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Safety of repeated sessions of transcranial direct current stimulation: A systematic review

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ABSTRACT

Background: Repeated sessions of transcranial direct current stimulation (tDCS) are increasingly used for therapeutic applications. However, adverse events (AEs) associated with repeated sessions have not been comprehensively evaluated.
Objective: The aim of this study was therefore to evaluate the safety of repeated sessions of tDCS, examining AE risk relative to tDCS exposure. Further, to identify whether certain participant populations are particularly at risk from tDCS.
Methods: A systematic review and meta-analysis included sham-controlled studies (up to June 2017) involving two or more tDCS sessions, spaced not more than a day apart. Data was extracted on AEs reported, total tDCS exposure (cumulative charge), and diagnostic groups (Healthy, Pain Disorder, Stroke, Neurocognitive Disorder, Neuropsychiatric Disorder, and Other). Univariate simple linear meta-regression analyses examined AE likelihood, comparing active and sham tDCS, with increasing exposure. Rates of AEs were compared for diagnostic groups.
Results: 158 studies (total 4130 participants) met inclusion criteria and were included for quantitative analyses. The incidence of AEs (examined per session, by proportion of participants, and by the number of studies reporting AEs) did not increase with higher levels of tDCS exposure. Furthermore, AE rates were not found to be greater for any diagnostic group.
Conclusions: Little evidence was found to suggest that repeated sessions of active tDCS pose increased risk to participants compared to sham tDCS within the limits of parameters used to date. Increased risks associated with greater levels of exposure to tDCS, or rare and under-reported AEs, however, cannot be ruled out.

Introduction

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation which passes a mild current (typically between 1 and 2 mA) between anodal and cathodal electrodes on the scalp. This modulates levels of cortical excitability, resulting in lasting alterations in neuronal activity at regions of interest [1].

tDCS is particularly promising as a research and clinical tool due to its low cost, portability, and the low incidence of side effects, which tend to be mild and transient in nature [2,3]. As a result, the field has expanded exponentially over the past decade [4]. tDCS has been trialled for the treatment of a wide range of neurological and psychiatric disorders, including major depressive disorder [5,6], stroke rehabilitation [7], chronic pain [8] and addiction [9]. Furthermore, it has been used as a means to augment cognitive functioning in healthy and clinical populations [10–12], among many other applications [13–16].

The safety of tDCS has been well researched, establishing the technique as a safe and tolerable form of non-invasive brain stimulation [3,4]. Adverse events (AEs) commonly consist of paraesthesia, such as mild tingling, burning and itching, as well as fatigue, headaches, and transient skin redness [2,3,17–19]. Iyer et al. [17] evaluated AEs following direct current stimulation to 103 participants using EEG, cognitive and psychomotor measures, and found no deficits. Recent reviews [4] and meta-analyses [3,20] have examined the rates of AEs across several treatment populations and have found tDCS to be safe for use, and highly tolerable in both healthy and neuropsychiatric populations. However, the question

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of whether AEs become more prevalent with increased exposure to stimulation has yet to be systematically addressed.

Over the last decade there has been a trend to increase the number of consecutive sessions of tDCS, thereby exposing participants to a higher effective dose of stimulation (i.e. cumulative charge), in an attempt to enhance therapeutic efficacy in treatment trials. For example, the earliest modern trials of tDCS for the treatment of major depressive disorder consisted of only five alternated days of stimulation at a current intensity of 1 mA [21], whilst more recent studies have delivered up to 30 stimulation sessions on consecutive weekdays using 2 mA [22]. Similar increases in session number to enhance effects have been adopted for multiple sclerosis [23], tinnitus [24], and primary progressive aphasia [25]. Evidence in support of improved therapeutic outcomes with increased tDCS exposure includes treatment of depression (e.g. Loo et al. [26] vs Loo et al. [22]), rehabilitation of motor function in stroke patients [27], and treatment of pain following traumatic spinal injury [8].

Although tDCS is considered safe, it is possible that the same principle of cumulative beneficial effects with greater exposure may also extend to increased risk of AEs. This has been minimally examined to date, though recognised as a possibility in the literature [3]. Additionally, despite the widespread use of tDCS across multiple diagnostic populations (e.g. stroke, chronic pain, neurocognitive disorder, neuropsychiatric disorder), it is not yet known whether particular groups may be at increased risk from greater exposure. For example, repeated stimulation of participants with bipolar disorder may carry a risk of switching to a hypomanic or manic state [28]. Similarly, participants prone to certain AEs, such as participants with neuropathic pain disorders [29], may require special monitoring to prevent worsening of symptoms over the duration of a course of treatment.

Objectives

This systematic review and meta-analysis assessed AEs reported in sham-controlled studies involving two or more sessions of tDCS given on consecutive days to: (i) determine whether increased exposure to tDCS from consecutive, repeated sessions increases the risk of AEs and (ii) determine whether risk for AEs is modified by diagnostic group.

Methods

A systematic literature review was conducted using PubMed and Google Scholar databases according to PRISMA guidelines [30] with the following search terms:

> ("transcranial direct current stimulation" OR "tDCS") AND ("repeated sessions" OR "multiple sessions" OR "consecutive sessions" OR "consecutive days" OR "serial tDCS" OR "daily tDCS" OR "twice daily")

No time restriction was applied to the literature search, which was concluded in June 2017. Given evidence that cumulative effects are more likely when sessions of tDCS are repeated up to 24 hours apart, compared to longer intervals [31], this review was restricted to studies that involved tDCS given on at least two consecutive days.

Inclusion criteria were: (i) peer-reviewed manuscripts written in English, or translated from their original language of publication to English; (ii) studies of human participants; (iii) tDCS protocols involving at least two sessions, spaced not more than one day apart.

Exclusion criteria were: (i) patient populations under 18 years of age, as immature brain anatomy and reduced cranial volume can modify current pathways and lead to an altered likelihood or pattern of AEs, thereby making comparisons with adult participants difficult [32]; (ii) protocols utilising alternative forms of transcranial electrical stimulation, such as, but not limited to, transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS), as the purpose of the review was to evaluate the AEs of tDCS, the most commonly used form of transcranial electrical stimulation in studies to date; (iii) lack of a sham-control group (here sham is defined as stimulation following the same procedure as for active stimulation, but with current typically ramped up and down within a minute, intended to elicit sensations similar to active tDCS but not expected to have neuromodulatory effects, used in order to preserve participant blinding).

Screening of the search results was by the following process. Initially, titles of manuscripts retrieved using the above search terms were assessed for relevancy. Secondly, abstracts were reviewed to confirm that the study used tDCS with a repeated sessions design. Finally, the full text was read and used to extract data for analysis. The reference list of each included article was used to identify further studies that fit the criteria and thereby broaden the literature search.

If publications could not be accessed from online journals, corresponding authors were contacted by email and asked to supply the publication. Authors were additionally contacted to collect detailed information of AEs on an individual basis. Two study authors (CH and SN) independently conducted the literature search using the above criteria. Once complete, lists were compared and any discrepancies were discussed, resulting in exclusion or inclusion of the study by consensus. All reports were thoroughly scrutinised for descriptions of AEs, with results recorded. Additional information, such as current intensity, stimulation duration, and number of sessions, was collected and is presented in Supplementary Table 1.

Statistical analyses

All statistical analyses were conducted using open source software, R, using the 'Metafor' package [33]. Significance level was set at $p < 0.05$. Graphs were created in R and made use of 'ColorBrewer2.0' for selection of plot colours [34]. Exposure to tDCS was quantified as cumulative charge. This metric was calculated using the following equation:

$$\text{Cumulative charge (C)} = \text{tDCS intensity (A)} \times \text{session duration (seconds)} \times \text{number of sessions}$$

Therefore, cumulative charge provides a summary metric that captures current intensity as well as the total duration of stimulation experienced by participants during a course of tDCS. Other measures, such as the total number of stimulation sessions and number of stimulation days, were considered for quantification of exposure to tDCS. However, correlation analysis revealed that these measures were highly inter-correlated, and thus would obtain similar outcomes.

Studies were initially sorted so that each study was assigned to one of four discrete categories according to the level of detail of AE reporting provided: (i) studies that provided numerical data on specific AEs, such that the number of participants experiencing each AE was reported ("detailed reporting"); (ii) studies that reported the occurrence of specific AEs but without quantitative data ("undetailed reporting"); (iii) studies that specifically reported on the absence of AEs ("reported specific absence of AEs"); and (iv) studies that made no mention of AEs ("AEs not mentioned"). Additionally, studies were classified according to the major diagnostic groups of the participants involved. These consisted of

Healthy, Pain Disorders, Stroke, Neurocognitive Disorders (e.g. dementia), Neuropsychiatric Disorders (e.g. schizophrenia, depression), and Other (e.g. multiple sclerosis).

The most common AEs reported were burning (skin sensation with no physical lesions), discomfort (e.g. mild to moderate pain sensation), dizziness, erythema (skin redness), fatigue, headache, itching and tingling – these were included in formal analyses of incidences of specific AEs. For analysis, burning, tingling, and itching were grouped together as "paraesthesia". Due to varying levels of reporting detail on the incidence of AEs in the studies, analyses were conducted on three levels:

Incidence of AEs based on the number of sessions in which AEs occurred in the active and sham conditions: "Session incidence analysis"

This analysis was conducted on data from studies that provided AE incidence rates based on the proportion of tDCS sessions in which AEs occurred. These proportions were used to calculate odds ratios for commonly reported AEs. Univariate simple linear random effects meta-regression analyses were conducted to examine the effect of cumulative charge. Odds ratios were used as the effect estimate, and cumulative charge as a continuous independent variable. For this level of analysis there was an insufficient number of studies to analyse AE rates for individual diagnostic groups.

Incidence of AEs based on number of participants who experienced AEs in active and sham conditions: "Participant incidence analysis"

This analysis included studies that reported participant incidence rates of AEs, i.e. number of participants who experienced a specific AE, at any time over the duration of the study, comparing active and sham conditions. For this level of analysis there was an insufficient number of studies to analyse AE rates for individual diagnostic groups.

1 First, forest plots were generated to assess the prevalence of AEs without considering the effect of cumulative charge as a moderator.
2 Then, univariate simple linear random effects meta-regression analyses were conducted for the most commonly reported AEs to examine the effect of cumulative charge. Odds ratios comparing the proportion of participants experiencing AEs in active versus sham conditions were used as the effect estimate, and cumulative charge was included as a continuous independent variable.

Incidence of AEs based on occurrence (Yes/No) of AEs in studies: "Study incidence analysis"

Studies that reported whether AEs occurred or were absent, including studies which did not give more detailed information on incidence rates of AEs in active and sham conditions, were included for analysis. AE data from each study were categorised as yes (occurred) or no (did not occur), in the respective active and sham tDCS conditions, such that AE type was not taken into account. Studies were entered into 2 × 2 contingency tables using the variables: tDCS condition (active tDCS versus sham tDCS), and AE outcome (AE versus no AE). Odds ratios were calculated for the likelihood of an AE occurring in active versus sham conditions and used as the dependent variable for all study incidence analyses.

1 Fisher's exact tests comparing incidence of AEs with active versus sham tDCS were conducted for each diagnostic group (i.e. Healthy, Pain Disorders, Stroke, Neurocognitive Disorders, Neuropsychiatric Disorders, and Other) to determine whether any populations were particularly susceptible to AEs. The same test was then used on combined data from all diagnostic groups to determine overall AE likelihood comparing active to sham tDCS conditions.
2 To examine whether tDCS exposure influenced the likelihood of AEs, studies were categorised into tertiles based on total cumulative charge such that an approximately even number of studies were present in each of the following categories: Low (2–12 Coulombs (C)), Medium (12–14C), and High (16–72C). Fisher's exact tests were used to calculate AE likelihood in each tertile, omitting studies that did not specify in which condition an AE occurred.
3 The above analysis (2) was repeated using a conservative approach by assigning AEs to the active tDCS condition if the study did not specify in which condition an AE occurred. This is similar to the methodology described by Brunoni et al. [3].

Results

A total of 152 sham-controlled studies were identified in the systematic review and thus included for analysis (Supplementary Fig. 1). Some studies described multiple sub-experiments as well as testing of different participant cohorts, including both patient populations and healthy controls, for example. In these cases, the additional experiments were extracted and treated as unique datasets. As such, the number of studies included for analysis increased to 158 (see Table 1).

Session incidence analysis

Only seven studies were found that reported AEs on a per-session basis from which odds ratios could be calculated for the

Table 1
Reporting of AEs in sham-controlled studies using repeated sessions of tDCS according to participant diagnostic population.

Population	Detailed AE reports			Undetailed AE reports			Reported specific absence of AEs			AEs not mentioned		
	k	%	N	k	%	N	k	%	N	k	%	N
Healthy	5	17.2	185	12	41.4	547	1	3.4	11	11	37.9	265
Pain Disorder	19	67.9	548	5	17.9	232	1	3.6	19	3	10.7	42
Stroke	6	14.6	245	10	24.4	236	9	22.0	191	16	39.0	174
Neurocognitive Disorder	3	25.0	57	3	25.0	53	1	8.3	15	5	41.7	114
Neuropsychiatric Disorder	6	33.3	282	5	27.8	127	2	11.1	25	5	27.8	133
Other	12	40.0	249	7	23.3	159	8	26.7	173	3	10.0	48
All Populations	51	32.3	1566	42	26.6	1354	22	13.9	434	43	27.7	776

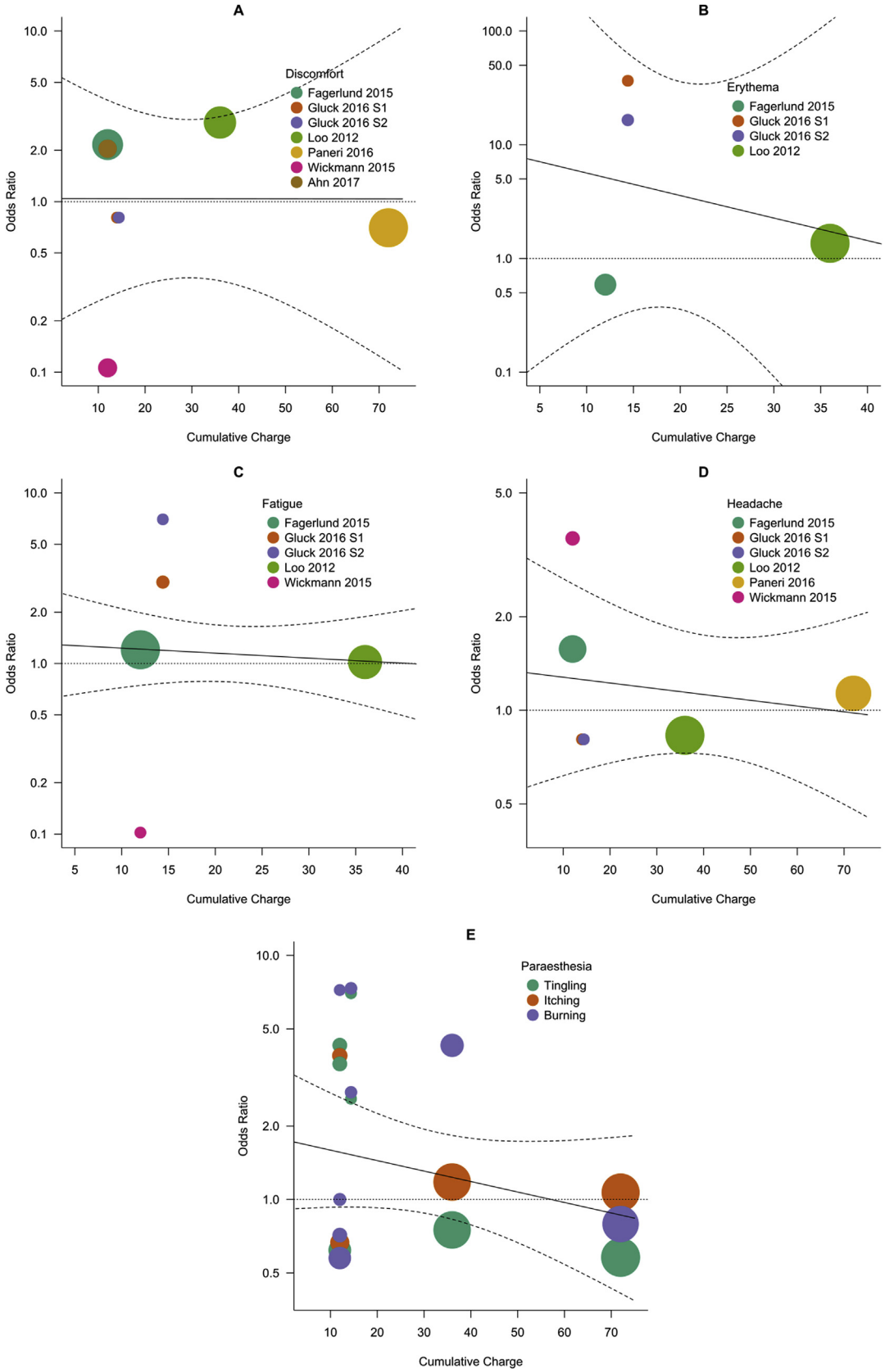

Fig. 1. Weighted bubble plots displaying the odds ratio (OR) for AEs in active tDCS versus sham tDCS, plotted against the cumulative charge experienced during the course of each study for session-level data. The size of each bubble is proportional to the magnitude of the inverse of the variance of the OR in the log scale (e.g. the larger the bubble the greater the weighting assigned to the study during regression analysis). The solid line represents simple linear univariate meta-regression outcomes fit to the data, with dotted lines showing the 95% confidence interval. AEs graphed include: A) Discomfort; B) Erythema; C) Fatigue; D) Headache; and E) Paraesthesia (the plot for paraesthesia has been split into the comprising symptoms rather than studies, as for previous plots, for the sake of simplicity).

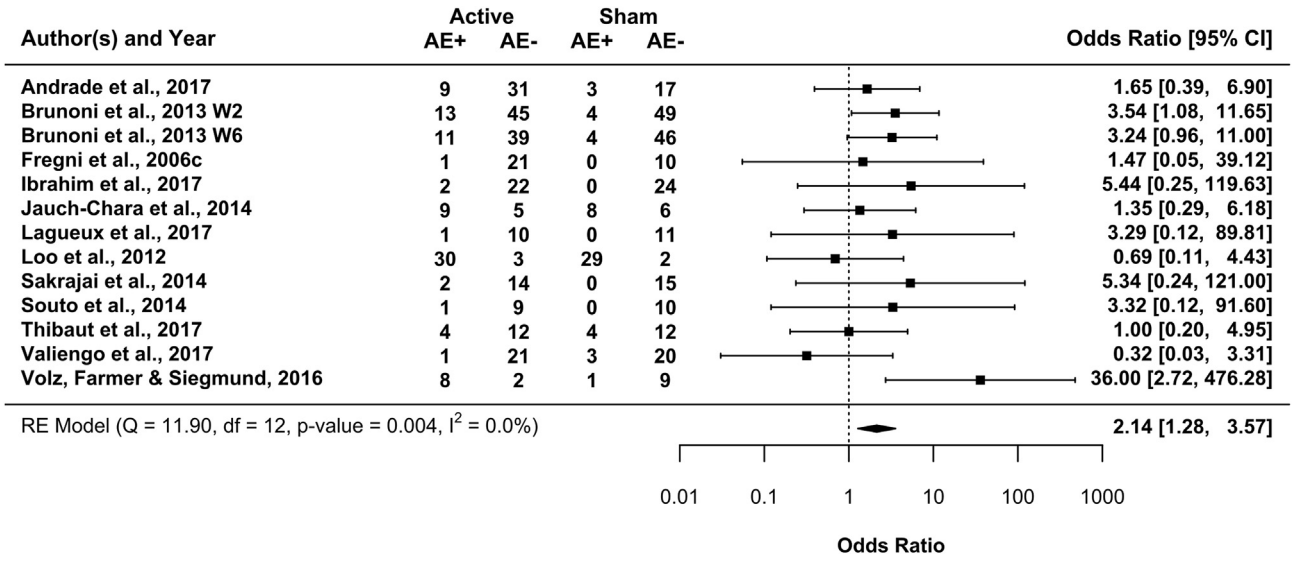

Fig. 2. Forest plot of studies used to calculate summary odds ratios (ORs) for incidence of erythema (i.e. skin redness) using a random effects (RE) model. An OR > 1 indicates increased likelihood of an adverse event in the active condition, while an OR < 1 indicates that the adverse event is more likely to occur in the sham condition.

most commonly reported AEs [22,35–39]. Outcomes of the meta-regressions based on these odds ratios are summarised in Supplementary Table 2. None of the AEs analysed showed a significant effect of cumulative charge (see Fig. 1 for bubble plots of most commonly reported AEs: discomfort, erythema, fatigue, headache, and paraesthesia). Monte-Carlo simulations were performed to estimate the number of studies and sample size required for cumulative charge to achieve significance (see Supplementary Table 3).

Participant incidence analysis

Of the sham-controlled studies identified in the systematic review, 44 provided data on the number of participants who experienced AEs within the active and sham conditions. Similar to the session incidence analysis, from these 44 studies odds ratios were calculated for the likelihood of the most commonly reported AEs.

Summary odds ratios are provided for each AE, calculated without incorporating tDCS exposure, as seen in Supplementary Table 4. Only erythema and paraesthesia were found to be significantly more likely under active tDCS conditions (erythema: OR 2.14, 95% CI [1.28 3.57, p = 0.004, Fig. 2; paraesthesia: OR 1.52 95% CI [1.17 1.96], p = 0.0015, Fig. 3).

None of the meta-regression analyses examining the effect of tDCS exposure showed a significant increase in risk for active tDCS versus sham tDCS with greater cumulative charge. The results of these meta-regressions are summarised in Supplementary Table 5; see Fig. 4 for participant incidence rate bubble plots of most commonly reported AEs: discomfort, dizziness, erythema, fatigue, headache, and paraesthesia. Monte-Carlo simulations were performed to estimate the number of studies and sample size required for cumulative charge to achieve significance (see Supplementary Table 3).

Study incidence analysis

The number of studies (k) and participants (N) identified within the six diagnostic populations (i.e. Healthy, Pain Disorders, Stroke, Neurocognitive Disorders, Neuropsychiatric Disorders, and Other) are summarised in Table 1. The distribution of studies and their associated cumulative charge is shown in Fig. 5.

None of the diagnostic populations demonstrated a significantly increased risk of AEs in the active condition compared to sham (Table 2). Combining all diagnostic populations did not result in a significantly greater overall AE likelihood in active tDCS (Table 2).

Analysis of the effect of tDCS exposure (cumulative charge) showed no significant differences in any of the tertile groups for active compared to sham stimulation (Low: 1.54, 95% CI [0.16 19.84], p = 1.000, n = 30, median cumulative charge = 6C; Medium: 1.14, 95% CI [0.37 3.60], p = 1.000, n = 32, median cumulative charge = 12C; High: 1.64, 95% CI [0.55 5.05], p = 0.454, n = 36, median cumulative charge = 24C; see Fig. 6A).

For the conservative approach, which assigned AEs to the active tDCS condition unless otherwise specified, Low and Medium levels of cumulative charge were not found to have a significantly higher likelihood of AEs in the active tDCS group compared to sham (Low: 4.11, 95% CI [0.70 44.04], p = 0.148, n = 32, median cumulative charge = 6C; Medium: 1.71, 95% CI [0.62 4.83], p = 0.352, n = 40, median cumulative charge = 12C). Studies that used the highest levels of cumulative charge, however, had a significantly higher likelihood for AEs with active tDCS (OR = 4.68, 95% CI [1.69 13.98], p = 0.002, n = 43, median cumulative charge = 24C; see Fig. 6B).

Discussion

This systematic review and meta-analysis investigated AEs associated with repeated sessions of tDCS in sham-controlled studies using cumulative charge as a measure of stimulation exposure. Analysis of studies that reported detailed incidence rates in terms of numbers of sessions or participants in which AEs occurred indicated no effect of cumulative charge across any of the AEs examined. Likewise, analysis of studies that reported less detailed study incidence data indicated no effect of cumulative charge. None of the diagnostic groups were found to have higher rates of AEs in active tDCS compared to sham. To our knowledge this is the first meta-analysis to systematically assess AEs with repeated sessions of tDCS using detailed reporting of diagnostic group, per session and per participant incidence rates, and examine the effect of cumulative tDCS exposure. Our assessment suggests

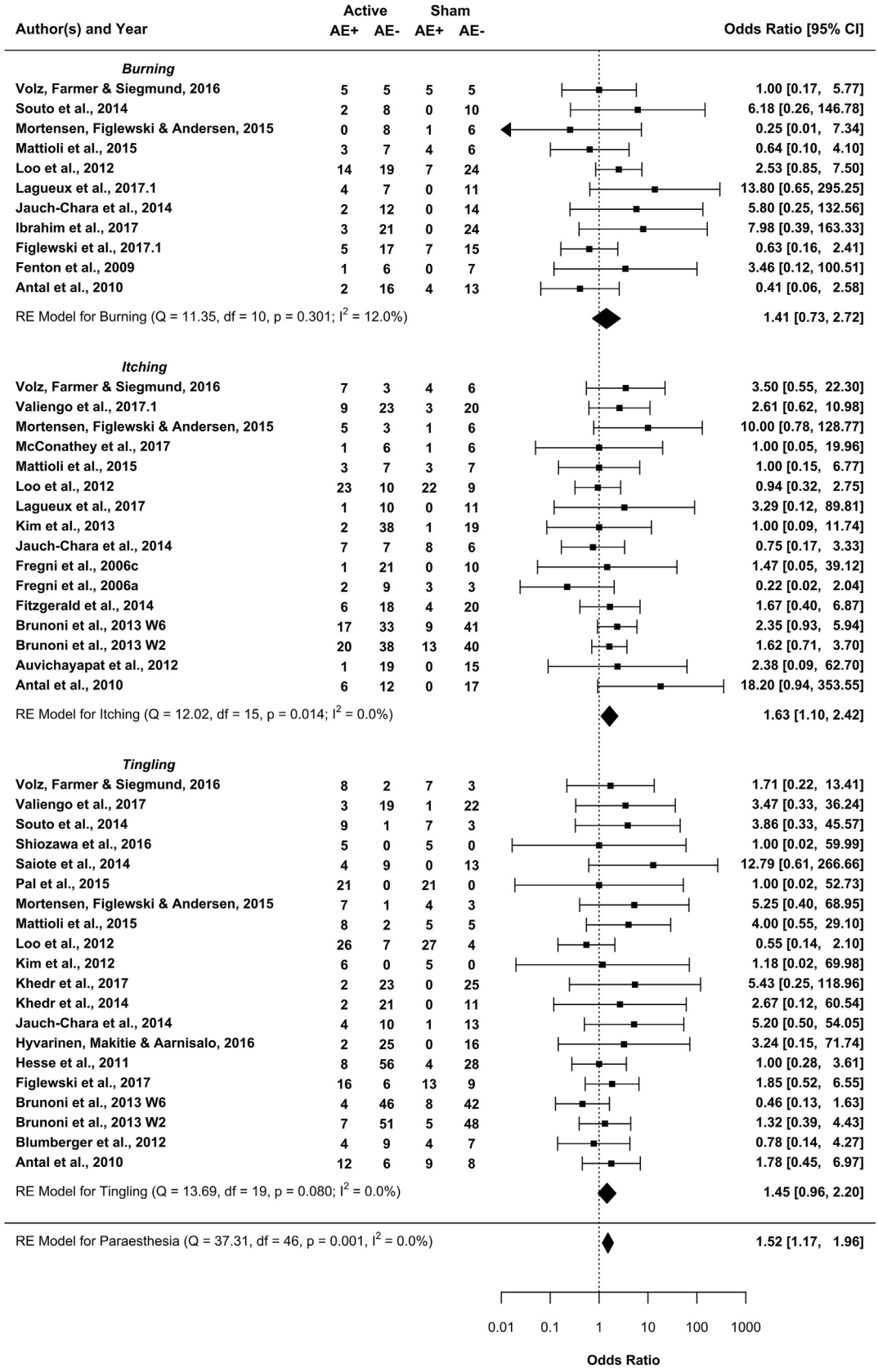

Fig. 3. Forest plot of studies used to calculate summary odds ratios (ORs) for incidence of paraesthesia, comprising the sensations of burning, itching, and tingling using a random effects (RE) model. An OR > 1 indicates increased likelihood of an adverse event in the active condition, while an OR < 1 indicates that the adverse event is more likely to occur in the sham condition.

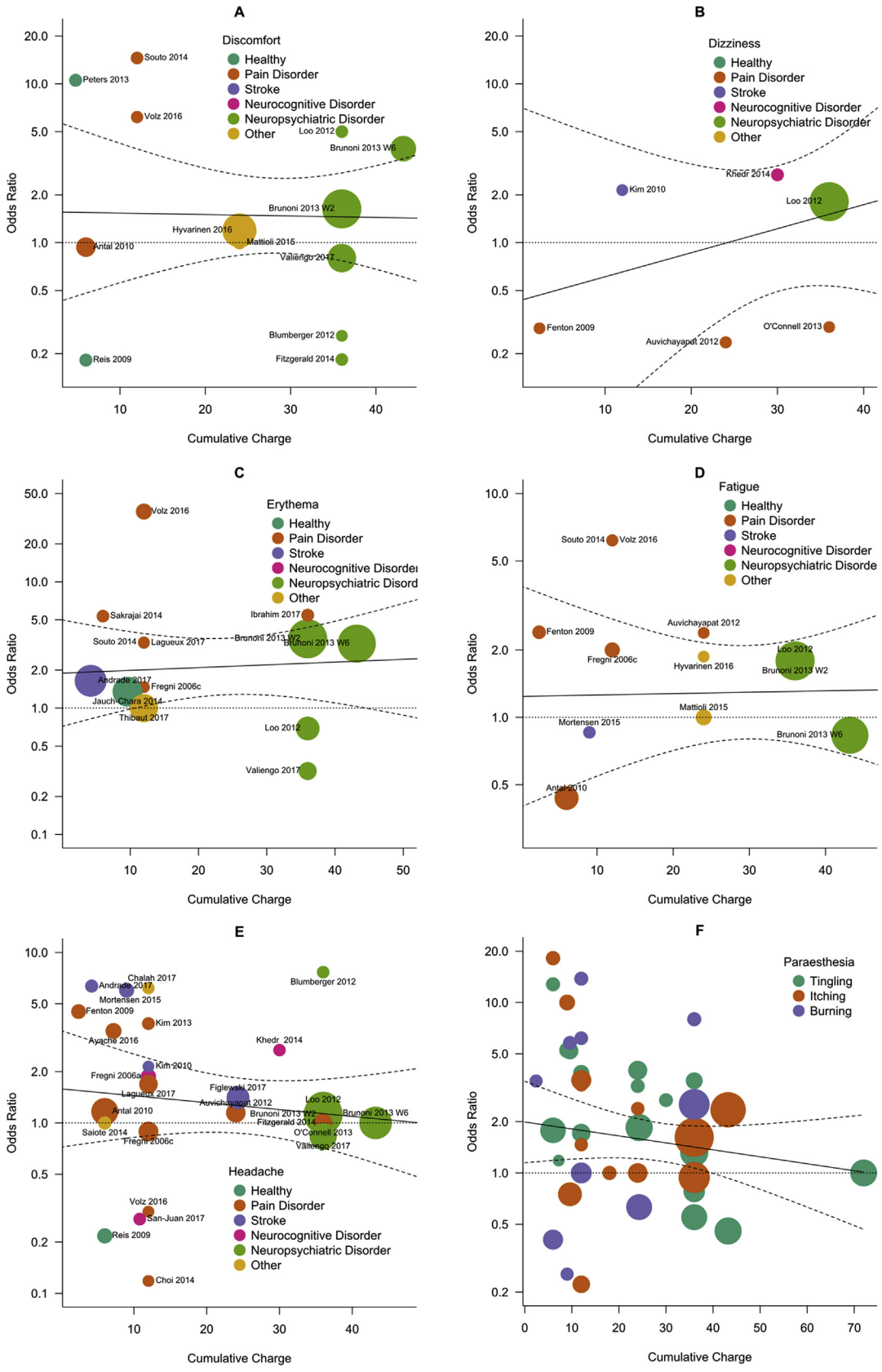

Fig. 4. Weighted bubble plots displaying the odds ratios (OR) for AEs in active tDCS versus sham tDCS, plotted against the cumulative charge experienced during the course of each study for studies reporting AE incidence rates (i.e. incidence rate data). The size of each bubble is proportional to the magnitude of the inverse of the variance of the OR in the log scale (e.g. the larger the bubble the greater the weighting assigned to the study during regression analysis). The solid line represents simple linear univariate meta-regression outcomes fit to the data, with dotted lines showing the 95% confidence interval. AEs graphed include: A) Discomfort; B) Dizziness; C) Erythema; D) Fatigue; E) Headache; and F) Paraesthesia (the plot for paraesthesia has been split into the comprising symptoms rather than studies, as for previous plots, for the sake of simplicity).

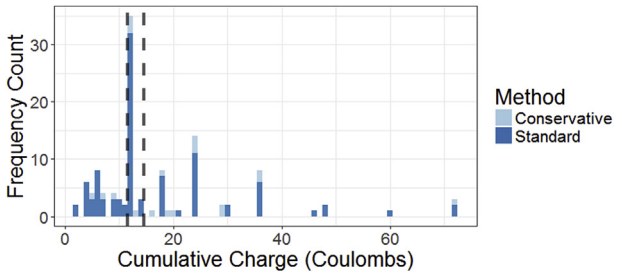

Fig. 5. Number of studies using repeated sessions by cumulative charge. Frequencies were tallied for studies that specified in which condition an adverse event occurred (Standard), as well as assigning AEs to active tDCS for studies that did not specify in which condition they occurred (Conservative). Grey dotted lines indicate the criteria used to categorise studies into Low (2–12 Coulombs (C); median = 6C), Medium (12–14C; median = 12C), and High (16–72C; median = 24C) tertile categories.

that there is little current evidence for an increase in AE risk with greater exposure to tDCS, within the parameters studied.

The safety of repeated, consecutive sessions of tDCS has not been systematically examined, and as such any concerns are at present speculative and grounded in theoretical concepts. For example, persistent skin lesions have been identified as a potential 'persistent adverse effect' of tDCS in a recent safety review, in which the authors also note that repeated sessions may have been a causal factor [40]. AEs such as fatigue, dizziness, and headaches may be related to changes in cerebral blood flow caused by tDCS [41,42], and it is unknown whether repeated sessions of tDCS can produce lasting changes that increase susceptibility to these adverse events. Consecutive sessions of tDCS have been demonstrated to enhance processes linked to plasticity [43]. This capability is thought to be responsible for tDCS's ability to restore and normalise pathological or physiological plasticity impairing brain functioning in patient populations, and to augment cognition in healthy participants [44]. Indeed, a recent study showed normalisation of impaired plasticity in depressed participants who received a 4-week course of tDCS [45,46]. It is theoretically conceivable, therefore, that repeated sessions of tDCS could also cause a shift to a similar, maladaptive, state of plasticity resulting in detrimental outcomes. Further, there is preliminary evidence to suggest that cognitive enhancement resulting from tDCS may come at the cost of a decline in other cognitive abilities [47]. Identification of such an effect is difficult as most tDCS studies of cognition examined outcomes on only a few select tasks and may therefore miss unexpected changes to cognitive domains not examined [48]. Comprehensive cognitive testing is therefore needed in future studies involving repeated exposure to tDCS to remedy this gap in the literature.

This study did not, however, find that higher tDCS exposure increased the risk of AEs, despite analysis of data within a range of cumulative charge extending from 2.4C [49] to 72C [36,50]. The present review, however, cannot rule out increased frequency or worsening of these common AEs, nor less common AEs, following tDCS exposure at levels higher than those examined. Although not included in the quantitative analysis, a case report of long term maintenance tDCS for auditory hallucinations in schizophrenia was identified in the systematic review [51]. Encouragingly, it details the successful use of daily 3 mA domiciliary tDCS for almost 3 years (cumulative charge approximately > 5000C), though reporting of safety was limited to "no adverse events attributable to tDCS". Case reports such as these provide pilot data that tDCS may be safe when given beyond the 1–4 weeks of stimulation typically involved in clinical trials. However, data from comprehensive assessments in carefully monitored trials is needed to conclusively demonstrate the safety of tDCS at higher cumulative charges.

Interestingly, analysis of study incidence data using a conservative approach, which assigned non-specific reports of AEs into the 'active tDCS' category, indicated that studies with the highest cumulative charges were associated with significantly increased risk. However, it is likely that the incidence of AEs was overestimated in this conservative approach. The discrepancy between results based on specifically reported absence or presence of AEs (excluding studies that did not provide this information), and the conservative approach (which assumed AEs were attributable to active tDCS where ambiguous), highlights the importance of clear safety reporting within studies, specifically, that provision of adequate information is necessary for an accurate appraisal of an intervention's safety profile. Omission of safety outcomes from publication, regardless of the reason, could lead to an underestimation of the risks associated with tDCS.

Importantly, regardless of the analysis approach used, AE incidence rates did not significantly differ between active and sham conditions according to diagnostic population, suggesting a comparable level of risk across participants. Vulnerable populations such as children [52], or pregnant participants [53,54], were beyond the scope of this review and thus their susceptibility to tDCS remains unknown, though preliminary studies have suggested similar incidence rates and pattern of AEs to those observed in the broader tDCS literature [55].

Although none of the AEs examined showed increased risk with greater cumulative charge, using participant incidence rate data both erythema and paraesthesia were more likely to occur in active conditions as compared to sham. These AEs are generally not considered severe enough to warrant concern from a safety perspective. However, their presence may undermine the integrity of blinding procedures used and therefore compromise study outcomes. This is not a novel finding, and has led to suggestions that experiments be modified to incorporate de facto masking (i.e. presenting both active and sham tDCS as 'active' to participants) and completion of participant ratings prior to electrode removal to prevent skin redness from unblinding investigators [56,57].

A number of excellent articles have examined the safety of tDCS [2–4,20,36,40]. Bikson et al. [4] conducted an evidence-based update of tDCS safety, including 1097 studies using repeated sessions in their analysis (defined by the authors as protocols consisting of three to seven sessions per week for at least one week). Though the authors did not assess the influence of cumulative charge, or a similar metric approximating the impact of consecutive tDCS sessions, they note that they were unable to identify any record of a serious AE among the subjects receiving repeated sessions of tDCS. In their systematic review of tDCS safety, Brunoni et al. [3] included a sub-analysis of the influence of session frequency on adverse outcomes and obtained a non-significant result. Our results agree with this finding and only suggest a possible increase in likelihood of AEs under active tDCS conditions for the highest tertile of cumulative charge, but this was based on a conservative approach, which probably over-estimated AEs. As part of their analysis, studies meeting inclusion criteria were categorised according to their design into "repeated session" and "1–2 sessions" groups, allowing comparison of the number of studies reporting AEs versus those not reporting any. The study-level analysis conducted in the present review closely resembles this approach, but differs in that studies were divided into groups according to cumulative charge. Thus, the present analysis provides a more detailed assessment of the impact of tDCS exposure, therefore extending previous assessments of tDCS safety.

Table 2
Odds ratios displaying the likelihood that a study will report any AE in the active tDCS condition versus the sham tDCS for each diagnostic population. p-values calculated using a 2-tailed Fisher's exact test.

Population	Studies reporting AEs	Studies reporting no AEs	Odds Ratio	95% Confidence Interval	p-value
Healthy			1.00	0.01–83.29	1.000
Active	16	1			
Sham	16	1			
Pain Disorder			1.83	0.30–13.47	0.700
Active	20	3			
Sham	18	5			
Stroke			1.00	0.23–4.37	1.000
Active	11	8			
Sham	11	8			
Neurocognitive Disorder			N/A	N/A	1.000
Active	5	0			
Sham	4	1			
Neuropsychiatric Disorder			1.00	0.10–9.94	1.000
Active	8	3			
Sham	8	3			
Other			1.70	0.45–6.65	0.550
Active	15	8			
Sham	12	11			
All Populations			1.37	0.69–2.73	0.419
Active	75	23			
Sham	69	29			

Limitations

As with most meta-analyses, compromises were made when grouping studies to allow meaningful comparisons. In the present study, factors such as electrode montage (cranial versus extracephalic), symptom improvement in clinical populations which could alter likelihood of AEs (e.g. mood improvements in depression may be associated with reduced fatigue), and participant blinding (e.g. expectation of a sham condition may reduce perception of AEs), were not assessed and warrant further exploration.

Reporting of adverse event severity in the studies reviewed was inconsistent, did not necessarily conform to pre-existing guidelines delineating categorisation of symptom severity [58] and was therefore problematic to analyse. As such, it is difficult to rule out whether severity of symptoms experienced by participants became more prominent whilst the likelihood of AEs remained relatively consistent with greater cumulative charge.

It was beyond the scope of this review to identify and rule out the possibility that a subsample of participants within each study may have been intrinsically more sensitive to the effects of tDCS, and thus responsible for the majority of findings. Participants within this subgroup could present with worsening AEs as the cumulative charge and number of repeated sessions increases, without altering the overall odds ratio calculations, thus masking a potentially concerning outcome. Such a scenario is difficult to examine due to the rarity and inconsistency of reporting of AE severity in the tDCS literature.

Conclusion

This systematic review and meta-analysis found little evidence to suggest that increased exposure to tDCS poses a serious risk to

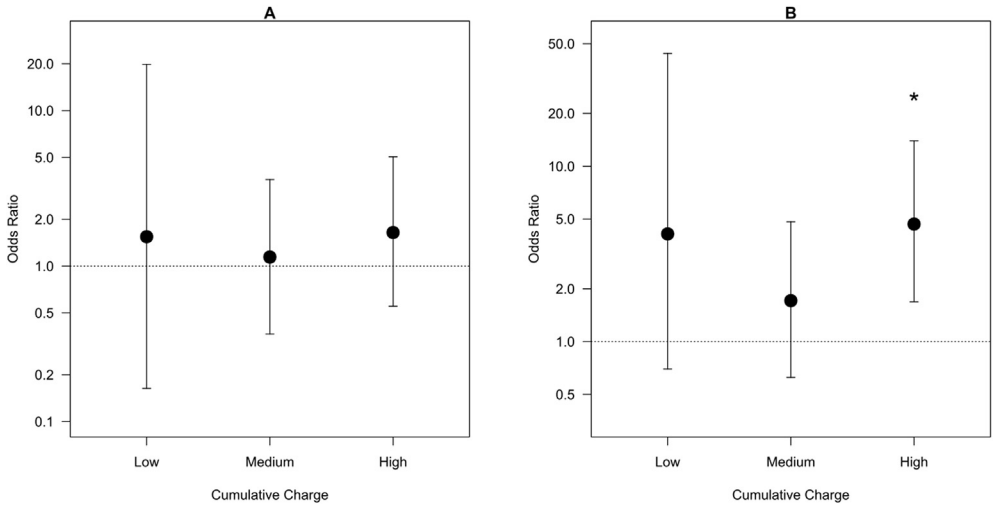

Fig. 6. Odds ratios (OR) for studies divided into groups based on cumulative charge experienced by participants. An OR larger than one represents greater incidence of AEs in active tDCS, whereas values less than one show greater likelihood under sham conditions. A) ORs calculated for tertile groups (Low: <12C, n = 30; Medium: 12–14C, n = 32; and High: >14C, n = 36) omitting studies that did not specify in which condition an AE was present. B) ORs calculated for tertile groups (Low: <12C, n = 32; Medium: 12–16C, n = 40; and High: >16C, n = 43) using a conservative approach that assigned ambiguously worded AEs to the active condition. Error bars represent 95% confidence intervals. *p < 0.005.

participants. Importantly, lack of significance must not be interpreted conclusively as a lack of effect of cumulative charge on AEs. While there does not seem to be sufficient evidence of a positive relationship between cumulative charge and the incidence of AEs in active tDCS, the data cannot conclusively rule out an increase in risk at higher doses beyond those analysed. No diagnostic populations were found to be particularly susceptible to AEs, however, this analysis did not include vulnerable groups such as children, or pregnant participants, for which there is limited data. More broadly speaking, this analysis agrees with the growing consensus that the AEs associated with tDCS are either rare [40], or mild [3,4], leading to a high degree of tolerability [2,20].

Echoing the previously published recommendations of Bikson et al. [4] and Brunoni et al. [3], we suggest that tDCS researchers actively collect data on participant side effects on a session-by-session basis for severity, causality, as well as AE type. Additionally, we recommend that this information be published to a publicly available data sharing site, such as GitHub (https://github.com) to facilitate future analyses of tDCS safety. We have elected to make the data accumulated in this review, including custom developed scripts for generating tables and graphs, open to researchers using the GitHub platform (source code available at: github. com/snikolin/safetyrepeatedsessions). It is our hope that researchers will voluntarily add their data to this database so that a clearer picture of the AEs associated with tDCS will emerge over time.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2017.10.020.

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