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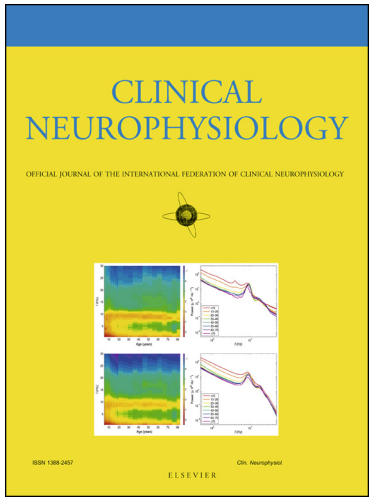

Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis

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PII: S1388-2457(15)00307-7
DOI: http://dx.doi.org/10.1016/j.clinph.2015.04.067
Reference: CLINPH 2007468

To appear in: *Clinical Neurophysiology*

Accepted Date: 15 April 2015

Please cite this article as: Tedesco Triccas, L., Burridge, J.H., Hughes, A.M., Pickering, R.M., Desikan, M., Rothwell, J.C., Verheyden, G., Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis, *Clinical Neurophysiology* (2015), doi: http://dx.doi.org/10.1016/j.clinph.2015.04.067

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Multiple sessions of transcranial direct current stimulation and upper extremity rehabilitation in stroke: A review and meta-analysis

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Highlights

- tDCS and rehabilitation had small non-significant effect on upper extremity impairments.
- Varied tDCS and rehabilitation programmes were identified in selected studies.
- Future research needs to further analyse tDCS and therapy interventions in stroke.

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Abstract

Objective: To systematically review the methodology in particular treatment options and outcomes and the effect of multiple sessions of transcranial direct current stimulation (tDCS) with rehabilitation programmes for upper extremity recovery post stroke.

Methods: A search was conducted for randomised controlled trials involving tDCS and rehabilitation for the upper extremity in stroke. Quality of included studies was analysed using the Modified Downs and Black form. The extent of, and effect of variation in treatment parameters such as anodal, cathodal and bi-hemispheric tDCS on upper extremity outcome measures of impairment and activity were analysed using meta-analysis.

Results: Nine studies (371 participants with acute, sub-acute and chronic stroke) were included. Different methodologies of tDCS and upper extremity intervention, outcome measures and timing of assessments were identified. Real tDCS combined with rehabilitation had a small non-significant effect of +0.11 (p=0.44) and +0.24 (p=0.11) on upper extremity impairments and activities at post-intervention respectively.

Conclusion: Various tDCS methods have been used in stroke rehabilitation. The evidence so far is not statistically significant, but is suggestive of, at best, a small beneficial effect on upper extremity impairment.

Significance: Future research should focus on which patients and rehabilitation programmes are likely to respond to different tDCS regimes.

Keywords: Transcranial direct current stimulation; rehabilitation; stroke; upper extremity; recovery; non-invasive brain stimulation.

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1. Introduction

Stroke is a health concern worldwide and one of the main causes of disability (Kolominsky-Rabas et al., 2001, Albert and Kesselring, 2012). Motor impairment is the main cause of disability after stroke, leading to major health problems (Boggio et al., 2007, Clarke, 1999). In Europe, stroke costs around 64.1 billion euros and in the United Kingdom, around £8.9 billion per annum is spent on community care and rehabilitation of people with stroke (Saka et al., 2009, Gustavsson et al., 2011). At six months, 33% to 66% of people with Upper Extremity (UE) impairments do not present with functional upper limb function and only 5-20% achieve full recovery (Kwakkel et al., 2003, Kwakkel and Kollen, 2013). Thus a number of approaches are now being investigated in an attempt to increase the effectiveness of stroke rehabilitation techniques for the UE.

Non-invasive methods of brain stimulation such as transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS) are extensively researched and are beginning to be used clinically to modulate brain activity (Paulus, 2003, Pascual-Leone et al., 2000, Hummel et al., 2005). Although these two methods have very different modes of action (rTMS stimulates axons in the brain and initiates new action potentials; tDCS polarises the neurones, and modulates their ongoing firing pattern) both of them, when applied over the motor cortex, produce changes in cortical excitability which, in the case of tDCS can last up to 90 minutes (Nitsche and Paulus, 2000, Nitsche and Paulus, 2001, Fitzgerald et al., 2006). They also enhance motor performance and can change reaction times, movement accuracy and speed (Nitsche et al., 2003b, Kobayashi et al., 2004). More importantly, in the context of possible therapeutic application, they can improve motor skill learning (Reis and Fritsch, 2011, Teo et al., 2011) or adapt already

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learned skills to new conditions (Galea et al., 2011). There has therefore been considerable interest in examining the potential of these interventions to augment recovery of motor function after stroke.

Initial investigations with non-invasive brain stimulation concentrated on using methods of rTMS to improve recovery in acute and chronic stroke (Khedr et al., 2005, Kim et al., 2006). However in recent years there has been increased interest in using tDCS because of two main advantages: firstly it is far less expensive than rTMS, and secondly, stimulation can potentially be applied during rehabilitation whereas rTMS (because the equipment is bulky and the head needs to remain still), it can only be given before (or after) a training session (Brunoni et al., 2012). From a practical viewpoint, anodal tDCS is usually assumed to increase excitability whereas cathodal tDCS reduces excitability (Nitsche and Paulus, 2000). In stroke rehabilitation this means that researchers will employ anodal tDCS over the stroke hemisphere to improve the response of that hemisphere to training protocols (Hummel et al., 2005). Alternatively, employing the logic of inter-hemispheric imbalance, cathodal stimulation of the non-stroke hemisphere will inhibit that hemisphere to reduce its trans-hemispheric inhibition of the affected hemisphere or bihemispheric stimulation by simultaneously modulating the unaffected and affected motor cortex (Nitsche et al., 2003a, Lindenberg et al., 2010).

In healthy volunteers, the effects of tDCS on cortical excitability and performance are short-lasting and variable (Nitsche and Paulus, 2000, López-Alonso et al., 2014, Wiethoff et al., 2014). However, it is usually assumed that multiple daily applications in stroke may lead to a build-up of effects that are larger and more persistent. The main evidence in favour of this comes from studies of rTMS to treat depression: a single session, or even two weeks daily treatment with rTMS has little effect on

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symptoms over and above placebo, whereas longer (>4 weeks) treatments can improve symptoms for several months (Dell'Osso et al., 2011, Galletly et al., 2012) . Thus most recent clinical trials of tDCS have employed several days or weeks of repeated treatment with rehabilitation programmes in an attempt to maximise outcome (Lee and Chun, 2014, Viana et al., 2014). Interestingly it is still unclear whether repeated daily session of tDCS have cumulative effects in the healthy and stroke population (Alonzo et al., 2012, Monte-Silva et al., 2013).

Recent meta-analyses have explored the effect of tDCS in addition to rehabilitation on UE activity in stroke (Bastani and Jaberzadeh, 2011, Adeyemo et al., 2012, Butler et al., 2013, Elsner et al., 2013). Adeyemo et al. (2012) demonstrated a significant effect size (0.58) of non-invasive brain stimulation on motor function. Bastani and Jaberzadeh (2011) showed that anodal tDCS had a small non-significant effect size of 0.39 on hand function in stroke, but a moderate significant effect size of 0.59 on motor evoked potential amplitude. Butler et al. (2013) also demonstrated a significant small effect size of 0.40 of anodal tDCS on UE motor recovery. A Cochrane review showed that tDCS has a small effect on UE motor impairments but not on activities of daily living at post-intervention (Elsner et al., 2013). However, at follow-up they showed an effect of tDCS on activities of daily living but not on UE motor impairments. No effect of tDCS in sub-groups involving people with acute, sub-acute and chronic stroke was found. The analyses in these reviews combined studies including one or multiple sessions of tDCS, and the pooled effects of only multiple tDCS sessions plus therapy remains uninvestigated.

The aim of the current study was to systematically review the methodology adopted in various studies of tDCS. In particular treatment options, outcomes reported, and the effect of multiple sessions of tDCS with rehabilitation programmes for UE

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recovery post stroke. We included trials in which anodal, cathodal or bi-hemispheric tDCS was applied in conjunction with UE rehabilitation programmes at any stage post stroke.

2. Methods

2.1 Search

A systematic search was conducted for articles written in English and published between 1990 and July 2014. Full text articles in electronic databases MEDLINE, EMBASE (Excerpta Medica Database), CINAHL (Cumulated Index of Nursing and Allied Health Literature), AMED (Allied and Complementary Medicine Database), PubMed, PEDro (Physiotherapy Evidence Database) were systematically searched by the first author (LTT). Combination of key words with the use of 'AND' and 'OR' were used for the searches (Table 1). Duplicates were removed and papers were then selected for analysis according to the eligibility criteria (Figure 1).

2.2 Eligibility Criteria

2.21 Participants

The type of participants included in the study needed to: a) have a confirmed clinical diagnosis of a haemorrhagic or an ischaemic stroke as defined by WHO (Monica, 1988); b) have experienced a single stroke or multiple strokes; c) be in the acute (starting intervention during 2-weeks post-stroke), sub-acute (2 weeks to three months post-stroke) or chronic phase (after three months post-stroke); d) have a subcortical or cortical stroke; e) be male or female over the age of 18 years; f) have any type of UE impairment; and g) received multiple sessions of tDCS, defined as two or more sessions, plus UE therapy.

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2.22 Study designs

All Randomised Controlled Trials (RCTs) utilising multiple sessions of tDCS in combination with rehabilitation were included regardless of blinding. Outcome measures were classified according to the International Classification of Functioning, Disability and Health (ICF) (WHO, 2001). Where possible we selected one outcome from each paper in each ICF category: impairment, activity and participation. The chosen primary outcome measure of UE impairment was Fugl-Meyer Assessment (FMA) and the outcomes of activity and participation were classed as secondary.

2.3 Process

Three review authors (LTT, AMH, GV) independently assessed the methodological quality of the included studies using a validated, reliable tool, the Modified Downs and Black (Eng et al., 2007). Disagreement between the reviewers was resolved through discussion between the three review authors. If no agreement was achieved, a fourth review author (JHB) was used to gain consensus. Papers with scores lower than 16 out of 27 points were excluded from the analysis due to poor quality (Eng et al., 2007).

2.4 Data synthesis and analyses

Different methodologies including study population, selection criteria and outcome measures, timing of assessment, intervention programmes (dosage/intensity, mode of delivery, frequency, duration and timing of tDCS delivery) and adverse reactions were extracted from the selected publications. The main characteristics of the population were calculated as percentages from the total sample. The studies were then assessed for heterogeneity to determine the appropriateness of a pooled analysis. Information from the selected papers was analysed using the Cochrane Collaboration's Review Manager software, RevMan (Version 5.3). Statistical heterogeneity was assessed using the I-squared and Chi-squared statistic. Due to

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the small number of studies included, a fixed effects model was adopted for all analyses (Borenstein et al., 2010). Paper authors were contacted with respect to any missing data of the included studies. Data of the FMA impairment outcome measure in relation to the effect of UE rehabilitation with real tDCS (anodal and/or cathodal or bihemispheric) versus sham tDCS or no stimulation as reported in the study of Lee and Chun (2014), were inputted in the program and meta-analysed. Studies reporting only the medians of the selected outcomes were not included in the meta-analyses (Wu et al., 2013). All outcome measures were analysed as continuous variables, using the mean, standard deviation and number of participants at immediate post-intervention, short-term (1- 12 weeks) or long-term follow-up (>12 weeks). Data relating to a different activity outcome measure abstracted from each study were also combined in the activity meta-analysis. The standardised mean differences (using Hedges' adjusted g) and 95% confidence intervals were calculated. All outcomes were standardised so that positive differences between tDCS and control groups favoured tDCS. Hedges' adjusted g, similar to Cohen's (d), was used to estimate the effect size and includes an adjustment for small sample bias of RCTs. The effect size was interpreted according to Cohen's convention of small (>0.2), moderate (>0.5), and large (>0.8) effects (Cohen 1992). A 95% confidence interval around the estimated effect size was calculated for each analysis. Meta-analysis of the neurophysiological data was not conducted due to limited data.

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3. Results

3.1 Search Results

The PRISMA flow chart (Figure 1) shows the search and selection results. Nine papers scored 16 points or above using the Downs and Black scoring were included in the qualitative analysis and eight were (Eng et al., 2007) (Table 2).

3.2 Main characteristics of the RCT's

In total, 371 participants with stroke (243 males) meeting the eligibility criteria for our review study were included in the nine selected studies. All participants had a single stroke apart from the ones in the study by Viana et al. (2014). Limited detail was reported regarding stroke location. Combined over studies included in the meta-analysis, 164 (44%) participants had cortico-subcortical or cortical strokes and 49 (11%) participants had subcortical stroke. Three studies did not describe the location of the strokes (Lindenberg et al., 2010, Wu et al., 2013; Viana et al., 2014). Four studies involved 65 (18%) participants with chronic stroke (Lindenberg et al., 2010, Bolognini et al., 2011, Nair et al. 2011, Viana et al., 2014), four studies involved 263 (71%) participants in the sub-acute stage (Kim et al., 2010, Hesse et al., 2011, Wu et al., 2013, Lee and Chun, 2014) and one study involved 40 (11%) people with acute stroke (Khedr et al. 2013).

One hundred and forty-five (39%) participants had moderate UE impairments (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al 2011, Nair et al., 2011, Lee and Chun 2014, Viana et al., 2014) and 226 (61%) participants had severe UE impairments (Hesse et al., 2011, Khedr et al., 2013, Wu et al., 2013) at baseline based on the FMA or MRC Scale (shoulder) (Lum et al., 2002).

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3.21 Outcome measures and timing of assessments

Eight studies used the FMA as an outcome measure of UE motor impairments (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al., 2011, Hesse et al., 2011, Nair et al., 2011, Wu et al., 2013, Lee and Chun, 2014, Viana et al., 2014) and one study used the Medical Research Council scale (Khedr et al., 2013). Only two studies explored the neurophysiological effects of tDCS, using measures of Resting and Active Motor Threshold (Khedr et al., 2013), motor evoked potential amplitude (Bolognini et al., 2011) and transcallosal inhibition to transcranial magnetic stimulation (Bolognini et al., 2011). Two studies employed functional MRI of brain activity as an outcome measure (Lindenberg et al., 2010, Nair et al., 2011). The Barthel Index or Modified Barthel Index and Motor Activity Log were utilised as measures of activities of daily living (Kim et al., 2010, Hesse et al., 2011, Bolognini et al., 2011, Khedr et al., 2013, Wu et al., 2013, Lee and Chun, 2014).

All studies included a baseline and post-intervention assessment. Follow-up assessments varied between seven days (Lindenberg et al., 2010); two weeks (Bolognini et al., 2011); four weeks (Wu et al., 2013, Bolognini et al., 2011); three months (Hesse et al., 2011, Khedr et al., 2013); and six months (Kim et al., 2010) post-intervention. Three studies reported additional assessments: at one day (Kim et al., 2010); three days (Lindenberg et al., 2010); and six days (Nair et al., 2011) after the intervention was ended as a follow-up assessment.

3.22 tDCS parameters

Three studies randomised participants to anodal, cathodal and sham group (Kim et al., 2010, Hesse et al., 2011, Khedr et al., 2013); one study involved an anodal and sham group (Viana et al., 2014); two studies randomised participants to cathodal and sham group (Nair et al., 2011, Wu et al., 2013); one study had a cathodal group and no stimulation as a placebo (Lee and Chun, 2014); and two studies randomised to

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bihemispheric tDCS and sham groups (Lindenberg et al., 2010, Bolognini et al., 2011). The tDCS parameters deployed in the studies are displayed in Figure 2.

The timing of tDCS delivery in relation to the rehabilitation was: during rehabilitation (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al., 2011, Hesse at al., 2011, Nair et al., 2011, Lee and Chun, 2014); before rehabilitation (Khedr et al., 2013, Viana et al., 2014); or not reported (Wu et al., 2013).

3.23 Rehabilitation programmes

The rehabilitation programme in one study was constraint induced movement therapy daily for 14 days (Bolognini et al., 2011). In three studies, it was conventional therapy (positioning, passive movements, stretching and movement/functional training and, goal-directed activities of practical) for 30 minutes; 5 days per week, for four weeks (Wu et al., 2013); daily for five weeks (Lindenberg et al., 2010, Nair et al., 2011); or for six days (Khedr et al., 2013). In the remaining studies it was an occupational therapy programme comprising of task practice as part of the WMFT for 10 sessions over 2 weeks (Kim et al., 2010); focused bilateral wrist robot therapy for 20 minutes for 30 sessions (Hesse et al., 2011); or virtual reality 5 sessions per week for 3 weeks of 30 minutes each session (Lee and Chun, 2014) or 3 sessions per week for 5 weeks of one hour each session (Viana et al., 2014).

3.24 Sensations and adverse reactions

Five studies reported sensations and adverse reactions from tDCS. Participants reported tingling or slight itching under the tDCS electrodes (Wu et al., 2013, Hesse et al., 2011, Lindenberg et al., 2010). One participant discontinued anodal tDCS due to a headache and one participant receiving cathodal tDCS reported dizziness (Kim et al., 2010, Hesse et al., 2011).

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3.3 Quantitative Analysis

3.31 The effect of real versus sham tDCS and rehabilitation on UE motor impairments

Seven studies (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al., 2011, Hesse et al., 2011, Nair et al., 2011, Lee and Chun, 2014, Viana et al., 2014) explored the effect of real (anodal, cathodal or bi-hemispheric) versus sham tDCS combined with rehabilitation programmes on UE motor impairments measured by FMA at immediate post-intervention (Figure 3). An overall small non-significant effect size of +0.11[-0.17, 0.38] (p=0.44) favoured real tDCS and rehabilitation compared to sham stimulation at post-intervention. A non-significant effect size +0.27 [-0.40, 0.95] (p=0.43) was noted between 7 days to 2 weeks follow-up (Lindenberg et al., 2010, Bolognini et al., 2011) (Figure 4). A small non-significant effect size +0.23 [-0.17, 0.62) (p=0.26) was noted at a long-term follow-up ranging between 3 to 6 months for UE global motor impairments in participants with sub-acute stroke (Kim et al., 2010, Hesse et al., 2011) (Figure 5). A small non-significant effect size of +0.01 [-0.39, 0.41] (p=0.96) was obtained favouring anodal over sham tDCS combined with rehabilitation on UE impairments was observed based on three studies (Kim et al., 2010, Hesse et al., 2011, Viana et al., 2014) (Figure 6). A small non-significant effect of 0.10 [-0.26, 0.47] (p=0.59) favoured cathodal stimulation and rehabilitation at post-intervention, based on three studies (Kim et al., 2010, Hesse et al., 2011, Lee and Chun, 2014) (Figure 7). Bihemispheric stimulation and UE rehabilitation showed a larger non-significant effect of +0.17 [-0.50, 0.84] (p=0.62) over sham stimulation, based on two studies involving chronic stroke participants (Lindenberg et al., 2010, Bolognini et al., 2011) (Figure 8).

3.32 Sub-analyses

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Five studies (Kim et al., 2010, Bolognini et al., 2011, Hesse et al., 2011, Khedr et al., 2013, Lee and Chun, 2014, Lee and Chun, 2014) using different outcome measures of generic activities of daily living showed a non-significant small effect size of 0.24 [-0.06,0.54] (p=0.11) favouring real tDCS in combination with rehabilitation at post-intervention (Figure 9). Three studies (Kim et al., 2010, Hesse et al., 2011, Khedr et al., 2013) explored the effect of anodal tDCS and rehabilitation on activities of daily living with a small non-significant effect of 0.19 [-0.12, 0.50] (p=0.23) favouring anodal tDCS and rehabilitation (Figure 10). Three studies (Hesse et al., 2011, Khedr et al., 2013., Lee and Chun, 2014) explored the effect of cathodal tDCS and rehabilitation on activities of daily living with a small significant effect of 0.38 [0.03,0.73] (p=0.03) favouring anodal tDCS and rehabilitation (Figure 11).

4. Discussion

Driven by the positive benefits of repeated sessions of rTMS to treat depression, many current trials apply the same logic when using tDCS to improve recovery of arm function after stroke. This is the first review to explore the effect of just multiple sessions of tDCS and UE rehabilitation programmes on outcome measures based on the ICF; impairment and activity. Therefore, it examines the potential clinical use of tDCS. We performed a meta-analysis of the data, in which this approach was used to provide a current overview of the expected effect size for subsequent trials. Nine studies met the inclusion criteria. The results of the meta-analysis showed that when tDCS is applied in conjunction with multiple sessions of rehabilitation it has no significant immediate effect, over and above therapy delivered alone, on UE impairment and activity after stroke. The two larger (greater than 0.10) immediate post-intervention effect sizes on UE impairments both favoured tDCS, and possibly larger sample sizes are needed to confirm such small effects. Unfortunately,

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although the analyses included data from studies in acute, sub-acute and chronic stroke they were insufficient to analyse specific effects dependent on stage of recovery.

There are a number of important limitations which may affect the validity of these conclusions. A limitation is that the ICF emphasises that in addition to measuring impairments and function, clinicians should also assess participation (Perenboom and Chorus, 2003, WHO, 2001). Most of the studies included only reported UE impairment outcome measures. Apart from the Motor Activity Log, the selected outcome measures do not specifically assess UE activities of daily living (Uswatte et al., 2006). In addition, including outcome measures such as the Stroke Impact Scale in clinical trials of tDCS plus rehabilitation (Duncan et al., 2003) would give an insight into the effect of intervention on participants' quality of life.

The wide variability in the methodology of both the tDCS method as well as the rehabilitation therapy used severely limit the conclusions we can draw from these studies. As far as the tDCS was concerned, the exact timing of the post-intervention assessment with respect to the last or first treatment session was often not reported. In addition, the duration, frequency, and timing of the intervention were different in every study. Hesse et al. (2011) used a treatment programme of 30 sessions whilst Lindenberg et al. (2010) used five sessions. Some studies evaluated tDCS applied before rehabilitation whereas in others it was applied during rehabilitation. In healthy individuals, anodal tDCS applied during motor learning can result in faster learning than if applied prior to motor learning (Stagg et al., 2011). Anodal tDCS can also result in prolonged skill acquisition through an effect on offline consolidation but whether the same advantage occurs in stroke is unknown (Reis et al., 2009). Finally, the parameters of stimulation differed between studies, some used 1mA and others

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2mA applied for durations varying from 10 to 40minutes. Whether different chosen currents are equally effective is unknown. In healthy individuals, the effects of cathodal tDCS on motor cortex excitability reverse from suppression to facilitation when the stimulus intensity increases from 1 mA to 2 mA (Batsikadze et al., 2013). However, it is not possible to extrapolate with confidence from effects on motor excitability in healthy individuals to effects on motor performance in disease.

The review has highlighted wide differences in protocols, and given these variations coupled with the small numbers of participants, it is not possible to form any firm conclusions about the efficacy of tDCS in improving the effect of UE rehabilitation after stroke. A further difficulty is that the efficacy of the tDCS may vary depending on the details, and efficacy of the associated UE rehabilitation programme. Variations in the rehabilitation therapy applied to patients were as widespread as those used in tDCS. Some patients only received “conventional” therapy for 6 days, whereas others were employed in robot training protocols or CIMT. It is possible for example that a “ceiling effect” occurred in some cases. That is, the therapy was sufficient on its own to produce an improvement in outcome that could not be boosted further by adding tDCS.

Greater insight into the effects might be obtained if sensitive cortical activity or neurophysiological outcome measures are utilised in all randomised controlled trials. Until this is addressed through large definitive trials the problem will persist. Outcome measures, participants’ characteristics and protocols need to be standardised. This occurred early in treatment trials of rTMS in depression, where a relatively “standard” treatment is 10 Hz rTMS of the left dorsolateral prefrontal cortex (O’Reardon et al., 2007). This standardisation allowed for more effective meta-

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analyses to be undertaken than is currently possible with tDCS interventions in stroke.

Recent studies on healthy participants have emphasised that the response to tDCS is highly variable between individuals (López-Alonso et al., 2014, Wiethoff et al., 2014). Several clinical trials involving participants with stroke have also reported highly variable responses (Hummel et al., 2005, Bolognini et al., 2011, Hesse et al., 2011, Khedr et al., 2013). Thus one important future consideration may be to determine which patients with stroke are most likely to benefit. In the study by Hesse et al., (2011), the participants had severe UE impairments and showed minimal effect from real tDCS and rehabilitation. However, it is unclear whether adding tDCS is more important for people with moderate than severe UE impairments. For instance there is evidence that robot therapy is more beneficial for people with moderate UE impairments compared to severely affected people with stroke (Ferraro et al., 2003). There is also a lack of evidence whether the different types of tDCS might be more beneficial for people in the acute or the chronic phase of stroke. Thus, stratifying participants according to their stage after stroke and their UE impairments in addition with tDCS application should be the next focus for future research.

The review has limitations: only a small number of eligible studies were identified; only absolute group summary statistics taken immediately post-intervention or at follow-up were included in the meta-analyses. A more powerful analysis would be possible if baseline data could be included in order to compare this with the post-intervention data. Finally, due to the statistical program used, studies reporting medians could not be included in the meta-analyses.

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5. Conclusions

Systematic reviews and meta-analyses have been a popular method of exploring the effect of tDCS on UE recovery in stroke. The results from this review showed that multiple sessions of tDCS regimes combined with UE rehabilitation had a small and non-significant effect on upper limb impairments and activities of daily living post-intervention. However, from this review there is wide variation in tDCS parameters adopted in the constituent trials and different UE therapy. Factors such as selection criteria, tDCS parameters, type of rehabilitation programmes and type and stage of stroke have to be further explored. Future research should focus on stratifying participants with stroke according to their UE impairments and evaluate which participants are more likely to benefit from tDCS in addition to stroke rehabilitation. This will increase the knowledge about the effect of tDCS and rehabilitation for UE motor recovery in stroke and eventually will contribute to further high quality meta-analyses.

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Conflicts of Interest Statement

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

Acknowledgments

We would to thank the Faculty of Health Sciences of the University of Southampton and also the Strategic Educational Pathways Scholarships from the European Union and the Maltese Government for funding this research project.

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Figure Legends

Figure 1: Study selection PRISMA flow diagram.

Figure 2: A flow diagram displaying the different tDCS parameters selected for the included studies.

Figure 3: Effect of real tDCS versus sham tDCS for UE global motor impairments measured by FMA at immediate post-intervention.

Figure 4: Effect of real tDCS versus sham tDCS for UE global motor impairments measured by FMA at short-term follow-up.

Figure 5: Effect of real tDCS versus sham tDCS for UE global motor impairments measured by FMA at long-term follow-up.

Figure 6: Effect of anodal tDCS versus sham tDCS for UE global motor impairments measured by FMA at immediate post-intervention.

Figure 7: Effect of cathodal tDCS versus sham tDCS for UE global motor impairments measured by FMA at immediate post-intervention.

Figure 8: Effect of bihemispheric tDCS versus sham tDCS for UE global motor impairments measured by FMA at immediate post-intervention.

Figure 9: Effect of real tDCS versus sham tDCS for activities of daily living at immediate post-intervention.

Figure 10: Effect of anodal tDCS versus sham tDCS for activities of daily living measured at immediate post-intervention.

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Figure 11: Effect of cathodal tDCS versus sham tDCS for activities of daily living measured at immediate post-intervention.

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Abstract

Objective: To systematically review the methodology in particular treatment options and outcomes and the effect of multiple sessions of transcranial direct current stimulation (tDCS) with rehabilitation programmes for upper extremity recovery post stroke.

Methods: A search was conducted for randomised controlled trials involving tDCS and rehabilitation for the upper extremity in stroke. Quality of included studies was analysed using the Modified Downs and Black form. The extent of, and effect of variation in treatment parameters such as anodal, cathodal and bi-hemispheric tDCS on upper extremity outcome measures of impairment and activity were analysed using meta-analysis.

Results: Nine studies (371 participants with acute, sub-acute and chronic stroke) were included. Different methodologies of tDCS and upper extremity intervention, outcome measures and timing of assessments were identified. Real tDCS combined with rehabilitation had a small non-significant effect of +0.11 (p=0.44) and +0.24 (p=0.11) on upper extremity impairments and activities at post-intervention respectively.

Conclusion: Various tDCS methods have been used in stroke rehabilitation. The evidence so far is not statistically significant, but is suggestive of, at best, a small beneficial effect on upper extremity impairment.

Significance: Future research should focus on which patients and rehabilitation programmes are likely to respond to different tDCS regimes.

Key Words: transcranial direct current stimulation; rehabilitation; stroke; upper extremity; recovery; non-invasive brain stimulation

Figure 1

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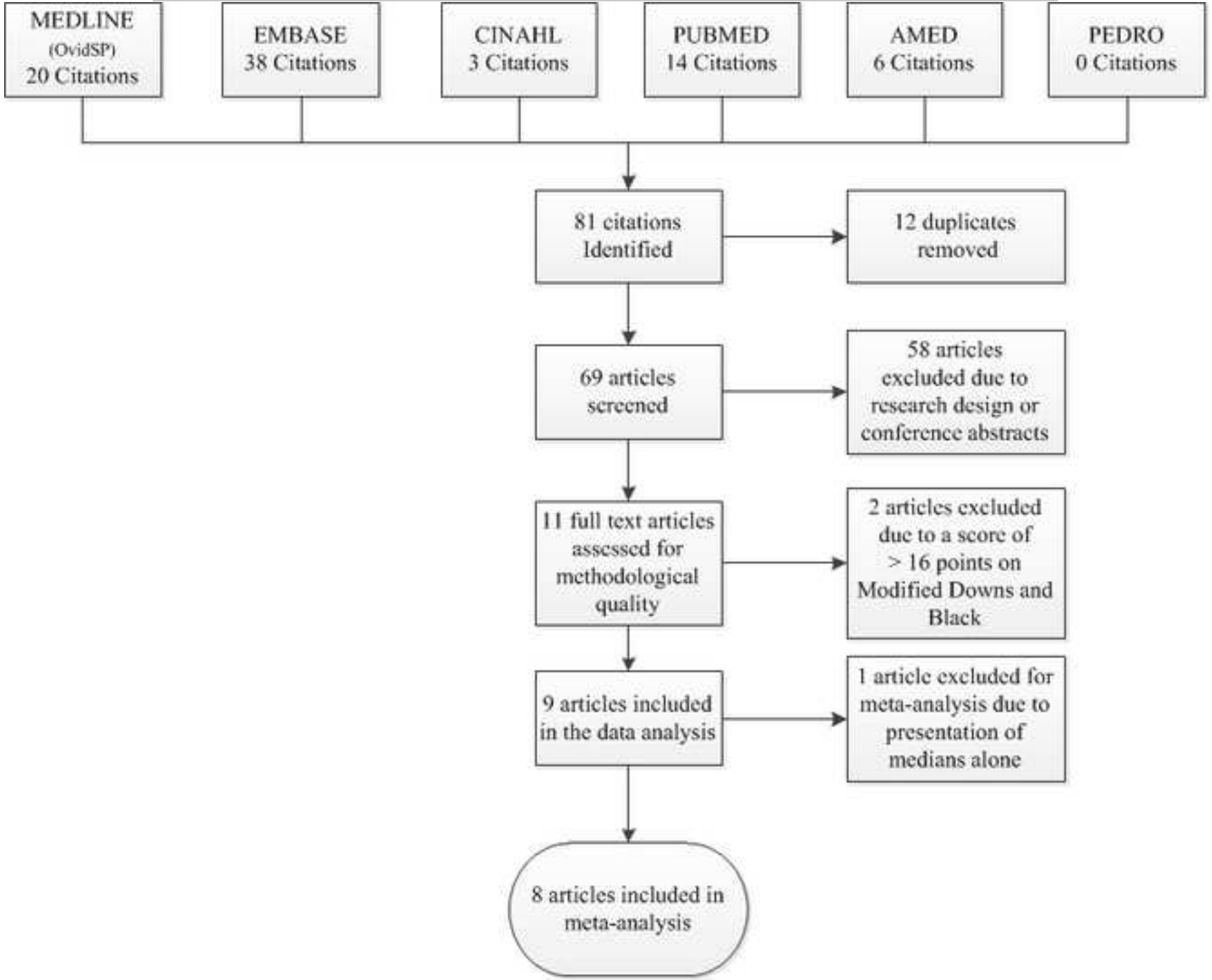

Figure 2

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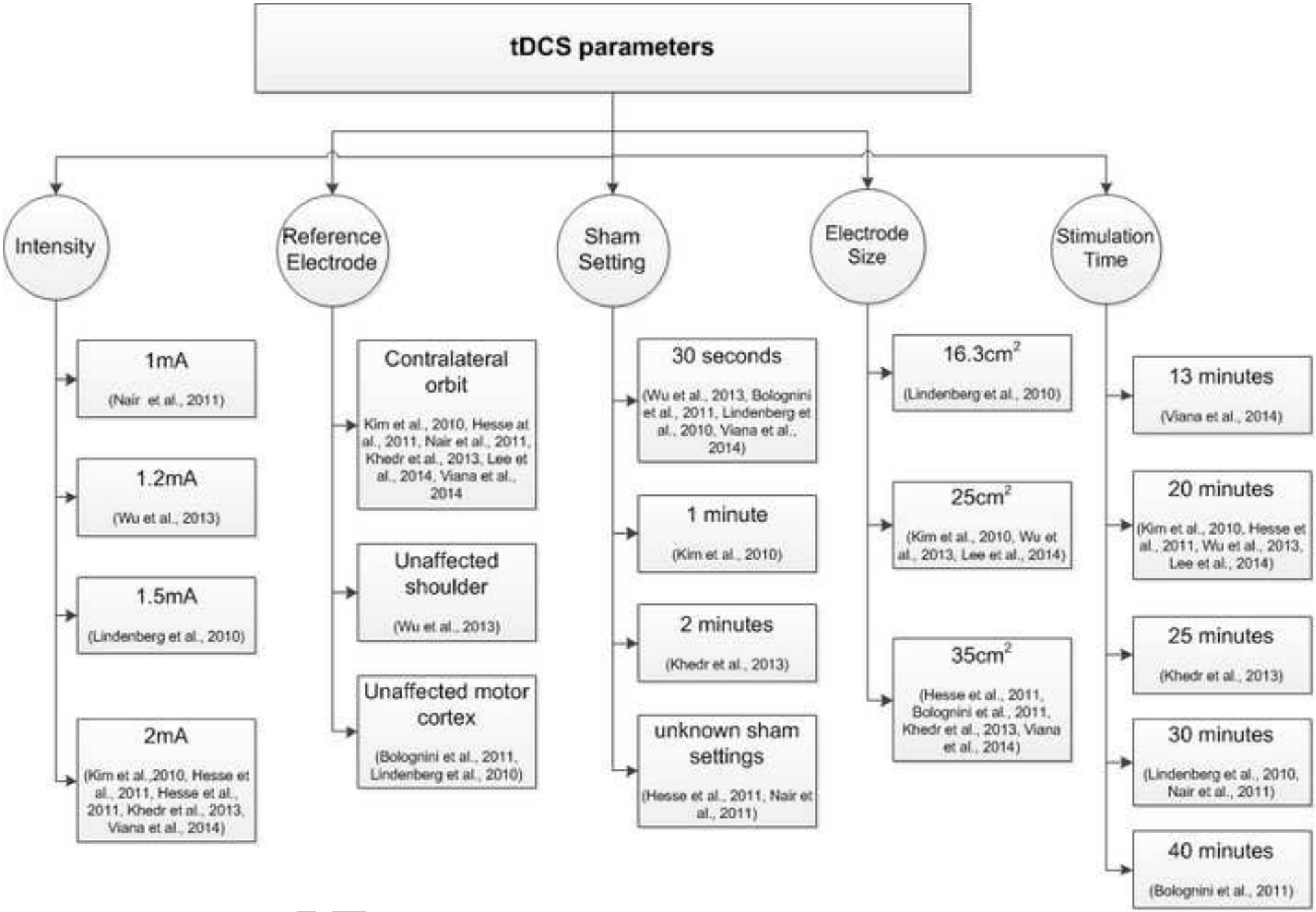

Figure 3

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Study or Subgroup	Real tDCS + Rehab Mean	SD	Total	Sham tDCS/No stim + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kim et al., 2010	48.9	15.2	11	49.3	10.2	6	7.6%	-0.03 [-1.02, 0.97]	2010
Lindenberg et al., 2010	43.8	12.3	10	41	11.8	10	9.7%	0.22 [-0.66, 1.10]	2010
Hesse et al., 2011	19	12.45	64	19.2	15	32	41.5%	-0.01 [-0.44, 0.41]	2011
Bolognini et al., 2011	31.7	31.1	7	29	20.3	5	5.7%	0.09 [-1.06, 1.24]	2011
Nair et al., 2011	33.7	12.9	7	32.3	9.8	7	6.8%	0.11 [-0.93, 1.16]	2011
Viana et al., 2014	50.6	13.4	10	46.9	12.4	10	9.6%	0.27 [-0.61, 1.16]	2014
Lee et al., 2014	47.7	21.3	20	41.6	21.3	20	19.2%	0.28 [-0.34, 0.90]	2014
Total (95% CI)			**129**			**90**	**100.0%**	**0.11 [-0.17, 0.38]**	

Heterogeneity: Chi² = 0.89, df = 6 (P = 0.99), I² = 0%
Test for overall effect: Z = 0.76 (P = 0.44)

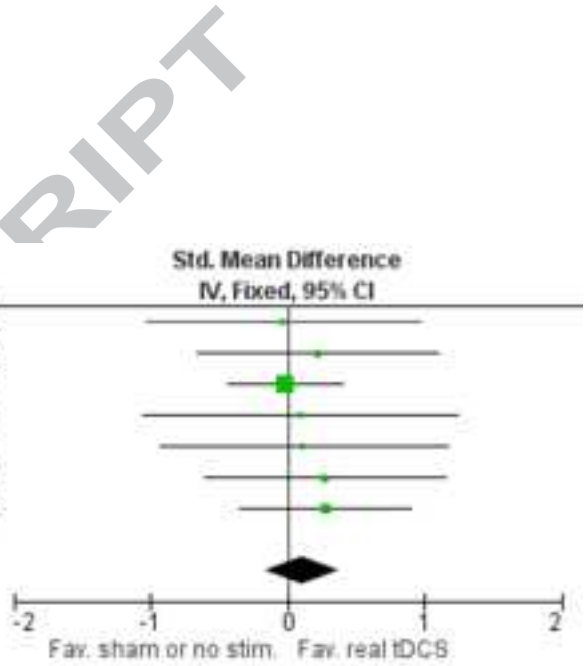

Figure 4

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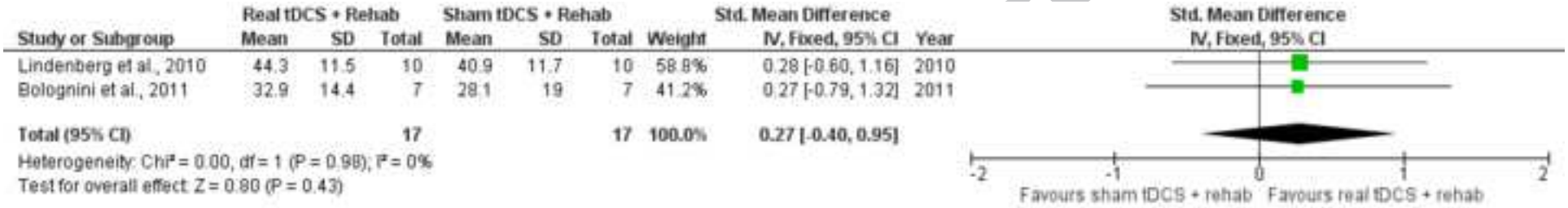

Figure 5

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Study or Subgroup	Real tDCS + Rehab Mean	SD	Total	Sham tDCS + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kim et al., 2010	58.6	5.6	11	43.3	16.5	7	13.7%	1.32 [0.25, 2.39]	2010
Hesse et al., 2011	23.4	16.4	64	22.5	17.1	32	86.3%	0.05 [-0.37, 0.48]	2011
Total (95% CI)			**75**			**39**	**100.0%**	**0.23 [-0.17, 0.62]**	

Heterogeneity: Chi² = 4.69, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.13 (P = 0.26)

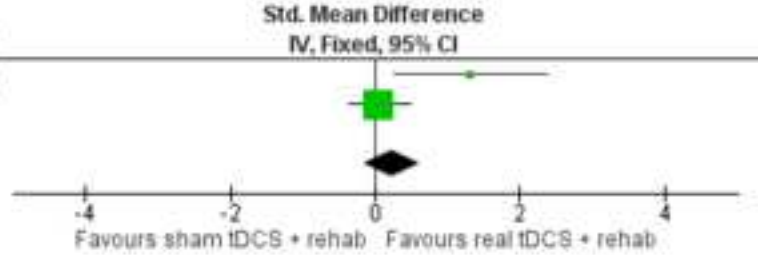

Figure 6

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Study or Subgroup	Real tDCS + Rehab Mean	SD	Total	Sham tDCS + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kim et al., 2010	45.4	12.4	7	49.3	10.2	6	13.2%	-0.32 [-1.42, 0.78]	2010
Hesse et al., 2011	19.1	14.4	32	19.2	15	32	66.3%	-0.01 [-0.50, 0.48]	2011
Viana et al., 2014	50.6	13.4	10	46.9	12.4	10	20.5%	0.27 [-0.61, 1.16]	2014
Total (95% CI)			**49**			**48**	**100.0%**	**0.01 [-0.39, 0.41]**	

Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

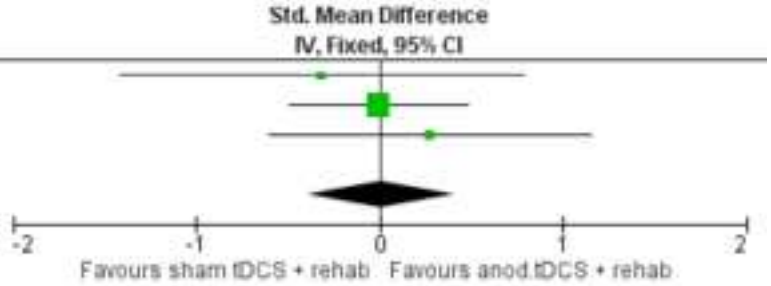

Figure 7

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Study or Subgroup	Cathodal tDCS + Rehab Mean	SD	Total	Sham tDCS/No Stim + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kim et al., 2010	52	18.7	5	49.3	10.2	7	10.1%	0.18 [-0.98, 1.33]	2010
Hesse et al., 2011	18.9	10.5	32	19.2	15	32	55.6%	-0.02 [-0.51, 0.47]	2011
Lee et al., 2014	47.7	21.3	20	41.6	21.3	20	34.4%	0.28 [-0.34, 0.90]	2014
Total (95% CI)			**57**			**59**	**100.0%**	**0.10 [-0.26, 0.47]**	

Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)

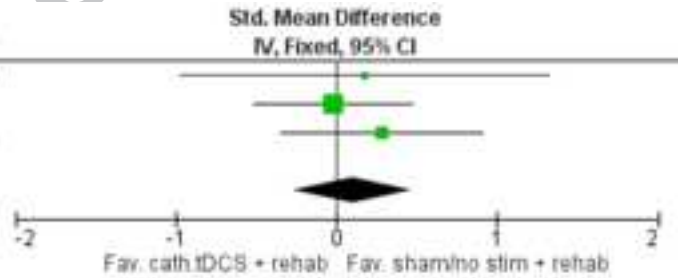

Figure 8

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Study or Subgroup	Real tDCS + Rehab Mean	SD	Total	Sham tDCS + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Lindenberg et al., 2010	43.8	12.3	10	41	11.8	10	58.7%	0.22 [-0.66, 1.10]	2010
Bolognini et al., 2011	31.7	31.1	7	29	20.3	7	41.3%	0.10 [-0.95, 1.14]	2011
Total (95% CI)			**17**			**17**	**100.0%**	**0.17 [-0.50, 0.84]**	

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

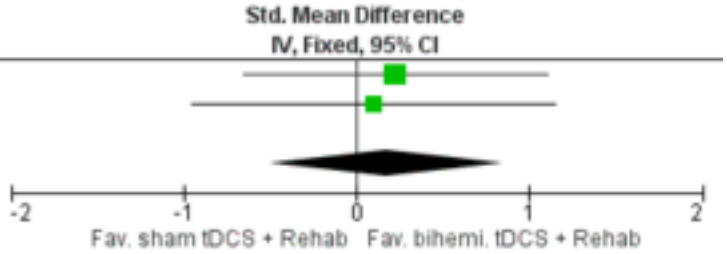

Figure 9

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Study or Subgroup	Real tDCS + Rehab Mean	SD	Total	Sham tDCS/No Stim + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kim et al., 2010	86.1	14.4	11	71	34.4	7	9.5%	0.60 [-0.37, 1.57]	2010
Hesse et al., 2011	56.4	13.5	64	56.3	15.5	32	50.2%	0.01 [-0.42, 0.43]	2011
Bolognini et al., 2011	2.5	1.5	7	2.5	0.8	7	8.2%	0.00 [-1.05, 1.05]	2011
Khedr et al., 2013	52.1	7	27	41.5	13.3	5	8.8%	1.27 [0.26, 2.28]	2013
Lee et al., 2014	70.6	15	20	64.3	24.5	20	23.2%	0.30 [-0.32, 0.93]	2014
Total (95% CI)			**129**			**71**	**100.0%**	**0.24 [-0.06, 0.54]**	

Heterogeneity: Chi² = 5.93, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 1.59 (P = 0.11)

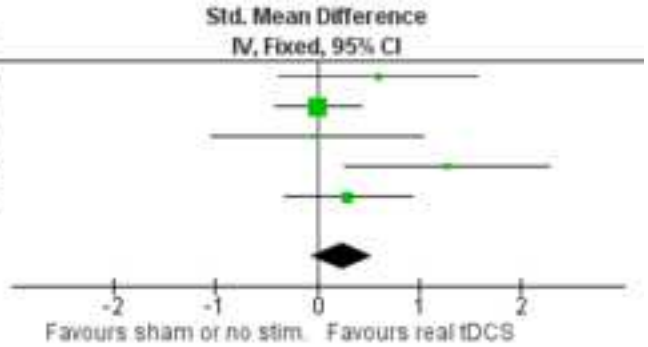

Figure 10

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Study or Subgroup	Anodal tDCS + Rehab Mean	SD	Total	Sham tDCS + Rehab Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
Kim et al., 2010	86.1	14.4	11	71	34.4	7	10.2%	0.60 [-0.37, 1.57]	2010
Hesse et al., 2011	56.4	13.5	64	56.3	15.5	64	80.4%	0.01 [-0.34, 0.35]	2011
Khedr et al., 2013	52	7	27	41	13	5	9.4%	1.33 [0.31, 2.35]	2013
Total (95% CI)			**102**			**76**	**100.0%**	**0.19 [-0.12, 0.50]**	

Heterogeneity: Chi² = 6.60, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 1.21 (P = 0.23)

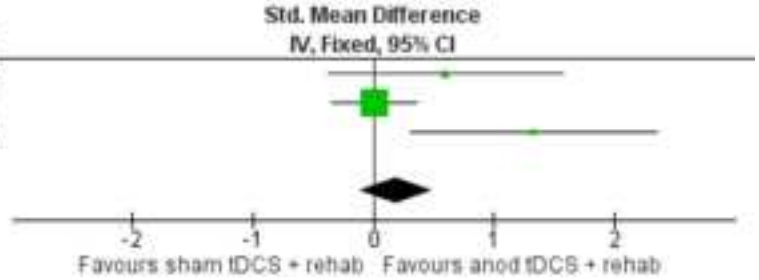

Figure 11

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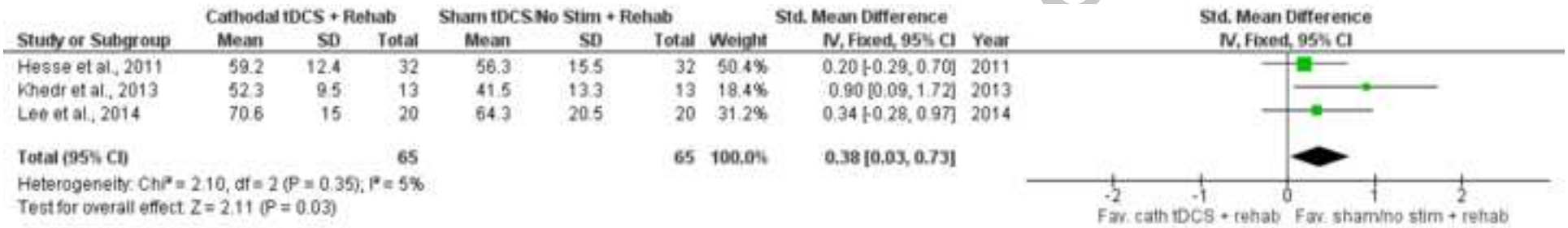

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Table 1 An example of a search strategy on MEDLINE

Database	MEDLINE
Date	26th July 2014
Strategy	#1 and #2 and #3
#1	'transcranial direct current stimulation'
#2	'stroke/ or exp brain stem infarctions/ or exp cerebral infarction/', 'cerebrovascular accident'
#3	'upper extremity/ or exp arm/ or exp axilla/ or exp elbow/ or exp forearm/ upper extremity/ or exp shoulder/', 'upper extremity/ or exp fingers/ or exp metacarpus/ or exp wrist',

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Table 2: Characteristics of studies included in the review

Study	Objective *To investigate*:	Design	Groups	N	Mean Age (years)	Mean Time since stroke	tDCS Stimulation Intensity/ Duration/ Hemisphere	Training Period (weeks)	Outcomes according to the ICF [I=Impairment, A= Activity, P=Participation]	Modified Downs and Black Score (score out of 27)
Kim et al. (2010)	tDCS and OT on UL motor recovery	Single-blinded, RCT	• Anodal and OT • Cathodal and OT • Sham and OT	• 6 • 5 • 7	• 55.3 • 53.6 • 62.9	• 34.0 days • 19.4 days • 22.9 days	(i) 2 mA (ii) 20 mins (iii) tDCS during rehabilitation (iv) Anodal: ipsi-lesional Cathodal: contra-lesional	10 sessions over 2 weeks and 30 mins OT*	FMA*(I) MBI* (A)	21
Lindenberg et al. (2010)	tDCS and PT and OT on UL motor recovery	Double-blinded RCT	• Bi-hemispheric and OT • Sham and OT	• 10 • 10	• 61.7 • 55.8	• 30.5 months • 40.3 months	(i) 1.5 mA (ii) 30 mins (iii) tDCS during rehabilitation (iv) Anodal: ipsi-lesional Cathodal: contra-lesional	5 daily sessions of 60 mins OT and PT	FMA (I) fMRI* (I) WMFT*(A)	17
Bolognini et al. (2011)	tDCS and CIMT on UL motor recovery	Double-blinded RCT	• Bi-hemispheric and CIMT • Sham and CIMT	• 7 • 7	• 42.6 • 50.9	• 44.4 months • 26.0 months	(i) 2mA (ii) 40 mins (iii) tDCS during rehabilitation (iv) Anodal: ipsi-lesional Cathodal: contra-lesional	14 daily sessions of four hours CIMT*	FMA (I) JTT* (I), HG*(I), Resting Motor Threshold and Trans-colossal inhibition (I), MAL*(A), BI (A)	16

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Study	Objective *To investigate*:	Design	Groups	N	Mean Age (years)	Mean Time since stroke	tDCS Stimulation Intensity/ Duration/ Hemisphere	Training Period (weeks)	Outcomes according to the ICF [I=Impairment, A= Activity, P=Participation]	Modified Downs and Black Score (score out of 27)
Hesse et al. (2011)	tDCS and RT on UL motor recovery	Double-blinded RCT	• Anodal and RT • Cathodal and RT • Sham and RT	• 32 • 32 • 32	• 63.9 • 65.4 • 65.6	• 3.4 weeks • 3.8 weeks • 3.8 weeks	(i) 2mA (ii) 20 mins (iii) tDCS during rehabilitation (iv) Anodal: ipsi-lesional, Cathode: contra-lesional	30 sessions over 6 weeks involving 20 mins RT	FMA (I), MRC* (I), MAS*(I), BI*(A), BBT* (I)	22
Nair et al. (2011)	Cathodal/ sham tDCS and OT on UL motor recovery	Double-blinded RCT	• Cathodal and OT • Sham and OT	• 7 • 7	• 61.0 • 56.0	• 33 months • 28 months	(i) 30 mins (ii) 1mA (iii) tDCS during rehabilitation (iv) Cathodal: contra-lesional	5 daily sessions of 1 hour OT	ROM* (I); FMA* (I) fMRI (I)	17
Khedr et al. (2013)	Anodal/ cathodal/ sham tDCS and Rehabilitation UL motor recovery	Double-blinded RCT	• Anodal and Therapy • Cathodal and Therapy • Sham and Therapy	• 14 • 13 • 13	• 58.1 • 60,0 • 57.0	• 13.8 days • 12.3 days • 12.6 days	(i) 25 mins (ii) 2mA (iii) tDCS before rehabilitation (iv) Anodal: ipsi-lesional Cathodal : contra-lesional	6 daily sessions of one hour rehabilitation (passive movement and range of motion exercises)	National Institute of Health Stroke Scale (I), Orgogozo MCA scale (I), MRC (I) Resting and Active Motor Threshold	25

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Study	Objective *To investigate*:	Design	Groups	N	Mean Age (years)	Mean Time since stroke	tDCS Stimulation Intensity/ Duration/ Hemisphere	Training Period (weeks)	Outcomes according to the ICF [I=Impairment, A= Activity, P=Participation]	Modified Downs and Black Score (score out of 27)
Wu et al. (2013)	Cathodal tDCS and rehabilitation on UL motor recovery and spasticity	Double-blinded RCT	• Cathodal and PT • Sham and PT	• 45 • 45	• 45.9 • 49.3	• 4.9 months • 4.9 months	(i) 20 mins (ii) 1.2mA (iii) ? tDCS delivery (iv) ? cathode placed on contra-lesional or ipsi-lesional M1	5 sessions per week for 4 weeks of 30 minutes (twice daily) PT	FMA(I), MAS (I), BI (A)	24
Lee & Chun (2014)	Cathodal tDCS and virtual reality Programme on UL impairments	Double-blinded Pilot RCT	• Cathodal and OT • No tDCS and virtual reality • Cathodal and virtual reality	• 21 • 22 • 21	• 60.3 • 60.6 • 63.1	• 17.4 days • 16.9 days • 17.8 days	(i) 20 minutes (ii) 2 mA (iii) tDCS during OT and virtual reality (iv) Cathode over contra-lesional M1	5 sessions per week for 3 weeks of 30 minutes each session of virtual reality	MAS (I), Manual Muscle Test (I), Manual Function Test (I). FMA (I). BBT (I). Korean MBI (A)	17
Viana et al. (2014)	Anodal tDCS and virtual reality on UL impairments	Double-blinded RCT	• Anodal tDCS and virtual reality • Sham tDCS and Virtual Reality	• 10 • 10	• 56.0 • 55.0	• 31.9 months • 35.0 months	(i) 13 minutes (ii) 2 mA (iii) ?before/during and after rehabilitation (iv) Anode over ipsi-lesional M1	3 sessions per week for 5 weeks of one hour each session	FMA (I), WMFT (I), MAS (I), Dynamometry (I), Stroke Specific Quality of Life Scale (P)	18

***BI=Barthel Index, BBT=Box and Block Test, CIMT= Constraint Induced Movement Therapy, fMRI=functional Magnetic Resonance Imaging, FMA=Fugl-Meyer Assessment, HG=Hand Grip, MAS=Modified Ashworth Scale, MAL=Motor Activity Log, MBI=Modified Barthel Index, MEP= Motor Evoked Potential, MRC=Medical Research Council Strength, ROM=Range of Motion, MT=Motor Threshold, OT= Occupational Therapy, PT= Physiotherapy, WMFT=Wolf Motor Function Test**