, et al. Reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in adult patients with severe brain injury: a comparison study. *Clin Rehabil* 2005; 19: 751–759.
 40. Malhotra S, Pandyan AD, Day CR, Jones PW, Hermens H. Spasticity, an impairment that is poorly defined and poorly measured. *Clin Rehabil* 2009; 23: 651–658.
 41. Di Pino G, Pellegrino G, Assenza G, Capone F, Ferreri F, Formica D, et al. Modulation of brain plasticity in stroke: a novel model for neurorehabilitation. *Nat Rev Neurol* 2014; 10: 597–608.
 42. Ulm L, McMahon K, Copland D, de Zubicaray GI, Meinzer M. Neural mechanisms underlying perilesional transcranial direct current stimulation in aphasia: a feasibility study. *Front Hum Neurosci* 2015; 9: 550.

APPENDIX I. Search strategy for MEDLINE (via OvidSP)

Search strategy for searching MEDLINE via Ovid

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp “intracranial embolism and thrombosis”/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc\$ or brain vasc\$ or cerebral vasc\$ or cva\$ or apoplex\$ or SAH).tw.
3. ((brain\$ or cerebr\$ or cerebell\$ or intracran\$ or intracerebral) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or oclus\$)).tw.
4. ((brain\$ or cerebr\$ or cerebell\$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage\$ or hemorrhage\$ or haematoma\$ or hematoma\$ or bleed\$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg\$ or hemipar\$ or paresis or paretic or hemineglect or hemi-neglect or ((unilateral or spatial or hemi?spatial or visual) adj5 neglect)).tw.
7. or/1-6
8. Electric Stimulation Therapy/
9. Electric Stimulation/
10. Electrodes/
11. (transcranial adj5 direct current adj5 stimulation).tw.
12. (transcranial adj5 DC adj5 stimulation).tw.
13. (transcranial adj5 electric\$ adj5 stimulation).tw.
14. (tDCS or A-tDCS or C-tDCS or S-tDCS or electrode\$ or anode or anodes or anodal or cathode or cathodes or cathodal).tw.
15. or/8-14
16. Randomized Controlled Trials as Topic/
17. random allocation/
18. Controlled Clinical Trials as Topic/
19. control groups/
20. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
21. double-blind method/
22. single-blind method/
23. Placebos/
24. placebo effect/
25. cross-over studies/
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
29. (random\$ or RCT or RCTs).tw.
30. (controlled adj5 (trial\$ or stud\$)).tw.
31. (clinical\$ adj5 trial\$).tw.
32. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
33. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
34. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
35. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
36. (cross-over or cross over or crossover).tw.
37. (placebo\$ or sham).tw.
38. trial.ti.
39. (assign\$ or allocat\$).tw.
40. controls.tw.
41. or/16-40
42. 7 and 15 and 41
43. exp animals/ not humans.sh.
44. 42 not 43