# Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke (Review)

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[Intervention Review]

# Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke

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## ABSTRACT

### Background

Stroke is one of the leading causes of disability worldwide. Aphasia among stroke survivors is common. Current speech and language therapy (SLT) strategies have only limited effectiveness in improving aphasia. A possible adjunct to SLT for improving SLT outcomes might be non-invasive brain stimulation by transcranial direct current stimulation (tDCS) to modulate cortical excitability and hence to improve aphasia.

### Objectives

To assess the effects of tDCS for improving aphasia in patients after stroke.

### Search methods

We searched the Cochrane Stroke Group Trials Register (April 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, March 2012), MEDLINE (1948 to March 2012), EMBASE (1980 to March 2012), CINAHL (1982 to March 2012), AMED (1985 to April 2012), Science Citation Index (1899 to April 2012) and seven additional databases. We also searched trials registers and reference lists, handsearched conference proceedings and contacted authors and equipment manufacturers.

### Selection criteria

We included only randomised controlled trials (RCTs) and randomised controlled cross-over trials (from which we only analysed the first period as a parallel group design) comparing tDCS versus control in adults with aphasia due to stroke.

### Data collection and analysis

Two review authors independently assessed trial quality and extracted the data. If necessary, we contacted study authors for additional information. We collected information on dropouts and adverse events from the trials.

### Main results

We included five trials involving 54 participants. None of the included studies used any formal outcome measure for measuring functional communication, that is measuring aphasia in a real-life communicative setting. All five trials measured correct picture naming as a surrogate for aphasia. There was no evidence that tDCS enhanced SLT outcomes. No adverse events were reported and the proportion of dropouts was comparable between groups.

**Authors' conclusions**

Currently there is no evidence of the effectiveness of tDCS (anodal tDCS, cathodal tDCS) versus control (sham tDCS). However, it appears that cathodal tDCS over the non-lesioned hemisphere might be the most promising approach.

## PLAIN LANGUAGE SUMMARY

**Direct electrical current to the brain for language impairment after stroke**

Stroke is one of the leading causes of disability worldwide. Most strokes take place when a blood clot blocks a blood vessel leading to the brain. Without a proper blood supply the brain quickly suffers damage, which can be permanent, and this damage often causes language impairment among stroke survivors. Current speech and language therapy (SLT) strategies have limited effectiveness in improving this language impairment. One possibility for enhancing the effects of SLT might be the addition of non-invasive brain stimulation provided by a technique known as transcranial direct current stimulation (tDCS). This technique manipulates brain functions and may be used to improve language impairment. However, the effectiveness of this intervention for improving SLT outcomes is still unknown. This review of five trials involving 54 participants found no evidence that tDCS enhanced SLT outcomes. There were no adverse events reported. Future research is needed in this area to determine the effectiveness of this intervention.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

**tDCS (A-tDCS or C-tDCS or dual-tDCS) alone or tDCS plus SLT or any other approach for improving aphasia compared with S-tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia or no intervention for treating aphasia after stroke**

**Patient or population: people (18+ years)** with aphasia after stroke
**Settings: rehabilitation**
**Intervention: A-tDCS or C-tDCS or dual-tDCS**
**Comparison: S-tDCS or any other approach for improving aphasia or no intervention**

| Outcomes | Absolute effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|
| **Language impairment: accuracy of naming until end of intervention phase (relative change in standard units)** Rule of thumb for interpretation: 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Patrick 2011) | (SMD 0.31; 95% CI -0.26 to 0.87) | 54 (5) | ⊕⊕⊕○ **Moderate** (downgraded because of serious concerns about limitations in the design) | No adverse events reported |

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

**A-tDCS:** anodal tDCS;**CI:** confidence interval; **C-tDCS:** cathodal tDCS; **SLT:** speech and language training; **SMD**: standardised mean difference; **S-tDCS:** sham tDCS; **tDCS:** transcranial direct current stimulation

## BACKGROUND

### Description of the condition

Every year nearly 15 million people suffer from stroke worldwide (WHO 2011). Nearly six million of them die because of their stroke (Mathers 2011). Moreover, approximately five million people annually experience permanent disability due to stroke (WHO 2011). Stroke is one of the main causes of death worldwide and contributes considerably to disease burden (WHO 2011). It is well known that stroke affects activities of daily living (ADL) and quality of life (Pohl 2011). About one-third of adult stroke patients suffer from aphasia when they are discharged from hospital (Dickey 2010), which means the language system in their brain has been impaired or lost due to brain damage and so they have difficulty comprehending or expressing language (Benson 1996). Other authors have found that almost 20% of all stroke survivors have chronic aphasic symptoms (Pedersen 1995). People with aphasia due to stroke are more likely to stay in hospital longer and to use rehabilitation services more often than stroke patients without

aphasia (Dickey 2010). Aphasia has not only a remarkable impact on quality of life but in every third patient aphasia is associated with depression 12 months after the stroke (Cruice 2003; Hilari 2010; Kauhanen 2000). Together with functional ADL performance, age and gender, aphasia seems to lead to reduced long-term social participation (Dalemans 2010). Therefore, effective treatment approaches are urgently needed to treat aphasia in people after stroke. There are several approaches to treating aphasia, such as intensive speech and language therapy (SLT), which might improve outcomes for patients affected after their stroke (Bhogal 2003). However, a recent review found only modest evidence for more intensive treatment and constraint-induced language therapy for individuals with stroke-induced aphasia (Cherney 2008). Another systematic review found insufficient evidence to draw any conclusions in relation to the effectiveness of one approach over another, but the authors observed "... significant benefits to patients' functional communication [...] receptive and expressive language" (Brady 2012). However, there is limited scope in the approaches for improving aphasia that are currently reviewed. The effectiveness of other approaches that might be used as an adjunct to common speech and language therapies should also be considered.

### Description of the intervention

Transcranial direct current stimulation (tDCS) is seen as an approach to modulate cortical excitability (Nitsche 2001). It is usually administered via saline-soaked surface sponge electrodes attached to the cranium and connected to a direct current stimulator with low intensities (Lang 2005). One might distinguish two different applications. Either the anodal electrode (+) is placed over the presumed brain area of interest and the cathodal electrode (-) is placed above the contralateral orbit (anodal stimulation), or the cathodal electrode is placed over the presumed brain area of interest and the anodal electrode is placed above the contralateral orbita (cathodal stimulation) (Hesse 2011).

tDCS is non-invasive and works by applying a direct current to the brain (Bindman 1964; Nowak 2009; Purpura 1965). It is relatively inexpensive when compared with other approaches such as repetitive transcranial magnetic stimulation or epidural stimulation (Hesse 2011).

Recent research suggests that in people after stroke, tDCS combined with SLT might lead to improvement of aphasia when compared with sham tDCS (Baker 2010; Fiori 2011; Floel 2011; Fridriksson 2011; Kang 2011).

### How the intervention might work

According to some studies tDCS can increase or decrease cortical excitability (Bindman 1964; Purpura 1965). This might be due to a shift of the resting potential of the brain's nerve cells (Flöel 2010; Purpura 1965). Anodal stimulation may lead to depolarisation of the neuronal membranes and therefore result in greater cortical excitability, whereas cathodal stimulation may lead to polarisation and therefore result in lower cortical excitability (Bindman 1964). Therefore, it might be possible that tDCS could generate significant after-effects, which could last up to several hours, if the stimulation lasted for longer than five minutes (Nitsche 2001; Nitsche 2003). Pilot studies suggest that tDCS might improve picture naming in both healthy individuals and aphasic patients, and also improve the detection of a violation of written artificial grammar in healthy individuals (De Vries 2010). However, optimal dosage, intensity and frequency, and its optimal combination with SLT are still unclear.

### Why it is important to do this review

In a recent Cochrane review, the authors concluded that SLT for improving aphasia after stroke showed promising indications of effectiveness (Brady 2012). tDCS given as an adjunct to therapies for aphasia may be a viable approach to further improve the efficiency of SLT for aphasia after stroke. Regardless of the fact that tDCS in combination with SLT might be beneficial and improve aphasia after stroke, it remains unclear which area of the brain (lesioned or non-lesioned, language dominant or non-language dominant), which kind of stimulation (anodal or cathodal) and at which frequency and intensity tDCS should be combined with SLT in practice. The trials undertaken thus far have used small sample sizes. Moreover, there is no systematic review to compile the effects of all available trials. Thus, a systematic review is needed in order to compile the available literature on the effectiveness and the acceptability of this treatment approach.

## OBJECTIVES

To assess the effects of tDCS for improving aphasia in patients after stroke.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included only randomised controlled trials (RCTs) and randomised controlled cross-over trials, from which we only analysed the first period as a parallel group design. We excluded quasi-randomised controlled trials.

### Types of participants

We included patients of either gender, aged 18 years and above and according to the World Health Organization (WHO) definition of stroke. When the WHO definition was not stated, we used a clinical definition of stroke instead. We did not make any restrictions on inclusion regarding type or level of impairment or duration of illness.

### Types of interventions

We compared tDCS alone or tDCS plus SLT or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention.

### Types of outcome measures

Types of outcome measures did not form part of the criteria for the inclusion of studies.

#### Primary outcomes

Our primary outcomes were measures of aphasia. Measuring aphasia in a real-life communicative setting (that is functional communication) is difficult to define and to evaluate (Brady 2012). Wherever possible we identified formal outcome measures. We prioritised the outcome measures in the following order:

1. Amsterdam-Nijmegen Everyday Language Test (ANELT) (Blomert 1994);
2. Communicative Abilities of Daily Living (CADL) (Holland 1980);
3. Boston Diagnostic Aphasia Examination (BDAE) (Goodglass 1972);
4. Scenario Test (Van der Meulen 2010);
5. Communicative Effectiveness Index (CETI) (Lomas 1989);
6. Discourse Analysis (DA) (Ulatowska 1983).

Depending on the data provided by the studies and researchers, all the review authors discussed and reached consensus on which measures to be included in the analysis for the primary outcome.

#### Secondary outcomes

For secondary outcomes we considered surrogate parameters for language impairment such as receptive or expressive language, or both. For this outcome we prioritised outcome measurements as follows:

1. Aachen Aphasia Test (AAT) (Huber 1991);
2. Western Aphasia Battery (WAB) (Kertesz 1982);
3. Porch Index of Communicative Abilities (PICA) (Porch 1967);
4. spoken language comprehension (we prioritised according to functional communication i.e. (1) discourse comprehension, (2) sentence comprehension, and (3) single word comprehension);
5. other measures of language ability, such as reading or writing.

Further secondary outcomes were dropouts and adverse effects with their appropriate outcome measurements as reported in the studies.

If other outcome measurements were provided, all review authors discussed and reached consensus about which of them should be included in the secondary outcomes analysis.

## Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We searched for relevant trials in all languages and arranged translation of trial reports published in languages other than English.

### Electronic searches

We searched the Cochrane Stroke Group Trials Register (April 2013) and the following electronic bibliographic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, March 2012) (Appendix 1);
2. MEDLINE (1948 to March 2012) (Appendix 2);
3. EMBASE (1980 to March 2012) (Appendix 2);
4. CINAHL (1982 to March 2012) (Appendix 3);
5. AMED (1985 to April 2012) (Appendix 2);
6. Science Citation Index (1899 to April 2012) (Appendix 4);
7. Physiotherapy Evidence Database (PEDro) at www.pedro.org.au/ (April 2012) (Appendix 5);
8. Linguistics and Language Behavior Abstracts (LLBA) (1973 to April 2012) (Appendix 6);
9. speechBITE at www.speechbite.com/ (April 2012) (Appendix 7);
10. PsycBITE at www.psycbite.com (April 2013) (Appendix 8);
11. Rehabdata at www.naric.com/?q=REHABDATA (1956 to April 2012);
12. Compendex (1969 to June 2012) (Appendix 9);
13. Inspec (1969 to June 2012) (Appendix 2).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Trials Search Co-ordinator and adapted it for the other databases.

We also searched the following ongoing trials and research registers (January 2013):

1. Stroke Trials Registry (www.strokecenter.org/trials/);
2. Current Controlled Trials (www.controlled-trials.com/);
3. ClinicalTrials.gov (http://clinicaltrials.gov);
4. EU Clinical Trials Register (www.clinicaltrialsregister.eu/);
5. WHO International Clinical Trials Registry Platform ( http://apps.who.int/trialsearch/).

### Searching other resources

In order to identify further published, unpublished and ongoing trials not available in the aforementioned databases, we undertook the following.

1. Handsearched the following relevant conference proceedings that have not already been searched by the Cochrane Stroke Group:
   i) third, fourth, fifth and sixth World Congress of NeuroRehabilitation (2002, 2006, 2008 and 2010); first, second, third, fourth and fifth World Congress of Physical and Rehabilitation Medicine (2001, 2003, 2005, 2007 and 2009);
   ii) Deutsche Gesellschaft für Neurotraumatologie und Klinische Neurorehabilitation (2001 to 2011);
   iii) Deutsche Gesellschaft für Neurologie (2000 to 2011);
   iv) Deutsche Gesellschaft für Neurorehabilitation (1999 to 2011); and
   v) first and second Asian Oceania Conference of Physical and Rehabilitation Medicine (2008 and 2010).
2. Screened reference lists from relevant reviews, articles and textbooks.
3. Contacted authors of identified trials and other researchers in the field.
4. Used Science Citation Index Cited Reference Search for forward tracking of important articles.
5. Contacted the following equipment manufacturers:
   i) Activatek, Salt Lake City, USA (http://www.activatekinc.com);
   ii) Changsha Zhineng Electronics, Changsha City, Hunan, China (http://www.cszhineng.diytrade.com);
   iii) DJO Global, Vista, USA (http://www.djoglobal.com);
   iv) Grindhouse (http://www.grindhousewetware.com);
   v) Magstim, Spring Gardens, United Kingdom (http://www.magstim.com);
   vi) Neuroconn, Ilmenau, Germany (http://www.neuroconn.de);
   vii) Neuroelectrics, Barcelona, Spain (http://www.neuroelectrics.com);
   viii) Newronika, Milano, Italy (http://www.newronika.it);
   ix) Soterix Medical, New York City, USA (http://www.soterixmedical.com);
   x) Trans Cranial Technologies, Hong Kong (http://www.trans-cranial.com).
6. Searched Google Scholar (http://scholar.google.com/).

## Data collection and analysis

### Selection of studies

One review author (BE) read the titles and abstracts of the records identified from the electronic searches and eliminated obviously irrelevant studies. We retrieved the full texts of the remaining studies and two review authors (JK, BE) ranked the studies as relevant, possibly relevant or irrelevant according to our inclusion criteria (types of studies, participants, aims of interventions). Two review authors (JM, MP) then examined whether the possibly relevant publications fitted the population, intervention, comparison, outcome (PICO) strategy of our study question. We resolved disagreements by discussion with all authors. If we needed further information, we contacted trial authors.

We listed as excluded studies those that did not match our inclusion criteria regarding the type of study, participants, or type of interventions, those that were not RCTs, and those that did not clearly state or did not utilise proper methods of generating the randomisation schedule or methods of allocation concealment.

### Data extraction and management

Two review authors (BE, JM) independently extracted trial and outcome data from the selected trials. If one of the review authors was involved in an included trial, another review author extracted the trial and outcome data from that trial. In accordance with the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we used checklists to independently assess:

1. methods of random sequence generation;
2. methods of allocation concealment;
3. blinding of assessors;
4. blinding of patients;
5. use of an intention-to-treat analysis (ITT);
6. adverse effects and dropouts;
7. important imbalances in prognostic factors at baseline;
8. participants (country, number of participants, age, gender, type of stroke, time from stroke onset to study entry, inclusion and exclusion criteria, educational background, socioeconomic status, handedness, cognition, pre-existing neurological impairment(s), neurological history);
9. comparison (details of interventions in treatment and control groups, duration of treatment, details of co-interventions in the groups);
10. outcomes; and
11. their time point of measurement.

Two review authors (MP, JK) checked the extracted data for agreement. If these two review authors could not reach consensus, a third review author arbitrated. If necessary, we contacted the researchers in order to get more information.

### Assessment of risk of bias in included studies

Two authors assessed the risk of bias in the included trials in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We described the agreement between authors during the assessment of risk of bias, and we resolved disagreement by reaching

consensus through discussion. We contacted trialists for clarification and to request missing information.

### Measures of treatment effect

For all outcomes representing continuous data, we entered means and standard deviations. We calculated a pooled estimate of the mean difference (MD) with 95% confidence interval (CI). If studies did not use the same outcome we calculated standardised mean differences (SMD) instead of MD. For all binary outcomes we calculated risk ratios (RR) with 95% CI. For all statistical comparisons we used Review Manager 2011.

### Dealing with missing data

We contacted the relevant principal investigators in order to retrieve missing data.

### Assessment of heterogeneity

We used the $I^2$ statistic in order to assess heterogeneity. We used a random-effects model, regardless of the level of heterogeneity. Thus, in the case of heterogeneity we did not violate the preconditions of a fixed-effect model approach.

### Subgroup analysis and investigation of heterogeneity

We conducted a subgroup analysis for the following factors:

1. duration of illness, acute or subacute phase (the first week after stroke and the second to the fourth week after stroke, respectively) versus post-acute phase (from the second to the sixth month after stroke) versus chronic phase (more than six months after stroke);
2. location of stimulation (affected or unaffected hemisphere, dominant or non-dominant hemisphere);
3. type of stimulation, cathodal or anodal.

### Sensitivity analysis

As there were not enough studies we have not undertaken our planned sensitivity analysis for risk of bias in our included studies in order to test the robustness of our results. We initially planned to consider concealed allocation, blinding of assessors and ITT analysis.

## RESULTS

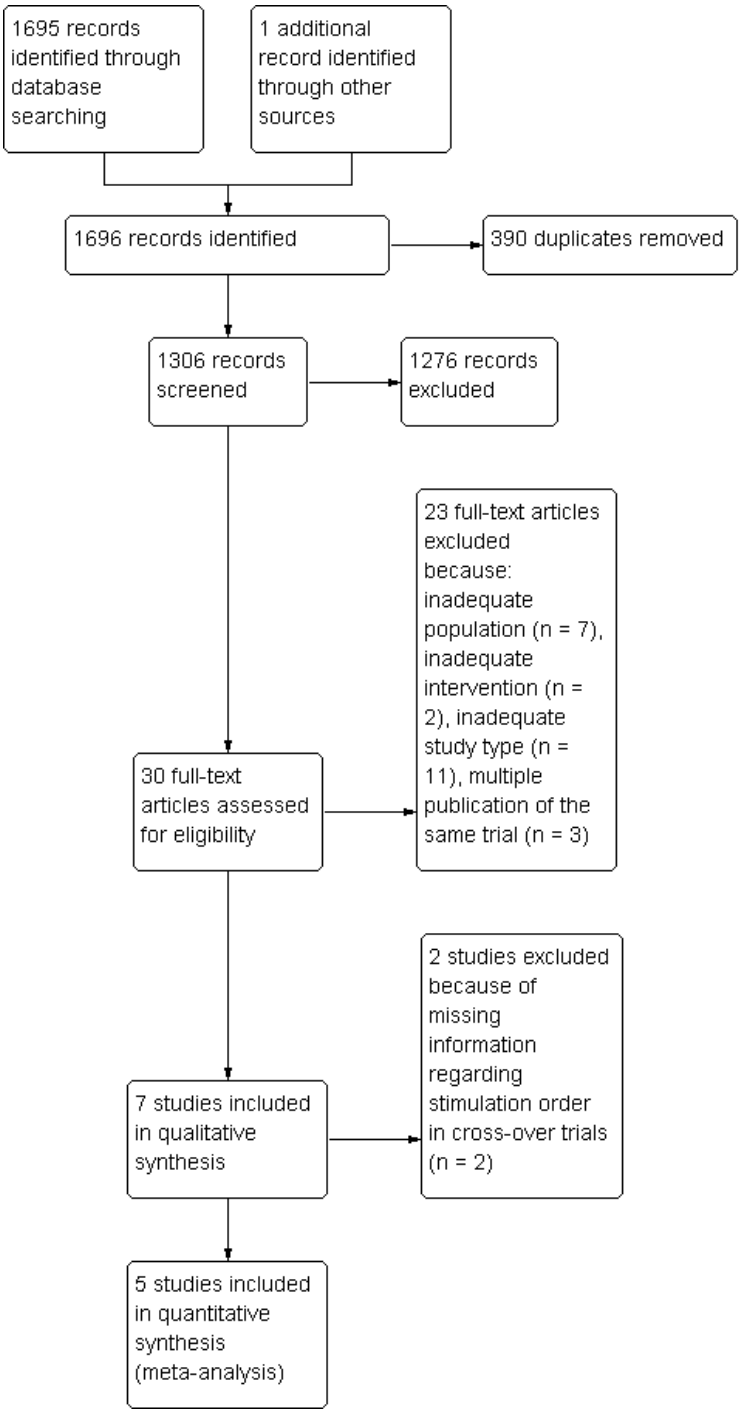
### Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies.

### Results of the search

We identified a total of 1306 unique records from the searches. After screening the titles and abstracts we excluded 1276 records and obtained the full texts of the remaining 30 articles. After further assessment five studies met the review inclusion criteria, we excluded five studies and two studies are awaiting classification as more information was required. We identified eight ongoing trials. The flow of references is shown in Figure 1.

**Figure 1. Study flow diagram**



### Included studies

We included five studies involving a total of 54 participants (Floel 2011; Kang 2011; Marangolo 2011; Monti 2008a; You 2011) (see Characteristics of included studies). All studies investigated the effect of tDCS versus sham tDCS. Four of them, with a total of 33 patients, were randomised cross-over trials (Floel 2011; Kang 2011; Marangolo 2011; Monti 2008a), whereas the remaining one, with 21 analysed patients, was an RCT (You 2011). Three studies had two intervention groups and one control group (Floel 2011; Monti 2008a; You 2011), whereas two studies had one intervention group and one control group (Kang 2011; Marangolo 2011). Two of the included studies were conducted in Italy, two in the Republic of Korea and one in Germany. The experimental groups received anodal tDCS (A-tDCS) or cathodal tDCS (C-tDCS), or both, and the control groups received sham tDCS (S-tDCS). A widely used outcome was 'accuracy in naming' performance. See Table 1 for a comprehensive summary of patient characteristics, and Table 2 for a comprehensive summary of intervention characteristics, dropouts and adverse events.

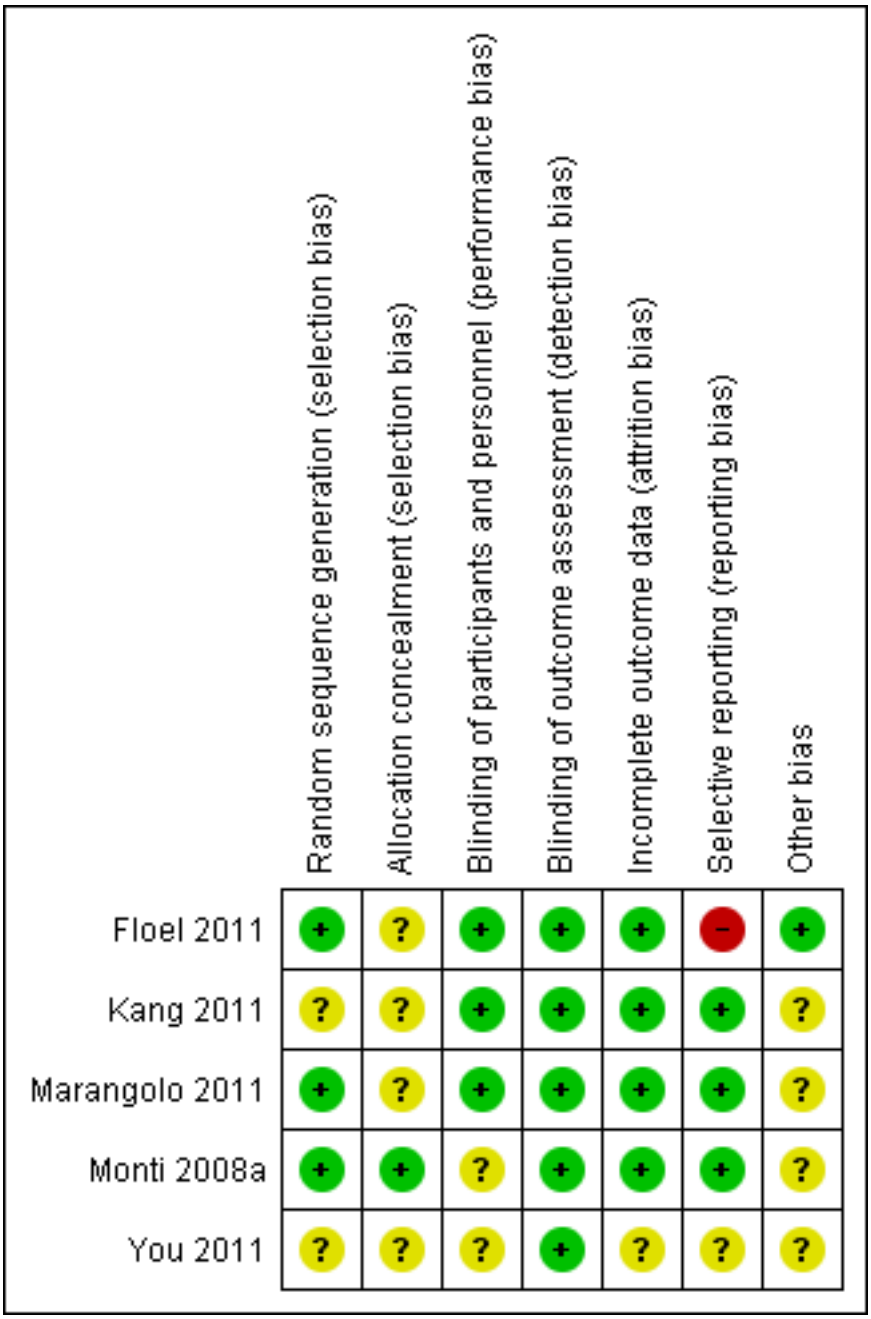
### Excluded studies

We excluded five trials (Cotelli 2011; Fiori 2011; Fridriksson 2011; Holland 2011; Monti 2008b), mainly because they were not RCTs (see Characteristics of excluded studies).

## Risk of bias in included studies

We have provided information about the risk of bias in the Characteristics of included studies table. We contacted all principal investigators of the included trials and of trials awaiting classification to request further information about methodological issues, in order to complete the rating of methodological quality. The contact was via letter and email, including email reminders once a month if we received no response. Some trialists provided all requested information and some did not answer our requests. We used the risk of bias tool, implemented in RevMan 5.1, to assess risk of bias according to the aspects listed in the Methods section. Two authors (BE, JM) independently assessed risk of bias in the included trials and two other authors (JK and MP) checked the extracted data for agreement. Information on risk of bias at the study level is provided in Figure 2. All authors discussed disagreements and, if necessary, sought arbitration by another author (JK). A detailed description of risk of bias can be found in Characteristics of included studies.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**



Three out of five included studies (60%) described a low risk of bias for sequence generation (Floel 2011; Marangolo 2011; Monti 2008a) and one (20%) described a low risk of bias for concealment of allocation by using random number generators (Monti 2008a). Three out of the five included studies (60%) described a low risk of bias for blinding of participants and personnel (Floel 2011; Kang 2011; Marangolo 2011), whereas all studies described a low risk of bias for blinding of outcome assessment. Four out of the five included studies (80%) were at a low risk of bias for incomplete outcome data, whereas one was at high risk (You 2011). Three out of the five included studies (60%) were at low risk of bias for selective outcome reporting (Kang 2011; Marangolo 2011; Monti 2008a) and one study was at high risk (Floel 2011). One study out of the five included studies (20%) (Floel 2011) was at low risk of bias for other biases with the remaining four studies (80%) having an unclear risk of bias.

## Effects of interventions

See: **Summary of findings for the main comparison**

### Primary outcome measure: formal outcome measures of aphasia

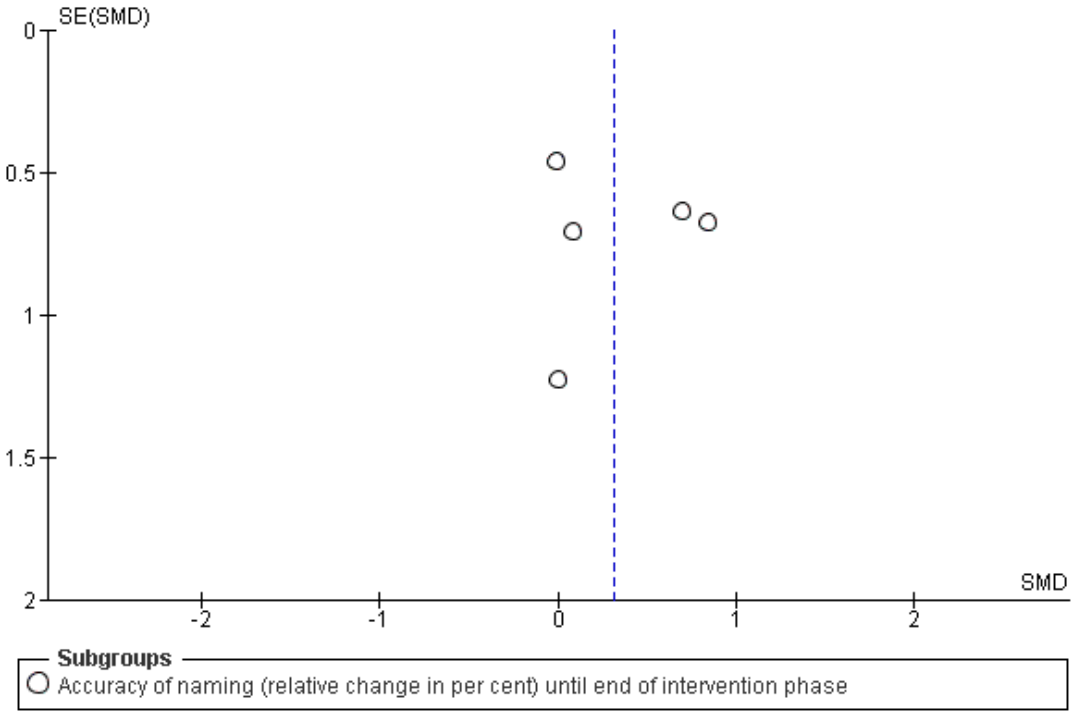
We found no study using any formal outcome measure for measuring functional communication, that is measuring aphasia in a real-life communicative setting.

### Secondary outcome measure: language impairment

#### Comparison 1.1: correct picture naming in per cent until end of intervention phase

Five trials with a total of 54 participants (Floel 2011; Kang 2011; Marangolo 2011; Monti 2008a; You 2011) measured correct picture naming as a surrogate for aphasia (Analysis 1.1). There was no evidence of effect regarding the change in naming accuracy when the data were analysed with collapsed intervention groups as stated in the protocol, that is A-tDCS or C-tDCS, or both, versus S-tDCS (SMD 0.31; 95% CI -0.26 to 0.87; inverse variance method with random-effects model). By graphical inspection of the funnel plot of Analysis 1.1 we could not find any evidence of small study effects (Figure 3).

**Figure 3. Funnel plot of comparison: 1 tDCS alone or tDCS plus speech and language therapy (SLT) or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention, outcome: 1.1 Language impairment: accuracy of naming until end of intervention phase**




#### Comparison 1.2: dropouts

Dropouts occurred in only one study out of the five included studies (20%). There was no evidence of effect regarding the difference in dropouts between intervention and control groups (RR 0.70; 95% CI 0.29 to 1.71; Mantel-Haenszel method with random-effects model). No adverse events have been reported and no deaths occurred (Analysis 1.2).

#### Comparison 2: planned subgroup analysis by duration of illness - acute or subacute versus chronic

In a planned subgroup analysis we analysed the effects of tDCS on the relative change in naming accuracy in the acute or subacute and chronic phases (Analysis 2.1). There was no evidence for different effects of tDCS between subgroups ($Chi^2 = 0.76$, df = 1 (P = 0.38); $I^2 = 0\%$).

#### All studies with people with aphasia in the acute or subacute phase

We included one study with 21 participants (You 2011). There was no evidence of effect regarding the difference in change in naming accuracy between the intervention and control groups (SMD -0.01; 95% CI -0.91 to 0.90).

#### All studies with people with aphasia in the chronic phase

We included four studies with 33 patients (Floel 2011; Kang 2011; Marangolo 2011; Monti 2008a). There was no evidence of effect regarding the difference in change in naming accuracy between the intervention and control groups regarding the time post-stroke (SMD 0.51; 95% CI -0.22 to 1.23; inverse variance method with random-effects model).

#### Comparison 3: planned subgroup analysis by location of stimulation (lesioned or non-lesioned hemisphere) and type of stimulation (A-tDCS, C-tDCS, S-tDCS)

We performed a planned subgroup analysis regarding the electrode positioning and hence location of stimulation (Analysis 3.1).

There was no evidence of effect regarding the difference in change in naming accuracy between intervention and control groups regarding the location and the type of stimulation ($Chi^2$ = 2.88, df = 3 (P = 0.41); $I^2$ = 0%).

#### A-tDCS over lesioned hemisphere

We included three studies with 27 participants (Marangolo 2011; Monti 2008a; You 2011). There was no evidence of effect regarding the difference in change in naming accuracy between the A-tDCS and S-tDCS groups (SMD -0.33; 95% CI -1.10 to 0.44; inverse variance method with random-effects model).

#### C-tDCS over lesioned hemisphere

We included one study with six participants (Monti 2008a). There was no evidence of effect regarding the difference in change in naming accuracy between the C-tDCS and the S-tDCS group (SMD 0.74; 95% CI -1.10 to 2.59; inverse variance method with random-effects model).

#### A-tDCS over non-lesioned hemisphere

We included one study with eight participants (Floel 2011). There was no evidence of effect regarding the difference in change in naming accuracy between the A-tDCS and the S-tDCS group (SMD 0.65; 95% CI -0.81 to 2.11).

#### C-tDCS over non-lesioned hemisphere

We included three studies with 32 participants (Floel 2011; Kang 2011; You 2011). There was no evidence of effect regarding the difference in change in naming accuracy between the C-tDCS and S-tDCS groups (SMD 0.42; 95% CI -0.29 to 1.13).

## DISCUSSION

### Summary of main results

The review focused on evaluating the effectiveness of tDCS (A-tDCS, C-tDCS) versus control (S-tDCS, any other approach for improving aphasia after stroke, or no intervention). We included five trials with a total of 54 patients. We found no study addressing our primary outcome measure, that is investigating the effect of tDCS versus control on functional communication (the ability to communicate in an everyday communicative situation) measured by formal outcome measures of aphasia. We found no evidence of effect regarding our secondary outcome measures and the confidence intervals are very wide. There was no effectiveness regarding surrogate markers of aphasia (that is language function) such as the relative change in naming accuracy (SMD 0.31; 95% CI -0.26 to 0.87).

This is true when analysing the effect with collapsed intervention groups as stated in the protocol, that is A-tDCS or C-tDCS, or both, versus S-tDCS (Analysis 1.1). However, it should be noted that when considering only C-tDCS over the non-lesioned hemisphere versus S-tDCS, as we did in our planned subgroup analysis (Analysis 3.1), not only does the magnitude of effect rise but the probability of error (P value) declines as well.

No adverse events were reported and the rate of dropouts was comparable between groups (Analysis 1.2). A summary of this review's main findings can be found in Summary of findings for the main comparison.

### Overall completeness and applicability of evidence

The results of this review seem to be quite generalisable for settings in industrialised countries. However, there are some factors producing uncertainty. These are:

1. most of the studies included participants with first-ever stroke;
2. the majority of participants suffered from ischaemic stroke; and
3. nearly all of the participants were right-handed.

Hence, the results may be of limited applicability for people with recurrent stroke, haemorrhagic stroke, and left-handed people.

There is currently insufficient high quality evidence to make conclusions about the benefits or harms of tDCS. However, as there is no evidence of side effects and it can be easily administered, further research into tDCS is justified.

Regarding the comparable rate of dropouts between groups, it should not be assumed that the small number of dropouts in the included trials would be transferred into normal practice (Schünemann 2011).

### Quality of the evidence

We found heterogeneity regarding trial design (parallel group or cross-over design, two or three intervention groups), therapy variables (type of stimulation, location of stimulation, dosage of stimulation) and participant characteristics (age, time post-stroke and aphasia severity).

There were too few studies to perform our planned sensitivity analysis examining the effects of methodological quality on the effectiveness of the intervention.

### Potential biases in the review process

The methodological rigour of Cochrane Reviews minimises bias in the process of conducting systematic reviews. However, some

aspects of this review are open to bias, such as only one review author (BE) eliminating obviously irrelevant publications according to their title and abstracts. This encompasses the possibility of unintentionally ruling out relevant publications. Another possibility is that publication bias could have affected our results. Although the funnel plot for our main outcome did not show evidence of publication bias, measured by visual inspection (Figure 3), this does not mean that publication bias is absent (Sterne 2011).

### Agreements and disagreements with other studies or reviews

As far as we know, no other systematic reviews of RCTs or randomised cross-over trials have been conducted so far. In contrast to the conclusions of many published trials, some of them included in this review (Baker 2010; Fiori 2011; Floel 2011; Fridriksson 2011; Holland 2011; Kang 2011; Marangolo 2011; Monti 2008a; You 2011), we did not find any evidence for the effectiveness of tDCS (A-tDCS, C-tDCS) versus control (S-tDCS or any other approach for improving aphasia after stroke, or no intervention).

## AUTHORS' CONCLUSIONS

### Implications for practice

There is no evidence of effect for the effectiveness of tDCS (A-tDCS, C-tDCS) versus control (S-tDCS or any other approach for improving aphasia after stroke, or no intervention) at the present time.

### Implications for research

There is a demand for further randomised controlled trials with a parallel group design and sample-size estimation in this area. Research on cathodal tDCS over the lesioned area appears particularly valuable as there is some indication of positive effects. Data on adverse events should be routinely collected and presented in further publications.

## ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

# CHARACTERISTICS OF STUDIES

## Characteristics of included studies *[ordered by study ID]*

**Floel 2011**

| | |
|---|---|
| Methods | Randomised, double-blind, sham-controlled cross-over trial<br>Deaths: none<br>Adverse events: none; rating of discomfort was negligible in all patients<br>Dropouts: none<br>ITT: yes |
| Participants | Country: Germany<br>12 patients (5 female) with first-time single left hemisphere ischaemic stroke, age in years 39 to 67 (mean 52.3) with chronic aphasia, all patients right-handed and native speakers of German<br>Inclusion criteria: not explicitly stated<br>Exclusion criteria: severe apraxia of speech |
| Interventions | Computerised picture naming task + either A-tDCS 1 mA or C-tDCS 1 mA or S-tDCS (Sham tDCS); each for 20 minutes over the right temporo-parietal cortex for 3 consecutive days |
| Outcomes | Proportional change of correct naming responses immediately after training and 2 weeks after the end of the treatment session |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random sequence generator with the constraint that identical number of patients had to start/have second/have third session with A-tDCS/C-tDCS/sham, respectively (Flöel 2012 [pers comm]) |
| Allocation concealment (selection bias) | Unclear risk | Only the person who applied stimulation knew about allocation (Flöel 2012 [pers comm]). Hence it is unclear if this person was involved in recruiting patients |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | For objective and subjective outcomes, participants were blinded: 'The respective stimulation conditions currents were subsequently turned off slowly out of the field of view of the patients, a procedure that does not elicit perceptions'. Personnel were blinded (Flöel 2012 [pers comm]) |

**Floel 2011** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcome assessor was blinded (Flöel 2012 [pers comm]) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Objective outcome measures: all patients apparently completed the study. No treatment withdrawals, no losses to follow up, no trial group changes and no major adverse events were stated |
| Selective reporting (reporting bias) | High risk | Objective outcome measures: no results have been provided for the Communicative-Activity-Log and Stroke-and-Aphasia-Quality-of-Life-Scale, which were stated as secondary outcome measures in the protocol |
| Other bias | Low risk | The duration of the resting period of 3 weeks used in this study seems to be more appropriate than the often used one week by other studies |

**Kang 2011**

| | |
|---|---|
| Methods | Randomised double-blind sham-controlled cross-over trial with 2 treatment phases of either C-tDCS or S-tDCS and vice versa<br>Deaths: none<br>Adverse events: not stated<br>Dropouts: none<br>ITT: yes |
| Participants | Country: South Korea<br>10 right-handed Korean patients (2 female) with post-stroke aphasia due to single left hemispheric infarction, age 46 to 73 years (mean ± SE, 61.9 ± 2.7) with mean full-time education time 0 to 16 (mean ± SE, 11.6 ± 1.5), mean time from stroke onset to study entry 52.4 ± 21.9 months (range 6.0 to 180.6 months)<br>Inclusion criteria: not clearly stated<br>Exclusion criteria: multiple brain lesions, unstable medical or neurologic conditions, metallic foreign body within the brain, pacemaker or artificial cochlear implant, severe depression, history of seizures and inability to perform protocol-related behavioural tasks |
| Interventions | Every patient underwent both of the following treatment conditions, each over right Broca's homologue area:<br>(1) word retrieval training + 5 days C-tDCS (2 mA for 20 minutes), at least 7 days rest period, word retrieval training + 5 days S-tDCS (20 minutes)<br>(2) word retrieval training + 5 days S-tDCS (20 minutes), at least 7 days rest period, word retrieval training + 5 days C-tDCS (2 mA for 20 minutes) |

**Kang 2011** (*Continued*)

| | | |
|---|---|---|
| Outcomes | Number of correct responses (0 to 60 with 60 reflecting highest correctness) and reaction time of an adapted, standardised, validated Korean version of the BNT at baseline and at the end of each treatment phase | |
| Notes | | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Not stated by the authors |
| Allocation concealment (selection bias) | Unclear risk | Not stated by the authors |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Objective outcome measures: (1) personnel: 'Word-retrieval training was provided by a speech and language pathologist who was unaware of the type of stimulation administered (C-tDCS or sham)', (2) participants: 'This sham procedure does not elicit patient's perceptions and was performed out of the patients' view' |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Objective outcome measures: 'A single rater, unaware of stimulation type, administered the BNT [...].' |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Objective outcome measures: all patients apparently completed the study. No treatment withdrawals, no trial group changes and no major adverse events stated |
| Selective reporting (reporting bias) | Low risk | All outcomes listed in the 'Methods' section reported |
| Other bias | Unclear risk | Potentially bias may have occurred because the resting period between interventions was 7 days (maximum 10 days) |

**Marangolo 2011**

| | |
|---|---|
| Methods | Randomised double-blinded cross-over trial<br>Deaths: none<br>Adverse events: not stated<br>Dropouts: none<br>ITT: yes |
| Participants | Country: Italy<br>3 participants (1 female) with single left hemispheric stroke, non-fluent aphasia and no signs of apraxia of speech<br>Inclusion criteria: native Italian proficiency, pre-morbid right-handedness, persisting symptoms for at least 6 months<br>Exclusion criteria: acute or chronic neurological symptoms requiring medication |
| Interventions | Each patient underwent 2 different treatment conditions (A. A-tDCS, 1 mA; B. S-tDCS, 20 minutes over the left inferior frontal gyrus (Broca's area)) in the following order:<br>1. 5 days language therapeutic repetition task + A, at least 7 days rest period, 5 days language therapeutic repetition task + B<br>2. 5 days language therapeutic repetition task + B, at least 7 days rest period, 5 days language therapeutic repetition task + A |
| Outcomes | Naming accuracy in per cent at baseline, 1 week, 1 month and 2 months after the end of intervention |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated random list (Marangolo 2012 [pers comm]) |
| Allocation concealment (selection bias) | Unclear risk | None (Marangolo 2012 [pers comm]) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Objective outcome measures: participants were blinded to stimulation condition, whereas personnel were not |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Objective outcome measures: outcome assessor was unaware of stimulation type |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Objective outcome measures: all patients apparently completed the study. No treatment withdrawals, no trial group changes and no major adverse events stated |
| Selective reporting (reporting bias) | Low risk | All outcomes listed in the 'Methods' section reported |

**Marangolo 2011** (*Continued*)

| | | |
|---|---|---|
| Other bias | Unclear risk | Potentially bias may have occurred because the resting period between interventions was 6 days |

**Monti 2008a**

| | |
|---|---|
| Methods | Randomised sham-controlled cross-over trial<br>Deaths: none<br>Adverse events: not stated<br>Dropouts: none<br>ITT: yes |
| Participants | Country: Italy<br>8 right-handed chronic non-fluent aphasic patients (4 females, age in years (mean ± SD, 60.38 ± 11.99), education in years (mean ± SD, 10.62 ± 4.86), mean time from stroke onset to study entry 3.93 ± 1.89 years<br>Inclusion criteria: not stated<br>Exclusion criteria: severely impaired auditory verbal comprehension (Token Test < 8), severe apraxia of speech, seizures in the last 12 months, psychiatric disease and dementia |
| Interventions | Each patient underwent 2 different treatment conditions (A: A-tDCS 2 mA; B: C-tDCS 2 mA; C: S-tDCS. Each for 10 minutes over the left Broca's region, order of intervention randomised) in the following order:<br>1. picture naming task + A or C, at least 7 days rest period, Picture naming task + C or A<br>2. picture naming task + B or C, at least 7 days rest period, Picture naming task + C or B |
| Outcomes | Naming accuracy in per cent, reaction time for naming pictures |
| Notes | |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Microsoft Excel random number generator (Priori 2012 [pers comm]) |
| Allocation concealment (selection bias) | Low risk | A third person, uninvolved in the rest of the experiment, assigned participants to their stimulation groups (Priori 2012 [pers comm]) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Objective outcome measures: participants were blinded, whereas personnel were not |

**Monti 2008a** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcome assessor was unaware of stimulation type |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Objective outcomes: all patients completed the study. No treatment withdrawals, no trial group changes and no major adverse events stated |
| Selective reporting (reporting bias) | Low risk | All outcomes listed in the 'Methods' section reported |
| Other bias | Unclear risk | Potentially bias may have occurred because the resting period between interventions was 'at least 1 week' |

**You 2011**

| | |
|---|---|
| Methods | Randomised double-blind sham-controlled trial<br>Dropouts: 12<br>ITT: no<br>Deaths: none<br>Adverse effects: none, but 3 patients refused therapy due to uncomfortable sensations |
| Participants | Country: South Korea<br>33 patients with subacute left middle cerebral artery ischaemic infarction, confirmed by MRI, age in years (mean ± SD) 66.57 ± 10.76, education in years (mean ± SD) 11.43 ± 3.31, time post-stroke (unit unknown, most likely in days; mean ± SD) 25.71 ± 7.07<br>Exclusion criteria: haemorrhagic stroke, history of previous stroke, seizures, multiple stroke lesions, metal implants in the brain, no adherence to speech therapy, medication with $Na^+$, $Ca^{2+}$ or NMDA receptor antagonists<br>All patients were diagnosed with global aphasia and right-handed |
| Interventions | 3 arms, patients received over 10 consecutive sessions, 5 times a week for 2 weeks, 1 of the following interventions (30 minutes each):<br>1. conventional speech and language therapy + A-tDCS (2 mA) over the left superior temporal gyrus<br>2. conventional speech and language therapy + C-tDCS (2 mA) over the right superior temporal gyrus<br>3. conventional speech and language therapy + S-tDCS over the left superior temporal gyrus |
| Outcomes | Aphasia quotient of the Korean Western Aphasia Battery, ranging from 0 to 100 with 100 being the best achievable result, measured at baseline and after treatment sessions |
| Notes | |

***Risk of bias***

**You 2011** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not described |
| Allocation concealment (selection bias) | Unclear risk | Not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Objective outcome measures: blinding of both patients and personnel not stated by the authors |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: 'One independent speech and language pathologist, who was blinded to the type of intervention performed, was used for these studies to measure patient outcomes.' |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Objective outcome measures: 12 dropouts (36%) were stated and not included in analysis. However, the proportion of dropouts is relatively balanced between groups |
| Selective reporting (reporting bias) | Unclear risk | Objective outcomes: all outcomes listed in the 'Methods' section reported |
| Other bias | Unclear risk | Reasons for dropouts not stated groupwise |

A-tDCS: anodal tDCS
BNT: Boston Naming Test
C-tDCS: cathodal tDCS
ITT: intention-to-treat analysis
NMDA: *N*-methyl-D-aspartate
MRI: magnetic resonance imaging
SD: standard deviation
S-tDCS: sham tDCS
SE: standard error
tDCS: transcranial direct current stimulation

## Characteristics of excluded studies *[ordered by study ID]*

| Study | Reason for exclusion |
|---|---|
| Cotelli 2011 | Irrelevant intervention (rTMS) |
| Fiori 2011 | Not a RCT (pseudo-randomisation of intervention) |
| Fridriksson 2011 | Not a RCT |
| Holland 2011 | Not a RCT (pseudo-randomisation of intervention) |
| Monti 2008b | In order to test the specificity of findings of Monti 2008a, this trial stimulated a biological implausible area (cerebellum) to improve aphasia and therefore has been excluded |

RCT: randomised controlled trial
rTMS: repetitive transcranial magnetic stimulation

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Baker 2010**

| | |
|---|---|
| Methods | Randomised sham-controlled double-blind cross-over trial<br>Deaths: none<br>Adverse effects: none<br>Dropouts: none<br>ITT: yes |
| Participants | Country: USA<br>10 patients (5 female) with chronic, stroke-induced aphasia, age 45 to 81 years (mean ± SD, 65.50 ± 11.44)<br>Inclusion criteria: 1-time stroke in the left hemisphere, 6 months after stroke onset, 85 years of age, premorbidly right-handed, native English speaker, and participant in a previous study that included fMRI examination<br>Exclusion criteria: seizures during the previous 36 months, sensitive scalp, previous brain surgery, and medications that raise the seizure threshold |
| Interventions | 2 arms (A: A-tDCS 1 mA; B: S-tDCS; 20 minutes each over the brain area with the highest activation during correct naming as measured by fMRI)<br>1. computerised anomia training + 5 days A, 7 days rest period, computerised anomia training + 5 days B<br>2. computerised anomia training + 5 days B, 7 days rest period, computerised anomia training + 5 days A |
| Outcomes | The change in correct picture naming in per cent at the end of treatment and at 7 days follow-up |
| Notes | |

**Vines 2011**

| | |
|---|---|
| Methods | Randomised sham-controlled double-blind cross-over trial<br>Dropouts: none<br>ITT: yes<br>Deaths: none<br>Adverse effects: none |
| Participants | Country: USA<br>6 patients (no females) with non-fluent aphasia with at least 1 year after their first-ever and only ischaemic stroke affecting their left frontal lobe, age in years 31 to 81 (mean ± SD 56.20 ± 16.32), times post-stroke in years (mean ± SD 4.56 ± 3.14), 5 out of 6 (83%) were native-speakers of English, 5 out of 6 (83%) were right-handed, the remaining one was mixed-handed, all patients have been classified as having a moderate to severe non-fluent Broca's aphasia with relatively unimpaired comprehension according to the BDAE<br>Inclusion criteria: participation in a preceding proof-of-concept experiment, which they had completed at least 6 months before<br>Exclusion criteria: not clearly stated |
| Interventions | 2 arms (A: A-tDCS 1.2 mA; B: S-tDCS; 20 minutes over the right and hence unaffected posterior inferior frontal gyrus (Broca's homologue area)):<br>1. melodic intonation therapy + 3 days A, at least 7 days rest period, melodic intonation therapy + 3 days B<br>2. melodic intonation therapy + 3 days B, at least 7 days rest period, melodic intonation therapy + 3 days A |
| Outcomes | Proportional change in the sum duration of fluency measures (duration of utterance) before and at the end of the third stimulation session |
| Notes | |

A-tDCS: anodal tDCS
BDAE: Boston Diagnostic Aphasia Examination
C-tDCS: cathodal tDCS
fMRI: functional Magnetic Resonance Imaging
ITT: intention-to-treat analysis
SD: standard deviation
S-tDCS: sham tDCS
tDCS: transcranial direct current stimulation

## Characteristics of ongoing studies *[ordered by study ID]*

**JPRN-UMIN000008467**

| | |
|---|---|
| Trial name or title | Transcranial direct current stimulation combined with speech therapy among patients with aphasia |
| Methods | Randomised cross-over trial |
| Participants | Estimated enrolment: 60 people with aphasia due to stroke<br>Inclusion criteria: time from stroke onset over 6 months, FIM comprehension item score > 5<br>Exclusion criteria: patients with implanted pacemaker, shunt or other implanted metal, medical history of seizure or the other medical complication which inhibit to recruit this experiment |

**JPRN-UMIN000008467** (*Continued*)

| | |
|---|---|
| Interventions | tDCS + speech therapy<br>Sham stimulation + speech therapy |
| Outcomes | Primary outcome measures: reaction time for naming task, Boston Naming Test<br>Secondary outcome measures: cerebral blood flow, Standard Language Test of Aphasia, communication section of FIM |
| Starting date | Not stated |
| Contact information | Toshiyuki Fujiwara, Keio University School of Medicine Rehabilitation Medicine, 35 Shinanomach, Shinjuku, Tokyo, Japan<br>Email: tofuji@xc5.so-net.ne.jp |
| Notes | |

**NCT00854893**

| | |
|---|---|
| Trial name or title | Enhance of language learning with neurostimulation (transcranial direct current stimulation) |
| Methods | Randomised double blind sham-controlled cross-over trial |
| Participants | Estimated enrolment: 70 people with aphasia due to ischaemic stroke with intact motor cortex at least 9 months since stroke, aged between 18 and 86 years<br>Exclusion criteria: severe head trauma in the past, seizures, cardial pacemaker, metal implants in the head/neck region, severe comorbidity, especially neurologic and psychiatric diseases, intake of illegal drugs, MMSE < 27, neuroactive substances, e.g. antidepressants, pregnancy |
| Interventions | A-tDCS or C-tDCS for 20 minutes or S-tDCS for 30 seconds during language learning<br>Intensity: 1 mA with the electrodes positioned over the primary motor cortex of language-dominant hemisphere and the reference electrode over contralateral supraorbital area |
| Outcomes | Primary outcome measure: relative change to baseline in learning new words in per cent<br>Time point of measurement: after the end of intervention period and 1 week after study end |
| Starting date | October 2009 |
| Contact information | Gianpiero Liuzzi, MD: +49 40 7410 ext 59278, g.liuzzi@uke.de<br>Friedhelm Hummel, MD: +49 7410 ext 53772, f.hummel@uke.de |
| Notes | |

**NCT01221779**

| | |
|---|---|
| Trial name or title | Chronic aphasia - improved by intensive training and electrical brain stimulation (CATS) |
| Methods | Randomised controlled double-blind trial |
| Participants | Estimated enrolment: 40 right-handed people with aphasia due to single first time left-hemisphere stroke, age between 18 and 70 years<br>Inclusion criteria: fluent or non-fluent chronic aphasia (more than 6 months post-stroke), anomia (PR > 10 and PR < 60 Aachen Aphasia Naming Subtest), native German speaker<br>Exclusion criteria: recurrent stroke, alcoholism, severe psychiatric conditions, other neurological conditions, other non-treated medical problems, severe microangiopathy, pregnancy |
| Interventions | 2 weeks of daily computerised anomia training (3 hours per day) + either A-tDCS or S-tDCS |
| Outcomes | Primary outcome measures: change in the Boston Naming Test's score 2 weeks after end of intervention period in relation to baseline<br>Secondary outcome measures:<br>• change in the Boston Naming Test's score from 2 weeks after the end of intervention period 3 months after end of intervention period<br>• change in naming performance (assessed during picture naming task) during functional magnetic resonance scanning from baseline to 2 weeks after the end of intervention period<br>• change in naming performance (assessed during picture naming task) during functional magnetic resonance scanning from 2 weeks after the end of intervention period 3 months after end of intervention period |
| Starting date | January 2011 |
| Contact information | Marcus Meinzer, PhD<br>Agnes Flöel, MD<br>Charite, University Medicine, Department of Neurology, Berlin, Germany |
| Notes | |

**NCT01486654**

| | |
|---|---|
| Trial name or title | Transcranial direct current stimulation and aphasia language therapy |
| Methods | Randomised controlled single-blind trial |
| Participants | Estimated enrolment: 12 right-handed people with single unilateral left-hemispheric infarction confirmed by CT or MRI at least 6 months post-stroke, with the age above 21 years, English native speaker<br>Inclusion criteria: non-fluent aphasia, minimum education: eighth grade, sufficient visual and auditory acuity<br>Exclusion criteria: other neurologic conditions such as Parkinson's Disease, Alzheimer's dementia, TBI, significant psychiatric history, active substance abuse, seizures, lesioned premotor cortex |
| Interventions | 3 arms: either A-tDCS, C-tDCS (1 mA, 5 days a week, for 6 weeks) or S-tDCS during the first 13 minutes of 90 minutes of speech language treatment |

**NCT01486654** (*Continued*)

| | |
|---|---|
| Outcomes | Primary outcome measures: change from baseline in AQ on the WAB in relation to 6 weeks after the end of intervention period<br>Secondary outcome measures:<br>• change from baseline in functional communication skills in relation to 6 weeks after the end of intervention period (assessed by language sample analyses)<br>• change from baseline in participation in everyday activities in relation to 6 weeks after the end of intervention period (CETI, BOSS, CCRSA)<br>• change from baseline in reading and writing scores of the WAB in relation to 6 weeks after the end of intervention period<br>• change in WAB-AQ from 6 weeks after the end of intervention period in relation to 12 weeks after the end of intervention period<br>• change in WAB-reading and writing scores from 6 weeks after the end of intervention period in relation to 12 weeks after the end of intervention period<br>• change from baseline in functional communication from 6 weeks after the end of intervention period in relation to 12 weeks after the end of intervention period (assessed by language sample analyses)<br>• change from baseline in participation in everyday activities from 6 weeks after the end of intervention period in relation to 12 weeks after the end of intervention period (CETI, BOSS, CCRSA) |
| Starting date | March 2010 |
| Contact information | Center for Aphasia Research and Treatment, Rehabilitation Institute of Chicago, Chicago, Illinois, United States<br>Contact: Leora R Cherney PhD (Principal investigator): Tel: +1 312-238-6163<br>Email: lcherney@ric.org |
| Notes | |

**NCT01651884**

| | |
|---|---|
| Trial name or title | High definition transcranial direct current stimulation (HD-tDCS) for stroke rehabilitation |
| Methods | Randomised single-blind cross-over trial |
| Participants | Estimated enrolment not stated. Right-handed people at the age of 25 to 80 years with aphasia due to first-time ever left-hemispheric ischaemic stroke, time post-stroke: at least 6 months, native speaker of English<br>Exclusion criteria: clinically reported history of dementia, alcohol abuse, psychiatric disorder, TBI, or extensive visual acuity or visual-spatial problems, factors contraindicative of tDCS administration (sensitive scalp, previous brain surgery), seizures during the previous year |
| Interventions | Cross-over assignment to either:<br>1. computerised language training + HD-tDCS (dosage not stated) and then computerised language training + tDCS (dosage not stated) or<br>2. computerised language training + tDCS (dosage not stated) and then computerised language training + HD-tDCS (dosage not stated)<br>Duration of resting periods not stated |
| Outcomes | Not described |

**NCT01651884** (*Continued*)

| | |
|---|---|
| Starting date | March 2012 |
| Contact information | Julius Fridriksson, PhD, University of South Carolina, Soterix Medical |
| Notes | |

**NCT01686373**

| | |
|---|---|
| Trial name or title | Transcranial direct current stimulation and aphasia treatment outcomes |
| Methods | Randomised controlled double-blind trial |
| Participants | Estimated enrolment: 75 right-handed people between 25 and 80 years of age with aphasia due to left-hemispheric first-time ever stroke more than 6 months post-stroke, who are native English speakers<br>Inclusion criteria: willing and able to give informed consent, willing and able to comply with study requirements, at least 65% accuracy on naming task during screening<br>Exclusion criteria: previous brain surgery, seizures during last 12 months, sensitive scalp (self-report), being able to name more than an average of 140 out of 175 items during the pre-treatment PNT, inability to overtly name at least an average of 5 out of 80 items during the pre-treatment fMRI sessions |
| Interventions | 'Real' tDCS (polarity not stated) versus S-tDCS (device: Activa Dose II) |
| Outcomes | Primary outcome measures: number of correctly named pictures on the PNT at follow-up (time point not stated) in relation to the end of intervention phase |
| Starting date | April 2012 |
| Contact information | Astrid Fridriksson MA, Tel: +1 803-777-2693; email: fridrika@mailbox.sc.edu<br>Ivia Smith MS, Tel: +1 803-777-1087; email: ivia.smith@sc.edu |
| Notes | |

**NCT01701713**

| | |
|---|---|
| Trial name or title | Safety study of transcranial direct current stimulation in aphasia therapy in acute and post-acute stroke |
| Methods | Randomised controlled double-blind trial |
| Participants | Estimated enrolment: 100 right-handed people with first-time ever infarction in the A. media area and resulting language impairment, aged between 18 and 85 years and with an NIHSS < 20<br>Exclusion criteria: previous epilepsy or epileptogenic events or epilepsy typical elements in EEG, hypersensitive skin on the head, metal implants in the head, pacemakers or other electronic implants, previous head/brain surgery, medication reducing seizure threshold, psychiatric history |
| Interventions | Behavioural naming therapy + tDCS (polarity not stated) versus behavioural naming therapy + S-tDCS |

**NCT01701713** (*Continued*)

| | |
|---|---|
| Outcomes | Primary outcome measures: skin irritation (type of assessment not stated)<br>Secondary outcome measures: improved language, measured by improved picture naming |
| Starting date | June 2009 |
| Contact information | Contact: Gerhard J Jungehuelsing MD; email: jan.jungehuelsing@charite.de, or Isabell Wartenburger, Prof MD; email: isabell.wartenburger@uni-potsdam.de |
| Notes | |

**NCT01709383**

| | |
|---|---|
| Trial name or title | Can enhancing left lateralization using transcranial direct current stimulation improve recovery from post-stroke aphasia? |
| Methods | Randomised controlled double blind trial |
| Participants | Estimated enrolment: 112 people above the age of 18 with aphasia due to left hemisphere stroke (diagnosed by a physician or speech-language pathologist)<br>Exclusion criteria: skull defect at or near the site of tDCS delivery, history of a significant stroke or TBI additional to the event that caused the aphasia, history of other brain conditions that could impact interpretation of results (such as multiple sclerosis, brain tumour, encephalitis, premorbid dementia), presence of metallic devices in the head, psychiatric history, pregnancy, severe comprehension deficits<br>Additional exclusion criteria for the optional MRI portion of the study: presence of metal in the body (except titanium), claustrophobia |
| Interventions | 2 arms; either<br>1. 60 minutes of speech and language treatment + dual-tDCS with the anodal electrode placed over the left hemisphere and the cathodal electrode placed over the right hemisphere at the beginning of each speech and language training session for 5 days a week for 1 week, or<br>2. 60 minutes of speech and language treatment + S-tDCS at the beginning of each speech and language training session for 5 days a week for 1 week |
| Outcomes | Primary outcome measures: WAB-R: Naming and Word Finding score (change from baseline to 1 day after intervention period)<br>Secondary outcome measures:<br>• WAB-R: spontaneous speech, repetition, auditory verbal comprehension and overall AQ immediately; 2 weeks after the end of intervention phase; 12 weeks after the end of intervention phase<br>• PNT immediately; 2 weeks after the end of intervention phase; 12 weeks after the end of intervention phase<br>• BDAE: verbal agility subtest immediately; 2 weeks after the end of intervention phase; 12 weeks after the end of intervention phase<br>• Subjective assessments including: CETI, Stroke and Aphasia Quality of Life Scale, and Stroke Aphasic Depression Questionnaire, immediately; 2 after weeks after the end of intervention phase; 12 weeks after the end of intervention phase<br>• CLQT immediately; 2 weeks after the end of intervention phase and 12 weeks after the end of intervention phase<br>• Reading assessments immediately; 2 weeks after the end of intervention phase and 12 weeks after the |

**NCT01709383** (*Continued*)

| | |
|---|---|
| | end of intervention phase<br>• Motricity Index immediately; 2 weeks after the end of intervention phase and 12 weeks after the end of intervention phase |
| Starting date | September 2012 |
| Contact information | Contact: Alexa Desko; Tel: +1 202 687 5205; email: ad655@georgetown.edu |
| Notes | |

A-tDCS: anodal tDCS
AQ: Aphasia quotient
BDAE: Boston Diagnostic Aphasia Examination
BOSS: Burden of Stroke Scale
C-tDCS: cathodal tDCS
CCRSA: Communication Confidence Rating Scale for Aphasia
CETI: Communicative Effectiveness Index
CLQT: Cognitive-Linguistic Quick Test
CT: computerised tomography
EEG: electroencephalography
FIM: Functional Independence Measure
fMRI: functional magnetic resonance imaging
HD-tDCS: high definition tDCS
MMSE: Mini Mental State Examination
MRI: magnetic resonance imaging
NIHSS: National Institute of Health Stroke Scale
PNT: Philadelphia Naming Test
S-tDCS: sham tDCS
TBI: Traumatic Brain Injury
tDCS: transcranial direct current stimulation
WAB: Western Aphasia Battery
WAB-R: Western Aphasia Battery - Revised

## DATA AND ANALYSES

**Comparison 1. tDCS alone or tDCS plus speech and language therapy (SLT) or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Language impairment: accuracy of naming until end of intervention phase | 5 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.1 Accuracy of naming (relative change in per cent) until end of intervention phase | 5 | 54 | Std. Mean Difference (IV, Random, 95% CI) | 0.31 [-0.26, 0.87] |
| 2 tDCS alone or tDCS plus SLT or any other approach for improving aphasia versus sham-tDCS alone or sham-tDCS plus SLT or any other approach for improving aphasia or no intervention: drop-outs | 5 | 66 | Risk Ratio (M-H, Random, 95% CI) | 0.7 [0.29, 1.71] |

**Comparison 2. Subgroup analysis by duration of illness: acute or subacute versus chronic**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Naming accuracy in per cent in all studies until the end of intervention phase | 5 | 54 | Std. Mean Difference (IV, Random, 95% CI) | 0.31 [-0.26, 0.87] |
| 1.1 All studies with people with aphasia in the acute/subacute phase | 1 | 21 | Std. Mean Difference (IV, Random, 95% CI) | -0.01 [-0.91, 0.90] |
| 1.2 All studies with people with aphasia in the chronic phase | 4 | 33 | Std. Mean Difference (IV, Random, 95% CI) | 0.51 [-0.22, 1.23] |

**Comparison 3. Planned subgroup analysis by location of stimulation (lesioned or non-lesioned hemisphere) and type of stimulation (A-tDCS, C-tDCS, S-tDCS)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Relative change in accuracy of naming in per cent until the end of intervention phase | 5 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 1.1 A-tDCS over lesioned hemisphere | 3 | 27 | Std. Mean Difference (IV, Random, 95% CI) | -0.33 [-1.10, 0.44] |
| 1.2 C-tDCS over lesioned hemisphere | 1 | 6 | Std. Mean Difference (IV, Random, 95% CI) | 0.74 [-1.10, 2.59] |
| 1.3 A-tDCS over non-lesioned hemisphere | 1 | 8 | Std. Mean Difference (IV, Random, 95% CI) | 0.65 [-0.81, 2.11] |
| 1.4 C-tDCS over non-lesioned hemisphere | 3 | 32 | Std. Mean Difference (IV, Random, 95% CI) | 0.42 [-0.29, 1.13] |

**Analysis 1.1. Comparison 1 tDCS alone or tDCS plus speech and language therapy (SLT) or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention, Outcome 1 Language impairment: accuracy of naming until end of intervention phase.**

Review: Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke

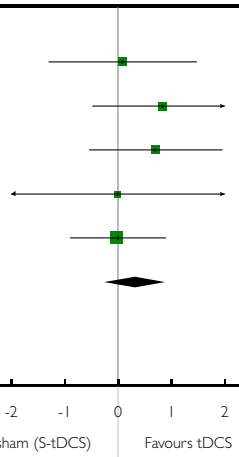
Comparison: 1 tDCS alone or tDCS plus speech and language therapy (SLT) or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention

Outcome: 1 Language impairment: accuracy of naming until end of intervention phase

| Study or subgroup | Experimental N | Experimental Mean(SD) | Control N | Control Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Accuracy of naming (relative change in per cent) until end of intervention phase | | | | | | | |
| Monti 2008a | 4 | 2.94 (5.88) | 4 | 2.27 (8.33) | | 16.7 % | 0.08 [ -1.31, 1.47 ] |
| Kang 2011 | 5 | 112.58 (162) | 5 | 5.56 (4.43) | | 18.2 % | 0.84 [ -0.48, 2.17 ] |
| Floel 2011 | 90.125 (10.133925) | | 8 | 4 | 69.75 (46.67) | | 20.6 % | 0.70 [ -0.55, 1.95 ] |
| Marangolo 2011 | 2 | 42.86 (41.07) | 1 | 0.01 (0.01) | | 5.6 % | 0.0 [ -2.40, 2.40 ] |
| You 2011 | 14 | 535.19 (1211.9) | 7 | 542.86 (1029.33) | | 39.0 % | -0.01 [ -0.91, 0.90 ] |
| **Subtotal (95% CI)** | **33** | | **21** | | | **100.0 %** | **0.31 [ -0.26, 0.87 ]** |

Heterogeneity: Tau² = 0.0; Chi² = 1.63, df = 4 (P = 0.80); I² =0.0%

Test for overall effect: Z = 1.07 (P = 0.29)



**Analysis 1.2. Comparison 1 tDCS alone or tDCS plus speech and language therapy (SLT) or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention, Outcome 2 tDCS alone or tDCS plus SLT or any other approach for improving aphasia versus sham-tDCS alone or sham-tDCS plus SLT or any other approach for improving aphasia or no intervention: drop-outs.**

Review: Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke

Comparison: 1 tDCS alone or tDCS plus speech and language therapy (SLT) or any other approach for improving aphasia versus sham tDCS alone or sham tDCS plus SLT or any other approach for improving aphasia, or no intervention

Outcome: 2 tDCS alone or tDCS plus SLT or any other approach for improving aphasia versus sham-tDCS alone or sham-tDCS plus SLT or any other approach for improving aphasia or no intervention: drop-outs

| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H,Random,95% CI | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|
| Floel 2011 | 0/8 | 0/4 | | 0.0 [ 0.0, 0.0 ] |
| Kang 2011 | 0/5 | 0/5 | | 0.0 [ 0.0, 0.0 ] |
| Marangolo 2011 | 0/2 | 0/1 | | 0.0 [ 0.0, 0.0 ] |
| Monti 2008a | 0/4 | 0/4 | | 0.0 [ 0.0, 0.0 ] |
| You 2011 | 7/22 | 5/11 | | 0.70 [ 0.29, 1.71 ] |
| **Total (95% CI)** | **41** | **25** | | **0.70 [ 0.29, 1.71 ]** |

Total events: 7 (Experimental), 5 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 0 ($P<0.00001$); $I^2 = 100\%$

Test for overall effect: Z = 0.78 (P = 0.43)

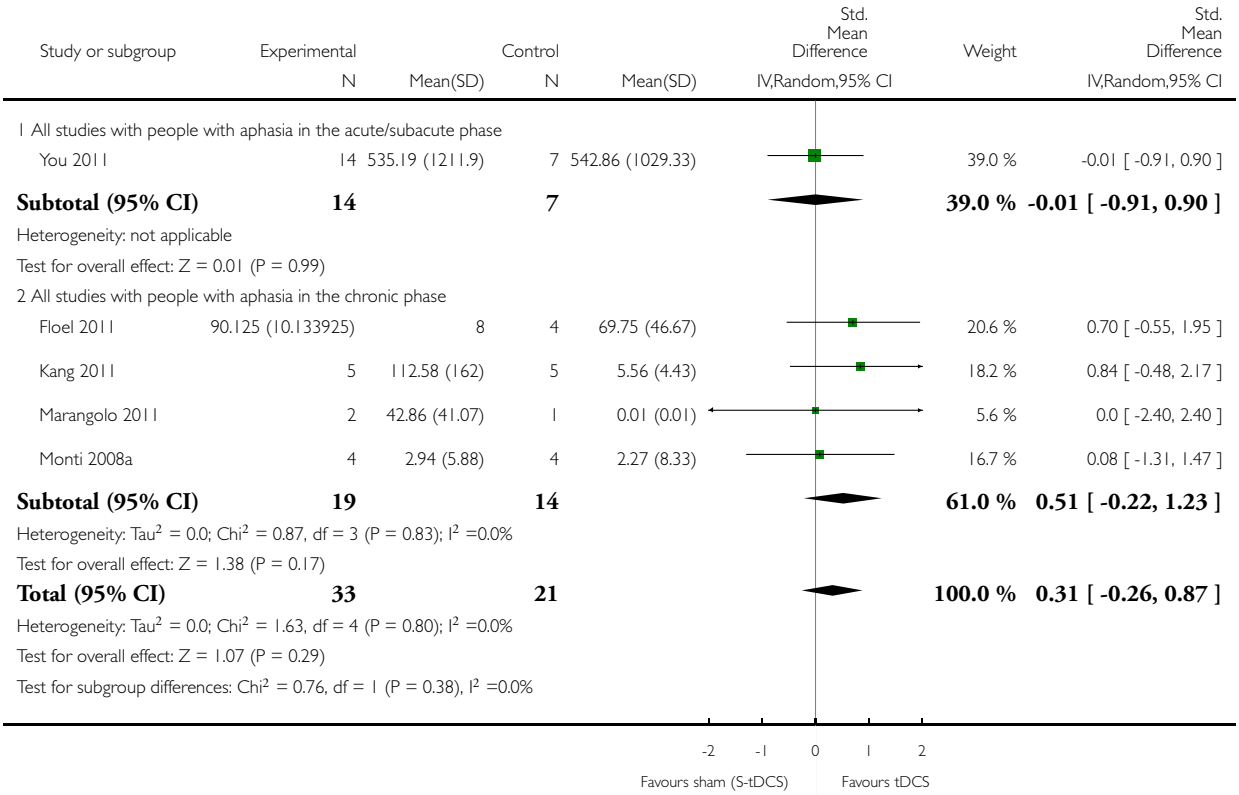
Test for subgroup differences: Not applicable

### Analysis 2.1. Comparison 2 Subgroup analysis by duration of illness: acute or subacute versus chronic, Outcome 1 Naming accuracy in per cent in all studies until the end of intervention phase.

Review: Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke

Comparison: 2 Subgroup analysis by duration of illness: acute or subacute versus chronic

Outcome: 1 Naming accuracy in per cent in all studies until the end of intervention phase



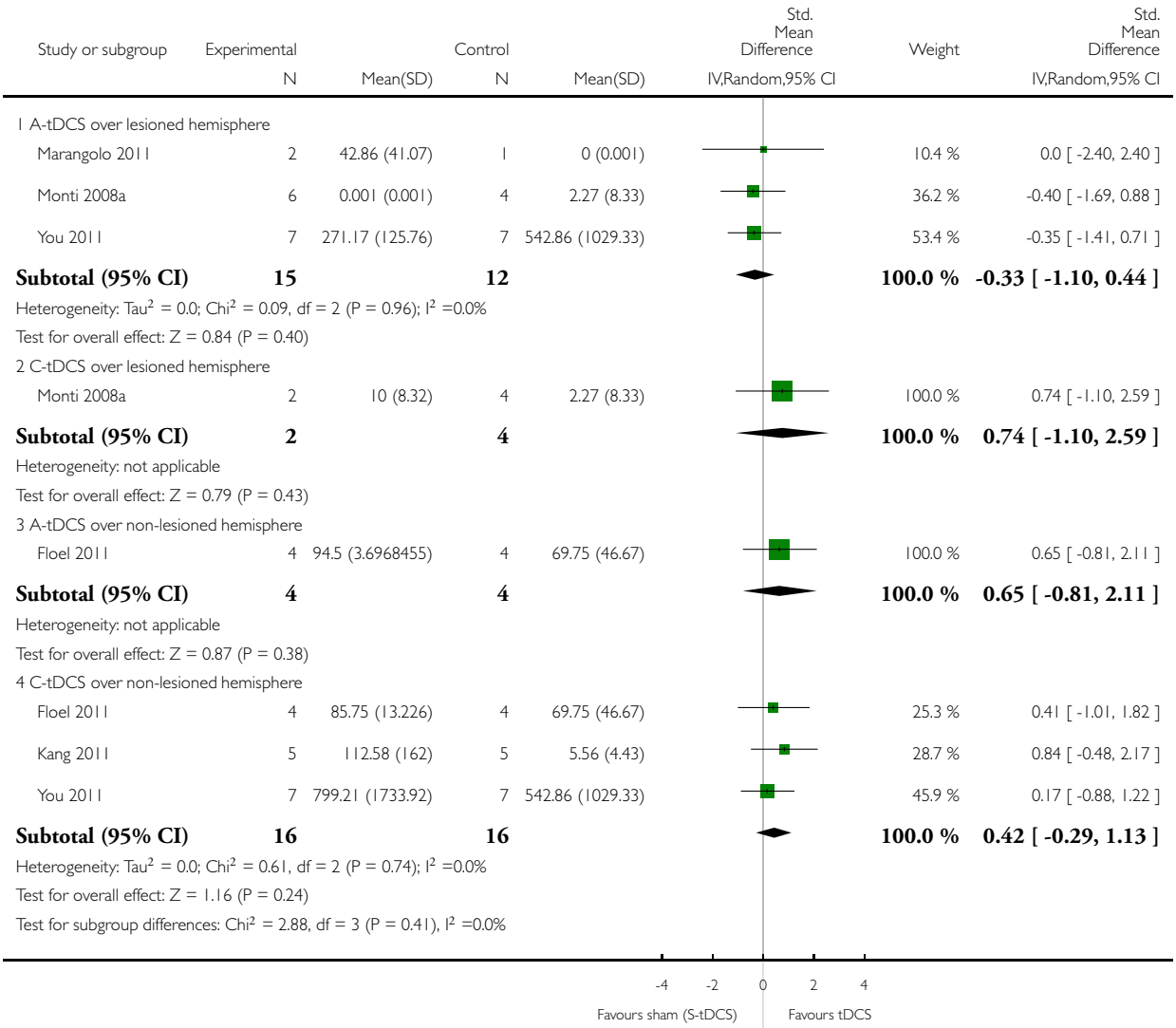
**Analysis 3.1. Comparison 3 Planned subgroup analysis by location of stimulation (lesioned or non-lesioned hemisphere) and type of stimulation (A-tDCS, C-tDCS, S-tDCS), Outcome 1 Relative change in accuracy of naming in per cent until the end of intervention phase.**

Review: Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke

Comparison: 3 Planned subgroup analysis by location of stimulation (lesioned or non-lesioned hemisphere) and type of stimulation (A-tDCS, C-tDCS, S-tDCS)

Outcome: 1 Relative change in accuracy of naming in per cent until the end of intervention phase

| Study or subgroup | Experimental N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Random,95% CI | Weight | Std. Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 A-tDCS over lesioned hemisphere | | | | | | | |
| Marangolo 2011 | 2 | 42.86 (41.07) | 1 | 0 (0.001) | | 10.4 % | 0.0 [ -2.40, 2.40 ] |
| Monti 2008a | 6 | 0.001 (0.001) | 4 | 2.27 (8.33) | | 36.2 % | -0.40 [ -1.69, 0.88 ] |
| You 2011 | 7 | 271.17 (125.76) | 7 | 542.86 (1029.33) | | 53.4 % | -0.35 [ -1.41, 0.71 ] |
| **Subtotal (95% CI)** | **15** | | **12** | | | **100.0 %** | **-0.33 [ -1.10, 0.44 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 2 (P = 0.96); $I^2 = 0.0\%$ | | | | | | | |
| Test for overall effect: Z = 0.84 (P = 0.40) | | | | | | | |
| 2 C-tDCS over lesioned hemisphere | | | | | | | |
| Monti 2008a | 2 | 10 (8.32) | 4 | 2.27 (8.33) | | 100.0 % | 0.74 [ -1.10, 2.59 ] |
| **Subtotal (95% CI)** | **2** | | **4** | | | **100.0 %** | **0.74 [ -1.10, 2.59 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | | | | |
| 3 A-tDCS over non-lesioned hemisphere | | | | | | | |
| Floel 2011 | 4 | 94.5 (3.6968455) | 4 | 69.75 (46.67) | | 100.0 % | 0.65 [ -0.81, 2.11 ] |
| **Subtotal (95% CI)** | **4** | | **4** | | | **100.0 %** | **0.65 [ -0.81, 2.11 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 0.87 (P = 0.38) | | | | | | | |
| 4 C-tDCS over non-lesioned hemisphere | | | | | | | |
| Floel 2011 | 4 | 85.75 (13.226) | 4 | 69.75 (46.67) | | 25.3 % | 0.41 [ -1.01, 1.82 ] |
| Kang 2011 | 5 | 112.58 (162) | 5 | 5.56 (4.43) | | 28.7 % | 0.84 [ -0.48, 2.17 ] |
| You 2011 | 7 | 799.21 (1733.92) | 7 | 542.86 (1029.33) | | 45.9 % | 0.17 [ -0.88, 1.22 ] |
| **Subtotal (95% CI)** | **16** | | **16** | | | **100.0 %** | **0.42 [ -0.29, 1.13 ]** |
| Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.61$, df = 2 (P = 0.74); $I^2 = 0.0\%$ | | | | | | | |
| Test for overall effect: Z = 1.16 (P = 0.24) | | | | | | | |
| Test for subgroup differences: $Chi^2 = 2.88$, df = 3 (P = 0.41), $I^2 = 0.0\%$ | | | | | | | |



## ADDITIONAL TABLES

**Table 1. Patient characteristics**

| Study ID | Experimental: age, mean (SD) | Control: age, mean (SD) | Experimental: time post-stroke | Control: time post-stroke | Experimental: sex | Control: sex | Experimental: affected hemisphere | Control: affected hemisphere | Experimental: education, mean (SD) | Control: education, mean (SD) | Handedness |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Floel 2011 | 52.3 (9.2) years | 52.3 (9.2) years | 69.9 (39.9) months | 112.8 (101.6) months | 6 male 2 female | 4 female | 8 (75%) left | 4 (25%) left | 12.8 (4.4) years | 13.5 (5.8) years | 12 (100%) |
| Kang 2011 | 62 (10) years | 61.8 (8.2) years | 22.9 (36) months | 87.9 (80.4) months | 4 male 1 female | 4 male 1 female | 5 (100%) left | 5 (100%) left | 14.4 (2.2) years | 8.8 (5.4) years | 10 (100%) |
| Marangolo 2011 | 67.5 (0.7) years | 63 (NA) | 9.5 (3.5) months | 48 (NA) months | 1 male 1 female | 1 male | 2 (100%) left | 1 (100%) left | 15 (2.8) years | 13 years (NA) | 3 (100%) |
| Monti 2008a | 63.5 (14.88) | 57.25 (9.36) | 52.5 (33) months | 42 (6.93) months | 2 male 3 female | 2 male 2 female | 5 (100%) left | 3 (75%) left 1 (25%) both | 8.75 (5.68) years | 12.5 (4.70) years | 8 (100%) |
| You 2011 | 68.14 (11.23) years | 63.43 (9.78) years | 25.93 (6.31) days | 25.29 (8.96) days | 7 male 7 female | 5 male 2 female | 14 (100%) left | 7 (100%) left | 11.07 (3.20) years | 10.71 (3.86) years | 33 (100 %) |

NA: not applicable
SD: standard deviation

**Table 2. Demographics of studies including dropouts and adverse events**

| Study-ID | Aphasia severity, mean (SD) | Type of stimulation (polarity) | Electrode position and size | Treatment intensity | Base-treatment | Drop-outs | Reasons for drop-outs and adverse-events in the experimental group | Reasons for drop-outs and adverse-events in the control group | Adverse events | Source of information |
|---|---|---|---|---|---|---|---|---|---|---|

**Table 2. Demographics of studies including dropouts and adverse events** (*Continued*)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Floel 2011 | AAT-Profile score: 54.8 (8.71) | A-tDCS | 35 cm² sponge electrode over the right temporo-parietal cortex (unaffected hemisphere) | 1 mA for 20 minutes | Base-treatment + either A-tDCS, C-tDCS or S-tDCS for 5 days once a day | Anomia training (picture naming) | 0 | NA | NA | None | NA |
| | | C-tDCS | | | | | | | | | |
| | | S-tDCS | | 1 mA for 30 seconds | | | | | | | |
| Kang 2011 | WAB-AQ: 39.5 (8.2) | C-tDCS | 25 cm² sponge electrode over the right Broca's homologue area (unaffected hemisphere) | 2 mA for 20 minutes | Base-treatment + either A-tDCS, C-tDCS or S-tDCS for 5 days once a day | Computerised anomia training (picture naming) | 0 | NA | NA | Not stated | NA |
| | | S-tDCS | | 1 mA for 1 minute | | | | | | | |
| Marangolo 2011 | AAT-Token test: 19.67 (9.61) | A-tDCS | 35 cm² sponge electrode over the left inferior frontal gyrus (Broca's area, affected hemisphere) | 1 mA for 20 minutes | Base-treatment + either A-tDCS, C-tDCS or S-tDCS for 5 days once a day | Tailored speech and language therapy | 0 | NA | NA | Not stated | NA |
| | | S-tDCS | | 1 mA for 30 seconds | | | | | | | |
| Monti 2008a | Accuracy in picture naming (0-20 | A-tDCS | 35 cm² electrodes over the left F-T | 2 mA for 10 minutes | Base-treatment + either A-tDCS, | Computerised anomia | 0 | NA | NA | None | NA |

**Table 2. Demographics of studies including dropouts and adverse events** (*Continued*)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | points with a higher value reflecting higher accuracy) : 12.2 (4.84) | C-tDCS | areas (Broca's area, affected hemisphere) | 2 mA for 10 minutes | C-tDCS or S-tDCS once | training (picture naming) | | | | | |
| | | S-tDCS | | 2 mA for 10 seconds | | | | | | | |
| You 2011 | K-WAB AQ: 22.81 (13.16) | A-tDCS | 35 $cm^2$ saline-soaked sponge electrodes either over the left supratemporal gyrus (affected hemisphere, for anodal and sham) or over the right supratemporal gyrus (unaffected hemisphere, cathodal) | 2 mA for 30 minutes | Base treatment + 10 consecutive sessions, 5 times a week for 2 weeks | Conventional speech and language therapy | 12 out of 33 (36%) | Not stated group-wise. Reasons were: (1) early discharge of 7 patients (2) three patients refused therapy due to uncomfortable sensations and (3) two patients were unable to receive therapy due to their sleep habits | | None | Published information |
| | | C-tDCS | | 2 mA for 30 minutes | | | | | | | |
| | | S-tDCS | | 2 mA for 60 seconds | | | | | | | |

AAT: Aachen Aphasia Test
A-tDCS: anodal tDCS
C: Coloumb (unit of electric charge; 1C = 1A *1s)
C-tDCS: cathodal tDCS
K-WAB AQ: Korean Western Aphasia Battery Aphasia Quotient
NA: not applicable
SD: standard deviation

S-tDCS: sham tDCS
tDCS: transcranial direct current stimulation
WAB-AQ: Western Aphasia Battery Aphasia Quotient

# APPENDICES

## Appendix 1. MEDLINE, EMBASE, AMED and INSPEC (OvidSP) search strategy

1. exp aphasia/
2. language disorders/ or speech disorders/ or anomia/
3. speech-language pathology/ or exp "rehabilitation of speech and language disorders"/
4. (aphasi$ or dysphasi$ or anomia or anomic).tw.
5. ((speech or language or linguistic) adj5 (disorder$ or impair$ or problem$ or dysfunction)).tw.
6. ((speech or language or linguistic) adj5 (therap$ or train$ or rehabilitat$ or treat$ or remediat$ or intervention$ or pathol$)).tw.
7. or/1-6
8. Electric Stimulation Therapy/
9. Electric Stimulation/
10. Electrodes/
11. (transcranial adj5 direct current adj5 stimulation).tw.
12. (transcranial adj5 DC adj5 stimulation).tw.
13. (transcranial adj5 electric$ 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. 7 and 15
17. exp animals/ not humans.sh.
18. 16 not 17

Number of records retrieved:

- MEDLINE: 390
- EMBASE: 610
- AMED: 13
- INSPEC: 40

## Appendix 2. CENTRAL search strategy

1. MeSH descriptor Aphasia explode all trees
2. MeSH descriptor Language Disorders explode all trees
3. MeSH descriptor Speech Disorders explode all trees
4. MeSH descriptor Anomia explode all trees
5. MeSH descriptor Speech-Language Pathology explode all trees
6. MeSH descriptor Rehabilitation of Speech and Language Disorders explode all trees
7. (aphasi$ or dysphasi$ or anomia or anomic)
8. ((speech or language or linguistic) NEAR/5 (disorder$ or impair$ or problem$ or dysfunction))
9. ((speech or language or linguistic) NEAR/5 (therap$ or train$ or rehabilitat$ or treat$ or remediat$ or intervention$ or pathol$))
10. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
11. MeSH descriptor Electric Stimulation Therapy explode all trees
12. MeSH descriptor Electric Stimulation explode all trees
13. MeSH descriptor Electrodes explode all trees

14. (transcranial NEAR/5 direct current NEAR/5 stimulation)
15. (transcranial NEAR/5 DC NEAR/5 stimulation)
16. (transcranial NEAR/5 electric$ NEAR/5 stimulation)
17. (tDCS or A-tDCS or C-tDCS or S-tDCS or electrode$ or anode or anodes or anodal or cathode or cathodes or cathodal)
18. (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
19. (#10 AND #18)

Number of records retrieved: 18

## Appendix 3. CINAHL search strategy (EBSCO)

1. (MH "Aphasia+")
2. (MM "Language Disorders")
3. (MM "Speech Disorders")
4. (MM "Anomia")
5. (MM "Speech-Language Pathology")
6. (MH "Rehabilitation, Speech and Language+")
7. TX (aphasi* or dysphasi* or anomia or anomic)
8. TX ((speech or language or linguistic) N5 (disorder* or impair* or problem* or dysfunction))
9. TX ((speech or language or linguistic) N5 (therap* or train* or rehabilitat* or treat* or remediat* or intervention* or pathol*))
10. S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
11. (MM "Electric Stimulation") OR (MM "Electrical Stimulation, Functional") OR (MM "Electrical Stimulation, Neuromuscular")
12. (MM "Electrodes")
13. TX (transcranial N5 direct current N5 stimulation)
14. TX (transcranial N5 DC N5 stimulation)
15. TX (transcranial N5 electric* N5 stimulation)
16. TX (tDCS or A-tDCS or C-tDCS or S-tDCS or electrode* or anode or anodes or anodal or cathode or cathodes or cathodal)
17. S11 or S12 or S13 or S14 or S15 or S16
18. S10 and S17
19. (MH "Animals+") OR (MM "Animal Studies")
20. S18 NOT S19

Number of records retrieved: 610

## Appendix 4. Web of Science search strategy

*DocType=All document types; Language=All languages;*

1. TS=(aphasia)
2. TS=(language disorders or speech disorders or anomia)
3. TS=(speech-language pathology or "rehabilitation of speech and language disorders")
4. TS=(aphasi$ or dysphasi$ or anomia or anomic)
5. TS=((speech or language or linguistic) NEAR/5 (disorder$ or impair$ or problem$ or dysfunction))
6. TS=((speech or language or linguistic) NEAR/5 (therap$ or train$ or rehabilitat$ or treat$ or remediat$ or intervention$ or pathol$))
7. #6 OR #5 OR #4 OR #3 OR #2 OR #1
8. TS=(Electric Stimulation Therapy)
9. TS=(Electric Stimulation)
10. TS=(Electrodes)
11. TS=(transcranial NEAR/5 "direct current" NEAR/5 stimulation)
12. TS=(transcranial NEAR/5 "DC" NEAR/5 stimulation)
13. TS=(transcranial NEAR/5 electric$ NEAR/5 stimulation)
14. TS=(tDCS or A-tDCS or C-tDCS or S-tDCS or electrode$ or anode or anodes or anodal or cathode or cathodes or cathodal)
15. #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8

16. #15 AND #7
Number of records retrieved: 223

## Appendix 5. LLBA search strategy

((DE=("aphasia" or "brocas aphasia" or "wernickes aphasia"))
or(DE="language pathology") or(DE="anomia") or(DE=("language therapy" or
"speech therapy" or "speech/language therapists")) or(TI=aphasi* or
dysphasi* or anomia* or anomic* or AB=aphasi* or dysphasi* or anomia* or
anomic*) or((TI=speech or language or linguistic or AB=speech or language
or linguistic) and(TI=disorder* or impair* or problem* or dysfunction or
therap* or train* or rehabilitat* or treat* or remediat* or intervention*
or pathol* or AB=disorder* or impair* or problem* or dysfunction or
therap* or train* or rehabilitat* or treat* or remediat* or intervention*
or pathol*))) and((TI=transcranial direct current stimulation or
AB=transcranial direct current stimulation) or(TI=transcranial DC
stimulation or AB=transcranial DC stimulation) or(TI=transcranial
electric* stimulation or AB=transcranial electric stimulation) or(TI=tDCS
or A-tDCS or C-tDCS or S-tDCS or electrode$ or anode or anodes or anodal
or cathode or cathodes or cathodal or AB=tDCS or A-tDCS or C-tDCS or
S-tDCS or electrode$ or anode or anodes or anodal or cathode or cathodes
or cathodal))
Number of records retrieved: 136

## Appendix 6. COMPENDEX search strategy

1. s ((vertebral (w) artery (w) dissection?)) or brain or carotid or intracran?
2. s stroke? or poststroke? or cerebr? or cva? or apoplex? or sah
3. s cerebell? or intracerebral or subarachnoid
4. s hemipleg? or hemipar? or paresis or paretic
5. s s1-s4
6. s ((electric (w) stimulation?)) or electrode?
7. s transcranial (5n) direct (5n) current (5n) stimulation?
8. s transcranial (5n) DC (5n) stimulation?
9. s transcranial (5n) electric? (5n) stimulation?
10. s tdcs or electrode? or anod? or cathod?
11. s s6-s10
12. s randomized (w) controlled (w) trial?
13. s random (w) allocation
14. s control (w) group?
15. s clinical (w) trial?
16. s blind (w) method?
17. s placebo?
18. s investigat? and therap???
19. s research (5n) design
20. s evaluation (w) stud???
21. s ((evaluation (w) stud???)) or ((comparative (w) stud???))
22. s random?
23. s ((controlled (5n) trial?)) or ((controlled (5n) stud???))
24. s (control or treatment or experiment? or intervention?) (5n) (group? or subject? or patient?)
25. s (multicent??? or therapeutic) (5n) (trial? or stud???)
26. s (control or experiment$ or conservative) (5n) (treatment or therap??? or procedure? or manage?)

27. s (singl? or doubl? or tripl? or trebl?) (5n) (blind? or mask?)
28. s (flip??? or toss?) (5n) coin
29. s versus
30. s ((cross (w) over)) or crossover)
31. s sham
32. s ((multiple (w) baseline)) or assign? or alternate or allocate? or counterbalance?
33. s control? ?
34. s s12-s33
35. s s5 and s11 and s34

Number of records retrieved: 650

### Appendix 7. PEDro search strategy

1. aphasia (Abstract & Title)
2. anomia (Abstract & Title)
3. #1 OR #2

Number of records retrieved: 20

### Appendix 8. PsycBITE search strategy

Target Condition: Aphasia/Dysphasia
Method: Randomised Controlled Trial
Search terms combined with AND
Age group: Adults (18+)
Number of records retrieved: 52

### Appendix 9. SpeechBITE search strategy

Target Area: Aphasia
Method: Randomised Controlled Trial
Age group: Adults
Number of records retrieved: 41

## CONTRIBUTIONS OF AUTHORS

All authors contributed to the conception and design of the review and approved the draft. All authors were involved in all stages of the review. BE was involved in screening titles and abstracts of publications identified by the searches. BE and JM extracted trial and outcome data from the selected trials and analysed outcome data. JM and MP were involved in assessing risk of bias in the included studies. All authors interpreted the results.

## DECLARATIONS OF INTEREST

None known

## SOURCES OF SUPPORT


### Internal sources

- Gesundheitswissenschaften/Public Health, Medizinische Fakultät Carl Gustav Carus der TU Dresden, Fetscherstr. 74, 01307 Dresden, Germany.
- Wissenschaftliches Institut, Private Europäische Medizinische Akademie der Klinik Bavaria in Kreischa GmbH, An der Wolfsschlucht 1-2, 01731 Kreischa, Germany.
- Lehrstuhl Therapiewissenschaften, SRH Fachhochschule für Gesundheit Gera gGmbH, Hermann-Drechsler-Str. 2, 07548 Gera, Germany.

### External sources

- No sources of support supplied


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We discarded the analysis of fatigue due to the diversity and high complexity of neurological symptoms of this outcome. The statistical pooling of pain and discomfort as a secondary outcome measure was not possible due to lack of published and unpublished data. Because there were too few included studies, we discarded our planned sensitivity analysis by trial methodology.