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REVIEW

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# A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation

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**Abstract**

Transcranial direct current stimulation (tDCS) is a non-invasive method of brain stimulation that has been intensively investigated in clinical and cognitive neuroscience. Although the general impression is that tDCS is a safe technique with mild and transient adverse effects (AEs), human data on safety and tolerability are largely provided from single-session studies in healthy volunteers. In addition the frequency of AEs and its relationship with clinical variables is unknown. With the aim of assessing tDCS safety in different conditions and study designs, we performed a systematic review and meta-analysis of tDCS clinical trials. We assessed Medline and other databases and reference lists from retrieved articles, searching for articles from 1998 (first trial with contemporary tDCS parameters) to August 2010. Animal studies, review articles and studies assessing other neuromodulatory techniques were excluded. According to our eligibility criteria, 209 studies (from 172 articles) were identified. One hundred and seventeen studies (56%) mentioned AEs in the report. Of these studies, 74 (63%) reported at least one AE and only eight studies quantified AEs systematically. In the subsample reporting AEs, the most common were, for active *vs.* sham tDCS group, itching (39.3% *vs.* 32.9%, $p>0.05$), tingling (22.2% *vs.* 18.3%, $p>0.05$), headache (14.8% *vs.* 16.2%, $p>0.05$), burning sensation (8.7% *vs.* 10%, $p>0.05$) and discomfort (10.4% *vs.* 13.4%, $p>0.05$). Meta-analytical techniques could be applied in only eight studies for itching, but no definite results could be obtained due to between-study heterogeneity and low number of studies. Our results suggested that some AEs such as itching and tingling were more frequent in the tDCS active group, although this was not statistically significant. Although results suggest that tDCS is associated with mild AEs only, we identified a selective reporting bias for reporting, assessing and publishing AEs of tDCS that hinders further conclusions. Based on our findings, we propose a revised adverse effects questionnaire to be applied in tDCS studies in order to improve systematic reporting of tDCS-related AEs.

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**Key words**: Adverse effects, brain stimulation, meta-analysis, systematic review, transcranial direct current stimulation.



## Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique that uses weak, direct electric currents delivered through the scalp to the neuronal tissue to induce changes in cortical excitability according to the parameters of stimulation (Fregni & Pascual-Leone, 2007). Although the technique is not new, being used since ancient times (Zago *et al*. 2008); its systematic study only started 12 yr ago, when seminal studies proved its neurophysiological effects (Nitsche & Paulus, 2000; Priori *et al*. 1998). Since then, several studies exploring this technique have been published, ranging from computational, current distribution models to preclinical and clinical studies.

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In fact, tDCS is an appealing intervention for neuropsychiatric disorders, combining interesting characteristics such as non-invasiveness, low-cost, ease of use and powerful effects on cortical excitability (Priori *et al*. 2009). Thus far, tDCS has been studied in many conditions, e.g. chronic pain (Fregni *et al*. 2007), major depressive disorder (Brunoni *et al*. 2009), stroke rehabilitation (Hummel *et al*. 2006), Parkinson's disease (Wu *et al*. 2008), and others, with mixed albeit generally positive results thereby fomenting further studies for exploring new conditions as well as for investigating its use in 'real-world' samples.

Therefore, it is important to assess the safety of tDCS. In fact, some animal (Agnew & McCreery, 1987; Akimova & Novikova, 1978; Liebetanz *et al*. 2009) and clinical (Iyer *et al*. 2005; Nitsche *et al*. 2004; Poreisz *et al*. 2007; Tadini *et al*. 2010) studies addressed this issue; however, the former is not appropriate to test subjective effects whereas most clinical studies performed hitherto reported mixed findings regarding the type and quantity of adverse effects (AEs) related to tDCS.

Due to the current relatively large number of human studies using tDCS, we aimed to assess one aspect of safety, i.e. reporting and analysis of AEs. We therefore performed a systematic review to assess AEs in published tDCS studies. The second aim of our study was to explore the relationship between the frequency of AEs and study characteristics such as number of subjects in real tDCS and sham groups, number of sessions, size and position of electrodes, intensity and duration of stimulation.

## Methods

Our systematic review was conducted according to the recommendations of the Cochrane Adverse Effects Methods Group (Loke *et al*. 2009), and the present report follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher *et al*. 2009) (see Supplementary material, available online).

### *Literature search*

We searched for articles published from the first data available [1998 – when the first study (Priori *et al*. 1998) using current tDCS methodology (i.e. electrode size, position, current intensity and duration) was published] to August 2010 in the following databases: Medline, Scopus, Web of Science and Google Scholar. The following key words were used: 'transcranial direct current stimulation' OR 'tDCS' OR 'brain polarization' OR 'galvanic stimulation'. We also looked for articles in the reference lists of retrieved articles and tDCS review articles and contacted experts in the field.

### *Selection criteria*

The following criteria were adopted: (1) articles written in English (although there were no manuscripts in other languages) and (2) original articles that reported tDCS effects in humans. We therefore excluded the following articles: (1) animal studies; (2) review articles; (3) articles reporting duplicate data or data extracted from original articles; (4) articles addressing only the effects of other brain stimulation techniques such as alternating current stimulation or transcranial magnetic stimulation.

### *Data extraction*

For each study, three authors extracted data independently (B.R.G., B.T.B., M.S.V.) and two other authors (J.A., A.R.B.) checked data extraction. Any discrepancies were resolved by consensus with the corresponding author (F.F.) consulted if necessary.

We elaborated a structured checklist in order to extract the following variables:

(1) Demographic and clinical characteristics, such as total sample, gender (percent of females), age (years), clinical condition (healthy *vs*. non-healthy subjects) and subjects' region of origin, which was divided in four groups: Americas (USA, Canada, Brazil), Asia & Oceania (Korea, Japan, Australia, New Zealand), Europe (UK, Italy, Switzerland, Belgium, Spain, France) and Germany (which was categorized separately because almost one third of all studies were from this country).
(2) Study design characteristics, such as frequency of stimulation (1–2 sessions *vs*. repeated sessions) and control group (no *vs*. yes).
(3) Treatment characteristics, which included anode and cathode positioning [divided into (over the) motor cortex, dorsolateral prefrontal cortex (DLPFC), supra-orbital area and other settings], dose of electric current [divided into low ($\leqslant$1.5 mA) and high (>1.5 mA)], size of electrodes (divided into $\leqslant 25$ cm² and $>25$ cm²), duration of session (min), current density (mA/cm²), which was calculated using the formula:

$$J = I/A,$$

where $J$ = current density, $A$ = cross-sectional area (in m²) and $I$ = electric current, and then grouped as $\leqslant 0.05$ and $>0.05$ (mA/cm²); finally, electric charge [C (Coulombs)], which was calculated from

the formula:

$$Q = I \cdot t,$$

where $Q$ = electric charge, $I$ = electric current, and $t$ = time (s).

(4) AEs, in which we considered either an 'all-or-none' reporting (e.g. 'all patients tolerated treatment well'; 'all subjects reported a tingling sensation'; 'no side-effects were reported', etc.) or a detailed description of adverse events – in such cases, we collected data on reporting of *itching*, *burning*, *tingling*, *discomfort*, and *headache*. These adverse events were chosen because comprehensive reviews and a consensus article regarded them as common (George & Aston-Jones, 2010; Nitsche *et al*. 2008). We also recorded in a separate form other reported events (e.g. somnolence, anxiety, others). Since the terms are used interchangeably, we considered AE reporting also when studies used the terms 'side-effects' or 'adverse events'. Finally, when the article did not specify in which group the AEs were observed, we took a conservative approach and classified them as belonging to the active group.

### *Quality assessment*

According to the Cochrane Adverse Effects Methods Group (Loke *et al*. 2009) we addressed the following issues that influence data quality: (1) selective outcome reporting (Chan *et al*. 2004) – we identified whether and to what extent AEs were reported; which method (passive monitoring *vs*. active surveillance) was used for assessing AEs; and whether studies reporting AEs discussed them or not; (2) year of publication – as rare and outcome of AEs might take more years to be identified and itemized (Loke *et al*. 2009); (3) presence of control group – in order to distinguish between adverse *events* (i.e. those which appear after intervention onset) and adverse *effects* (i.e. adverse events in which causality is likely).

Since our aim is to identify AEs related with tDCS, we took a conservative approach, as we did not discard studies based on risk bias; instead, we undertook separate analyses according to study quality.

### *Quantitative analysis*

All analyses were performed using Stata statistical software, version 10.0 (StataCorp, USA). According to study quality, separate analyses were performed:

(1) For studies that did not report AEs: we explored whether they differ from studies reporting AEs (referred in the text as 'reporting studies') according to the aforementioned variables using unpaired $t$ tests (for continuous variables) or, for categorical variables, the $\chi^2$ or Fisher's exact test.

(2) For all studies that reported AEs, including those presenting high risk of selective reporting bias (i.e. 'all-or-none' reporting): we tested which AEs were significantly more observed in the real tDCS group compared to placebo and, thereafter, we explored such AEs using the statistical tests previously described.

(3) For studies enrolling non-healthy volunteers: we used formal meta-analytical techniques, i.e. for each study we constructed contingency tables and calculated the odds ratio (Mantel–Haenszel or I–V method) of having the AE and being in the active group (*vs*. not having the AE and being in sham group) as the measure of association and then we measured the pooled odds ratio using the random- and fixed-effect models. We assessed heterogeneity using $\chi^2$ test, sensitivity analysis, Begg funnel plot and Egger test for each AE analysis. Due to the small number of studies left at this stage, further meta-regressions could not be performed.

## Results

Using the key words and date limits previously mentioned we retrieved 366 articles. However, after excluding studies according to our selection criteria, 172 articles with a total of 209 experiments (37 articles presented more than one experiment and four articles presented duplicated studies) remained (the description of each article can be found in the Supplementary file, available online). In the Results section and throughout this paper the term 'study' indicates *experiment* and not the *article*. Only 117 (56%) studies reported AEs, while 92 (44%) experiments did not. Finally, only eight out of 117 studies presented low risk of bias and adequate data reporting in order to perform meta-analysis (Fig. 1).

We evaluated 209 studies that assessed 3836 subjects. The mean age was 33.5 (S.D. = 12) yr and 50 (24%) were female. From these, 117 (56%) studies assessed AEs in 1851 (989 women) patients. When comparing studies describing *vs*. non-describing AEs, we observed some small but significant differences in the following variables: reporting studies included older subjects (mean ± S.D.) (35.3 ± 14.9 *vs*. 30.8 ± 10.5 yr, $t = 2.36$, $p = 0.02$), non-healthy subjects ($\chi^2 = 4.7$, $p = 0.03$) and delivered current densities $> 0.05$ mA/cm$^2$ ($\chi^2 = 4.6$, $p = 0.03$) compared to non-reporting studies. We also observed a trend for reporting studies

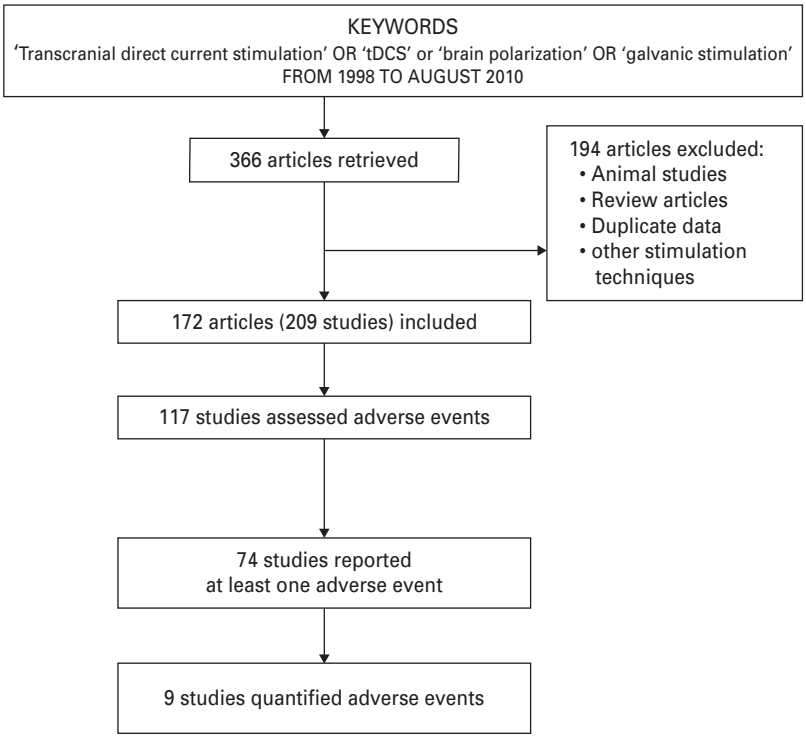


**Fig. 1.** Flow chart used in our review to identify and include relevant studies. Although 366 studies fulfilled our initial criteria (clinical trials for transcranial direct current stimulation), only 209 reported assessment (or assessed) adverse effects. Furthermore, only 74 studies described at least one adverse effect occurring throughout the entire trial, and only nine actively quantified the frequency of adverse effects.

that delivered electric currents $>1.5$ mA ($\chi^2=2.5$, $p=0.11$). No differences were observed regarding sample size, gender, region of study, year of publication, characteristics of study design and other characteristics of treatment (Table 1).

Next, we analysed *reporting studies* only and compared studies reporting 'no AEs' *vs.* studies reporting AEs, either quantitatively (number of AEs) and/or qualitatively (type of AEs). Here, 117 (56%) studies reported some AEs and 43 (37%) studies simply stated that no AEs were observed. We observed that studies published more recently (August 2009–August 2010) were more likely to report at least one AE ($p<0.01$). No other statistical differences were observed (Table 2).

In this subsample, the most common AEs were, in the active group (117 studies), itching ($n=46$, 39.3%), tingling ($n=26$, 22.2%), headache ($n=17$, 14.8%), burning sensation ($n=10$, 8.7%) and discomfort ($n=12$, 10.4%). In the sham group (82 studies), the most common AEs were itching ($n=27$, 32.9%), headache ($n=13$, 16.2%), tingling ($n=15$, 18.3%), burning sensation ($n=10$, 8.7%), and discomfort ($n=8$, 10%) (Table 3). It should be noted that all studies employed similar sham methods, which consisted of inducing the initial fade-in phase, where the current is increased in order to reach the targeted dose, and, after 30–60 s, the device turned off.

Since itching and tingling were the AEs most commonly observed, we explored predictors associated with them: (1) for itching, we observed that studies with larger sample sizes and older publications (1999–2003) reported more itching than recent ones ($p=0.05$ and $p<0.01$, respectively); (2) for tingling, we only observed that tingling was reported more in studies using smaller electrodes ($p<0.01$) (Table 4).

For the final step, we performed a meta-analysis of studies conducted with non-healthy volunteers that quantitatively reported itching. Only eight studies were identified, which addressed itching in patients with major depression (Boggio *et al*. 2008*a*; Loo *et al*. 2010), fibromyalgia (Fregni *et al*. 2006*b*), spinal cord injury pain (Fregni *et al*. 2006*a*), nicotine dependence (Fregni *et al*. 2008*a*), alcohol dependence (Boggio *et al*. 2008*b*), binge-eating disorder (Fregni *et al*. 2008*b*) and chronic pain (Antal *et al*. 2010). For itching, we

**Table 1.** The clinical, design and treatment characteristics of studies reporting *vs.* not reporting adverse effects (AEs)

| | Studies reporting AEs ($n=117$) | Studies not reporting AEs ($n=92$) | Test | $p$ |
|---|---|---|---|---|
| **Clinical characteristics** | | | | |
| Sample | 15.8 (11.5) | 22.1 (5.3) | 1.29 | 0.2 |
| % female | 50 (25) | 51 (20) | 0.35 | 0.72 |
| Age (yr) | 35.3 (14.9) | 30.8 (10.5) | 2.36 | **0.02** |
| Condition (count) | | | 4.7 | **0.03** |
| Healthy | 82 | 74 | | |
| Non-healthy | 35 | 15 | | |
| Region (count) | | | 5.75 | 0.13 |
| Asia & Oceania | 8 | 5 | | |
| Americas | 42 | 21 | | |
| Europe | 33 | 24 | | |
| Germany | 34 | 39 | | |
| Year (count) | | | 5 | 0.17 |
| 1998–2003 | 8 | 8 | | |
| 2004–2006 | 35 | 17 | | |
| 2007–2009 | 44 | 45 | | |
| 2009–2010 | 30 | 19 | | |
| **Study design** | | | | |
| Frequency | | | 0.03 | 0.95 |
| 1–2 sessions | 32 | 24 | | |
| Repeated sessions | 85 | 65 | | |
| Presence of control group | | | 0.03 | 0.85 |
| Yes | 79 | 59 | | |
| No | 38 | 30 | | |
| **Treatment characteristics** | | | | |
| Electric current (mA) | | | 2.48 | 0.11 |
| $\leqslant 1.5$ mA | 82 | 71 | | |
| $>1.5$ mA | 35 | 18 | | |
| Electrode size | | | 3.32 | 0.19 |
| $\leqslant 25$ cm$^2$ | 23 | 23 | | |
| $>30$ cm$^2$ | 87 | 58 | | |
| Current density (mA/cm$^2$) | | | 4.6 | **0.03** |
| $\leqslant 0.05$ | 81 | 70 | | |
| $>0.05$ | 29 | 11 | | |
| Duration (min) | 14.7 (7.4) | 14.1 (6) | 0.56 | 0.57 |
| Electric charge (C) | 1.25 (0.9) | 1.11 (0.8) | 1.2 | 0.23 |
| Anode positioning | | | 4.57 | 0.1 |
| DLPFC | 28 | 13 | | |
| Motor cortex | 55 | 38 | | |
| Other settings | 30 | 33 | | |
| Cathode positioning | | | 1.53 | 0.21 |
| Supra-orbital area | 68 | 44 | | |
| Other settings | 49 | 45 | | |

DLPFC, Dorsolateral prefrontal cortex.

For continuous variables (sample, percent female, age, duration, electric charge) results are expressed as mean (standard deviation) and the test used was the unpaired $t$ test. The other variables were categorical/ordinal and the results are expressed as the number of events. The tests used were $\chi^2$ test or Fisher's exact test. All results are considered significant at a $p$ level of 0.05 and are highlighted in bold.

In study region, Asia & Oceania refers to Korea, Japan, New Zealand, Australia; Americas refers to USA, Canada, Brazil; Europe refers to Italy, Switzerland, UK, Belgium, Spain, France, and Germany refers to Germany alone.

**Table 2.** The clinical, design and treatment characteristics of studies describing absence of adverse effects (AEs) *vs.* at least one AE

| | At least one AE reported ($n=74$) | Reported there were 'no AEs' ($n=43$) | Test | $p$ |
|---|---|---|---|---|
| Total | 74 | 43 | | |
| **Clinical characteristics** | | | | |
| Sample | 17.1 (10.9) | 13.7 (12.3) | 1.5 | 0.12 |
| % female | 53.5 (24) | 44.8 (26) | 1.7 | 0.08 |
| Age (years) | 35.2 (15.1) | 35.7 (15.0) | 0.17 | 0.87 |
| Condition (count) | | | 0.23 | 0.63 |
| Healthy | 53 | 29 | | |
| Non-healthy | 21 | 14 | | |
| Region (count) | | | 2.64 | 0.45 |
| Asia & Oceania | 4 | 4 | | |
| Americas | 26 | 16 | | |
| Europe | 19 | 14 | | |
| Germany | 25 | 9 | | |
| Year (count) | | | 16.69 | **<0.01** |
| 1998–2003 | 7 | 1 | | |
| 2004–2006 | 18 | 17 | | |
| 2007–2009 | 22 | 22 | | |
| 2009–2010 | 27 | 3 | | |
| **Study design** | | | | |
| Frequency | | | 0.01 | 0.92 |
| 1–2 sessions | 54 | 31 | | |
| Repeated sessions | 20 | 12 | | |
| Presence of control group | | | <0.01 | 0.99 |
| Yes | 50 | 29 | | |
| No | 24 | 14 | | |
| **Treatment characteristics** | | | | |
| Electric current (mA) | | | 2.62 | 0.11 |
| ⩽1.5 mA | 48 | 34 | | |
| >1.5 mA | 26 | 9 | | |
| Electrode size | | | 4.97 | 0.08 |
| ⩽25 cm² | 18 | 5 | | |
| >30 cm² | 52 | 35 | | |
| Two different sizes | 4 | 0 | | |
| Current density (mA/cm²) | | | 0.06 | 0.81 |
| ⩽0.05 | 51 | 30 | | |
| >0.05 | 19 | 10 | | |
| Duration (min) | 14.9 (7.7) | 14.4 (7) | 0.38 | 0.7 |
| Electric charge (C) | 1.34 (0.96) | 1.12 (0.89) | 1.19 | 0.24 |
| Anode positioning | | | 3.2 | 0.2 |
| DLPFC | 20 | 8 | | |
| Motor cortex | 31 | 24 | | |
| Other settings | 22 | 8 | | |
| Cathode positioning | | | 1.37 | 0.24 |
| Supra-orbital area | 40 | 28 | | |
| Other settings | 34 | 15 | | |

DLPFC, Dorsolateral prefrontal cortex.

For continuous variables (sample, percent female, age, duration, electric charge) results are expressed as mean (standard deviation) and the test used was the unpaired $t$ test. The other variables were categorical/ordinal and the results are expressed as the number of events. The tests used were $\chi^2$ test or Fisher's exact test. All results are considered significant at a $p$ level of 0.05 and are highlighted in bold.

In study region, Asia & Oceania refers to Korea, Japan, New Zealand, Australia; Americas refers to USA, Canada, Brazil; Europe refers to Italy, Switzerland, UK, Belgium, Spain, France, and Germany refers to Germany alone.

**Table 3.** Frequency of adverse effects in 117 (active group) and 82 (sham group) experiments. We considered the presence of adverse effect if the study reported its occurrence in at least one patient

| Sensation | Active group | Sham group |
|---|---|---|
| Itching | 46 (39.3%) | 27 (32.9%) |
| Tingling | 26 (22.2%) | 15 (18.3%) |
| Headache | 17 (14.8%) | 13 (16.2%) |
| Burning | 10 (8.7%) | 8 (10%) |
| Discomfort | 12 (10.4%) | 11 (13.4%) |
| Total | 117 studies | 82 studies |

observed that the odds ratio (OR) for presenting this AE and being in the active group was 1.06 (95% CI 0.62–1.8) and 0.95 (95% CI 0.28–3.94) in the fixed- and random-effects model, respectively (Fig. 2). As heterogeneity was significant ($I^2 = 65\%$, $p = 0.02$ in the $\chi^2$ test), other analyses were performed only with the random-effects model. In the funnel plot, we observed that all studies except two exceeded the limits of the graph (Fig. 3*b*), although Egger's test was not significant for publication bias ($p = 0.4$); further, sensitivity analyses showed a wide variation of results when each study was excluded one at a time (Fig. 3*a*).

## Discussion

Our study reviewed 172 articles (total of 209 studies) using tDCS in human subjects. Our aim was to identify the main AEs related to this technique. Because there was an important heterogeneity in the reporting methods, we created different categories for our results in order to analyse, at different stages, (1) studies that did not mention lack or presence of AEs, (2) studies stating that there were no AEs observed, (3) studies reporting AEs that were collected passively and (4) phase II, sham-controlled studies that collected AEs actively. Our main finding is in line with previous studies showing that tDCS is a safe technique when used in 1–2 sessions for healthy volunteers. However, we found evidence of selective reporting bias in most studies, which hinders the generalizability of safety in clinical contexts, i.e. neuropsychiatric conditions and/or prolonged tDCS daily sessions. Furthermore, some AEs were reported more in active than sham groups, which might be a concern when designing studies due to blinding.

In a systematic review of AEs, one important issue is identifying selective outcome reporting (McGrath *et al*. 2004) as studies are usually designed and powered for efficacy – therefore, traditional methods for identifying study quality (i.e. randomization, allocation, *a priori* hypothesis selection, etc.) might not apply for reporting and measurement of AEs. On the other hand, one should not exclude studies based on quality for AEs, as, differently for efficacy meta-analysis, a higher rate of false-positive findings is preferred than false-negative findings. Therefore, as recommended (Loke *et al*. 2009) in our review we included studies of different quality, as well as observational and case-report studies and thereafter explored our findings in successive sensitivity analyses. In the first step (Table 1), we observed that studies not reporting the absence/presence of AEs were significantly different than those describing AEs in clinical detail, as studies in older people and in patients (not healthy volunteers) more often reported the presence/absence of AEs. Although the difference in age is no longer significant when controlling for health status – as age is a confounder for healthy subjects; thereby supporting that the main difference is the increased likelihood of reporting AEs in clinical studies with patients compared to studies with healthy subjects. In addition, AEs were reported more often in studies using higher current densities. Taken together, these findings might either indicate that researchers planned in advance the collection of AE data in such studies (since clinical studies with neuropsychiatric patients usually enrol older subjects and use high current density therefore being a potential safety concern) or simply that these patients spontaneously described more AEs and hence they were collected retrospectively. Still, the fact that only 56% of all reviewed studies reported presence/absence of AEs is important evidence of selective reporting bias in tDCS studies. Furthermore, more recent studies did not report describe/report more AEs than older studies, which is an opposite trend than observed in psychopharmacological interventions whose trials have improved AE reporting over time (Brunoni *et al*. 2010*a*). Therefore, it appears that AEs are being neglected during tDCS research, despite no definite conclusion on safety being reached, and newer studies are better designed and use more heterogeneous samples. One possible reason for this is the general subjective feeling in the field that tDCS is a technique associated with mild and few AEs; therefore investigators are less interested in collecting or reporting this outcome.

We explored separately studies reporting AEs. First we compared those that reported no AEs *vs*. those that reported at least one AE, which might be an indicative

**Table 4.** The clinical, design and treatment characteristics of studies describing the adverse effects of itching and tingling

| Adverse effect | Itching | Test | *p* | Tingling | Test | *p* |
|---|---|---|---|---|---|---|
| | Yes *vs.* No | | | Yes *vs.* No | | |
| Total | 46 *vs.* 71 | | | 26 *vs.* 91 | | |
| **Clinical characteristics** | | | | | | |
| Sample | 18.4 (13) *vs.* 14 (10) | 2 | **0.05** | 17 (8) *vs.* 15 (12) | 0.46 | 0.65 |
| % female | 55 (25) *vs.* 47 (25) | 1.53 | 0.13 | 48 (23) *vs.* 51 (26) | 0.47 | 0.64 |
| Age (yr) | 35 (14) *vs.* 35 (15) | 0.11 | 0.91 | 34 (16) *vs.* 35 (15) | 0.48 | 0.63 |
| Condition (count) | | 0.86 | 0.36 | | 0.14 | 0.71 |
| Healthy | 30 *vs.* 52 | | | 19 *vs.* 63 | | |
| Non-healthy | 16 *vs.* 19 | | | 7 *vs.* 28 | | |
| Region (count) | | 5.82 | 0.12 | | 2.47 | 0.48 |
| Asia & Oceania | 3 *vs.* 5 | | | 3 *vs.* 5 | | |
| Americas | 17 *vs.* 25 | | | 11 *vs.* 31 | | |
| Europe | 8 *vs.* 25 | | | 5 *vs.* 28 | | |
| Germany | 18 *vs.* 16 | | | 7 *vs.* 27 | | |
| Year (count) | | 12.27 | **0.01** | | 7.19 | 0.07 |
| 1998–2003 | 7 *vs.* 1 | | | 0 *vs.* 8 | | |
| 2004–2006 | 12 *vs.* 23 | | | 5 *vs.* 30 | | |
| 2007–2009 | 12 *vs.* 32 | | | 10 *vs.* 34 | | |
| 2009–2010 | 15 *vs.* 15 | | | 11 *vs.* 19 | | |
| **Study design** | | | | | | |
| Frequency | | 0.061 | 0.81 | | 0.003 | 0.96 |
| 1–2 sessions | 34 *vs.* 51 | | | 19 *vs.* 66 | | |
| Repeated sessions | 12 *vs.* 20 | | | 7 *vs.* 25 | | |
| Presence of control group | | 1.79 | 0.18 | | 0.14 | 0.71 |
| Yes | 29 *vs.* 53 | | | 19 *vs.* 63 | | |
| No | 17 *vs.* 18 | | | 7 *vs.* 28 | | |
| **Treatment characteristics** | | | | | | |
| Electric current (mA) | | 1.79 | 0.18 | | 0.75 | 0.39 |
| ⩽1.5 mA or less | 29 *vs.* 53 | | | 20 *vs.* 62 | | |
| >1.5 mA | 17 *vs.* 18 | | | 6 *vs.* 29 | | |
| Electrode size | | 2.5 | 0.29 | | 18.38 | <**0.01** |
| ⩽25 cm² or less | 6 *vs.* 17 | | | 11 *vs.* 12 | | |
| >30 cm² | 38 *vs.* 49 | | | 12 *vs.* 75 | | |
| Two different sizes | 2 *vs.* 2 | | | 3 *vs.* 1 | | |
| Current density (mA/cm²) | | 0.03 | 0.86 | | 1.06 | 0.3 |
| ⩽0.05 | 23 *vs.* 49 | | | 15 *vs.* 66 | | |
| >0.05 | 12 *vs.* 17 | | | 8 *vs.* 21 | | |
| Duration (min) | 14.2 (7) *vs.* 15.1 (7.7) | 0.67 | 0.5 | 15.5 (9) *vs.* 14.5 (6.9) | 0.59 | 0.56 |
| Electric charge (C) | 1.3 (1) *vs.* 12 (0.9) | 0.55 | 0.58 | 1.2 (0.9) *vs.* 1.3 (1) | 0.32 | 0.75 |
| Anode positioning | | 3.62 | 0.16 | | 0.11 | 0.95 |
| DLPFC | 14 *vs.* 14 | | | 7 *vs.* 21 | | |
| Motor cortex | 17 *vs.* 38 | | | 12 *vs.* 43 | | |
| Other settings | 14 *vs.* 16 | | | 7 *vs.* 23 | | |
| Cathode positioning | | 0.44 | 0.51 | | 0.16 | 0.69 |
| Supra-orbital area | 25 *vs.* 43 | | | 16 *vs.* 52 | | |
| Other settings | 21 *vs.* 28 | | | 10 *vs.* 39 | | |

DLPFC, Dorsolateral prefrontal cortex.

For continuous variables (sample, percent female, age, duration, electric charge) results are expressed as mean (standard deviation) and the test used was the unpaired *t* test. The other variables were categorical/ordinal and the results are expressed as the number of events. The tests used were $\chi^2$ test or Fisher's exact test. All results are considered significant at a *p* level of 0.05 and are highlighted in bold. In some lines the sum is less than 87, as some studies did not report all variables.

In study region, Asia & Oceania refers to Korea, Japan, New Zealand, Australia; Americas refers to USA, Canada, Brazil; Europe refers to Italy, Switzerland, UK, Belgium, Spain, France, and Germany refers to Germany alone.

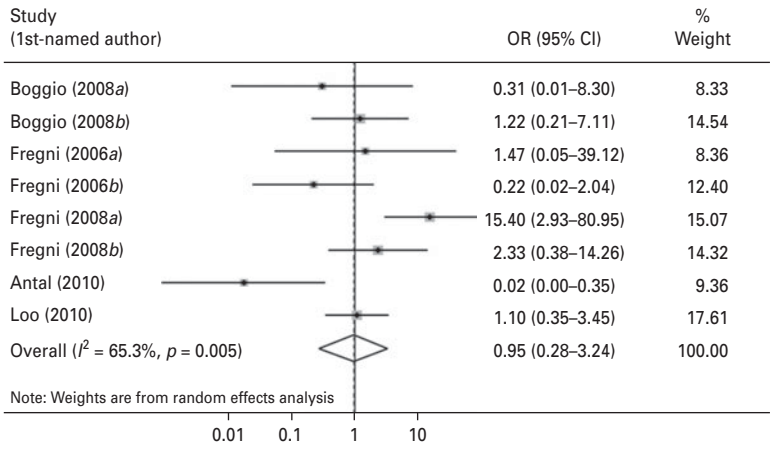


**Fig. 2.** Meta-analysis for the adverse effect of itching that was performed using a random-effects model for the pooling model. The effect size is the odds ratio of having itching and being in the active group *vs*. not having itching and being in the sham group (2 × 2 model). The figure is the Forest plot that presents the net effect size of the analysis.

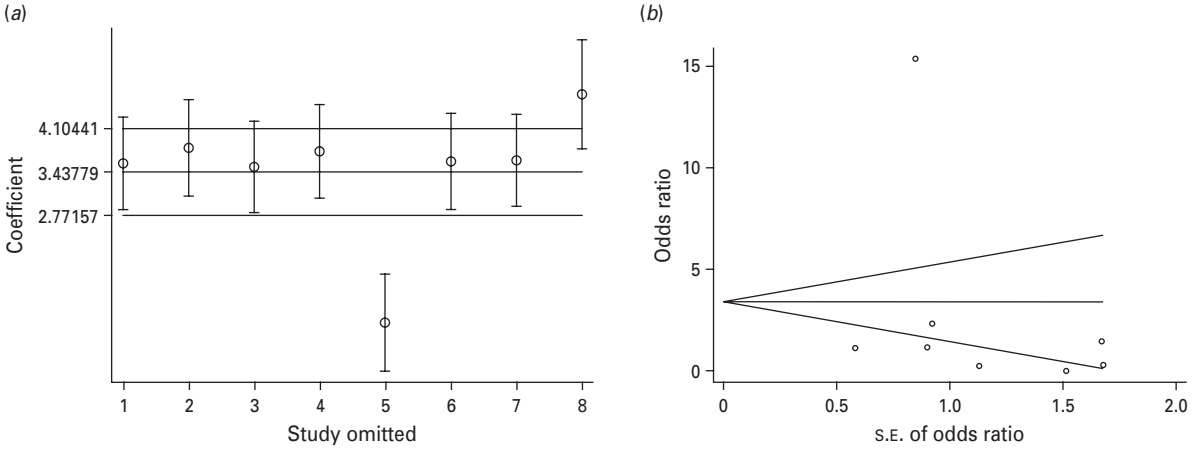


**Fig. 3.** Meta-analysis for the adverse effect of itching. (*a*) Sensitivity analysis in which one study at a time was omitted to reveal whether the results of a particular study influence the net effect size. It can be seen that when two studies are omitted, the net effect size (dots) is lower, suggesting heterogeneity. (*b*) Begg funnel plot used to assess between-study heterogeneity due to publication bias. It can be seen that all but three studies (represented as dots) exceeded the range of the upper and lower boundaries of the confidence interval (inclined lines). This is evidence of heterogeneity.

of poor assessment of AEs. *Itching* and *tingling* were the most common AEs observed in active and sham groups (39.3% *vs*. 32.9% and 22.2% *vs*. 18.3%, respectively), while *headache* and *burning* were observed in about 10% and 15% of studies, respectively, for both groups. Here, it should be underscored that the quality of reporting at this stage forced us to analyse the results in an 'all-or-none' basis, i.e. the absence of AE was only considered if none of the subjects reported the symptom. Thus, even considering the assessment limitations above discussed, the frequency of AEs seems to be low. In addition, severe AEs are more likely to be reported either in the original article or a further communication such as a letter to the editor, e.g. in one case of skin burning following tDCS (Palm *et al*. 2008).

Our final step was conducting a formal meta-analysis only for phase II studies in order to explore safety/toxicity directly related to clinical practice. Moreover, at this stage we hypothesized that the signal-to-noise ratio was stronger because: (1) phase II studies are usually sham-controlled; therefore

allowing us to distinguish between adverse *effects* and adverse *events*; (2) as long-lasting, beneficial effects are expected to be achieved with daily tDCS sessions (Brunoni *et al*. 2010*b*; Nitsche *et al*. 2008); AEs could also be enhanced and observed more often with such design; (3) phase II studies usually assess AEs in a quantitative and qualitative manner. However, many studies did not report AEs in both arms and therefore the point-estimate of such studies could not be defined [i.e. 'the zero cells' issue (Sweeting *et al*. 2004)]. To overcome this matter, we selected the AE most frequently reported (itching) and excluded studies that did not report events – although the best method for dealing with this issue is still under dispute (Tian *et al*. 2009), we applied the standard method. Nevertheless, although we failed to identify an increased odds ratio in the active group for itching in this reduced sample analysis; the tests of heterogeneity including publication bias were significant and thus no definite conclusions can be drawn.

Another limiting factor in our analysis is that most studies did not distinguish between adverse *effect* and adverse *event*, i.e. whether one observed side-effect was either casual or causal. We aimed to address this issue by comparing AEs observed in sham *vs*. active groups (as the sham group provides a baseline level for random occurrence of AEs) and observed an increased frequency in the active group (Table 3). In future studies not employing a sham group, another useful approach would be to correlate AEs with the intervention dosage. For instance for drugs, the World Health Organization classifies adverse drug reaction in dose related, non-dose-related, time-related and dose-related, and time-related (Edwards & Aronson, 2000). Because most of tDCS trials used a fixed dose, this issue has not been addressed in current tDCS research.

Despite these limitations, our findings indicate that the type of AEs is mild and frequency of AEs in tDCS studies is low, at least for healthy volunteers in 1–2 stimulation sessions. This is line with retrospective reviews with individual patient data (Chaieb *et al*. 2008; Poreisz *et al*. 2007; Yukimasa *et al*. 2006) that observed that in healthy volunteers the sensations of itching, tingling and headache were the most frequently observed, which did not differ from the sham group. Our findings extend these analyses that were limited to one setting and research group. Furthermore, we did not identify any report of more serious AEs such as a very brief respiratory arrest that was observed in a 1960 study (Redfearn *et al*. 1964). In fact the most severe AE found in healthy volunteers was skin lesions on the site the electrode was placed using a 2 mA current (Palm *et al*. 2008). Along these lines, one study performed in 58 rats delivering different doses of electric current showed that brain damage only occurred at doses 100 times higher than used in humans (Liebetanz *et al*. 2009).

However, although tDCS seems to be safe in healthy volunteers; a different scenario is observed in neuropsychiatric samples. In fact, we only identified 35 phase II studies composed of heterogeneous samples (with more than a dozen neuropsychiatric conditions evaluated and using a wide range of medicines) although only eight studies were suitable for analysis – as the others were either not sham-controlled or not reported AEs at all. Here, a selective reporting bias is very likely and might be related to the method used for detecting AEs, as the frequency of AEs reported is proportional to the extent they are sought (Higgins & Green, 2009). For example, in one study with hypertensive patients, the rates of AEs were 62% *vs*. 16% when they were monitored actively and passively, respectively (Olsen *et al*. 1999). Even in the eight studies that reported and quantified AEs, although meta-analysis did not show difference in active *vs*. sham groups for itching, definite conclusions could not be drawn due to between-study heterogeneity.

Hence, one implication of our review is that future tDCS phase II/III studies should collect data for AEs. Two aspects are important:

(1) Safety/toxicity: AEs should be monitored actively, using structured questionnaires in which the rater should ask for each specific AE. We include in this article a proposal for one questionnaire for AEs based on our findings (see Appendix) that might be useful as it actively enquires for AEs and also asks subjects to relate the AE with the effects of tDCS. For instance, subjects might refer headache but when enquired they can disclose that this is a common symptom and it is probably not related with the stimulation. Importantly, as the sensations are subjective and can be described using different words (e.g. different patients could perceive the same sensation as *itching*, *burning*, *scratching*, etc.), raters should be trained and standardized when applying the questionnaire; similarly, since tDCS is researched worldwide, such questionnaires should be translated and tested in different languages. Moreover, more objective criteria should be used/developed to assess AEs; e.g. by measuring and reporting the dimensions of redness when observed. AEs should also be

explored considering the subject's condition, for instance, in major depression trials an important AE would be treatment-emergent mania that in fact was observed in recent studies (Arul-Anandam *et al*. 2010; Baccaro *et al*. 2010). These data could prove useful when designing phase III studies and using tDCS in clinical contexts.

(2) Blinding: reporting AEs is necessary in order to develop better blinding techniques – in fact, the fade-in phase is delivered to the sham group to mimic AEs and preserve blinding. In one study (Gandiga *et al*. 2006) subjects continued to feel tingling sensations even in the sham condition and were not able to differentiate in a reliable manner the sham from active tDCS condition. However, one recent study showed that subjects could detect higher tDCS doses, and that experienced *vs*. naive subjects could detect tDCS at lower doses (Ambrus *et al*. 2010). With daily tDCS sessions, skin lesions might be cumulative, leading to skin burn and early drop-out due to breaking of blinding or, in more severe cases, the impossibility of continued stimulation of the damaged area. Therefore, controlling AEs in active and sham arms is necessary for efficient blinding, for instance, using 140 mm saline solutions (Dundas *et al*. 2007) and topical anaesthetics (Nitsche *et al*. 2008). Future studies should address to what extent blinding and AEs relate, and develop methods to minimize AEs in order to preserve blinding; thus allowing the development of reliable phase II tDCS trials.

## Conclusion

Our review on AEs associated with tDCS indicates a selective reporting bias in tDCS trials as almost half of the studies did not report presence/absence or AEs, while only a few studies actively scrutinized the frequency and type of AEs observed. Therefore, it would be more precise to describe 'absence of evidence' rather than 'evidence of absence' regarding this matter, especially when focusing on sham-controlled, phase II studies. While tDCS research moves from bench to bedside, it is mandatory that future clinical research explores AEs in an active, systematic fashion, in order to guarantee that tDCS is a safe and sham-controllable technique.

## Appendix

***Proposal of a questionnaire surveying for tDCS adverse effects***

tDCS Adverse Effects Questionnaire – Session _____

| Do you experience any of the following symptoms or side-effects? | Enter a value (1–4) in the space below (1, absent; 2, mild; 3, moderate; 4, severe) | If present: Is this related to tDCS? (1, none; 2, remote; 3, possible; 4, probable; 5, definite) | Notes |
|---|---|---|---|
| Headache | | | |
| Neck pain | | | |
| Scalp pain | | | |
| Tingling | | | |
| Itching | | | |
| Burning sensation | | | |
| Skin redness | | | |
| Sleepiness | | | |
| Trouble concentrating | | | |
| Acute mood change | | | |
| Others (specify) | | | |

## Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/pnp).

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## Statement of Interest

None.

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