

Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability

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Meron, D., Hedger, N., Garner, M. and Baldwin, D. S. (2015) Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neuroscience and Biobehavioral Reviews*, 57. pp. 46-62. ISSN 0149-7634 doi: <https://doi.org/10.1016/j.neubiorev.2015.07.012> Available at <http://centaur.reading.ac.uk/87284/>

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To link to this article DOI: <http://dx.doi.org/10.1016/j.neubiorev.2015.07.012>

Publisher: Elsevier

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PII: S0149-7634(15)00197-9
DOI: <http://dx.doi.org/doi:10.1016/j.neubiorev.2015.07.012>
Reference: NBR 2237

To appear in:

Received date: 12-2-2015
Revised date: 24-7-2015
Accepted date: 26-7-2015

Please cite this article as: Meron, D., Hedger, N., Garner, M., Baldwin, D.S., Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability, *Neuroscience and Biobehavioral Reviews* (2015), <http://dx.doi.org/10.1016/j.neubiorev.2015.07.012>

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Highlights

- We identified 10 RCTs ($N=393$) of tDCS as treatment for MDE
- tDCS was superior to sham tDCS ($k=11$, $g=0.30$, 95% CI=[0.04, 0.57], $p= .027$)
- $N = 346$ to detect (80% power) this effect ($N = 49 / N = 12693$ for bounds of CI)
- Current data do not support the use of tDCS in treatment resistant depression
- Larger studies over longer periods of treatment are needed

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4 **Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-**
5 **analysis of efficacy and tolerability**
6

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37 **ABSTRACT**
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41 **Background** : Transcranial direct current stimulation (tDCS) is a potential alternative treatment option for major
42 depressive episodes (MDE). **Objectives**: We address the efficacy and safety of tDCS in MDE. **Methods**: The
43 outcome measures were Hedges' g for continuous depression ratings, and categorical response and remission
44 rates. **Results**: A random effects model indicated that tDCS was superior to sham tDCS ($k=11$, $N = 393$, $g=0.30$,
45 95% CI=[0.04, 0.57], $p= .027$). Adjunctive antidepressant medication and cognitive control training, negatively
46 impacted on the treatment effect. The pooled log odds ratios (LOR) for response and remission were positive, but
47 statistically non-significant (response: $k= 9$, $LOR = 0.36$, 95% CI[-0.16, 0.88], $p = .176$, remission: $k= 9$, $LOR =$
48 0.25, 95% CI [-0.42, 0.91], $p = .468$). We estimated that for a study to detect the pooled continuous effect
49 ($g=0.30$) at 80% power ($\alpha = .05$), a total N of at least 346 would be required (with the total N required to
50 detect the upper and lower bound being 49 and 12693 respectively).
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4 **Conclusions:** tDCS may be efficacious for treatment of MDE. The data do not support the use of tDCS in
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6 treatment-resistant depression, or as an add-on augmentation treatment . Larger studies over longer treatment
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8 periods are needed.
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11 Key words: Depression, meta-analysis, non-pharmacological therapies, systematic review, transcranial direct
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13 current stimulation, tDCS, Response, Remission, Cognitive Control Training.
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16 17 **1. BACKGROUND**

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21 Depressive disorders are prevalent, recurrent, often run a chronic course, and are associated with significant
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23 worldwide morbidity and mortality^{2,3}. Treatment with antidepressant medication is often suboptimal in terms of
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25 efficacy, safety and tolerability^{4,5}. Psychological interventions are associated with significant rates of suboptimal
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27 effectiveness, even when combined with antidepressant medication⁶. Electro-Convulsive Therapy (ECT) is highly
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29 effective, but is associated with significant stigma, and adverse effects⁶. Other invasive and non-invasive
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31 neurostimulation modalities have been proposed for the treatment of depression, but their utility may be limited
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33 by issues such as cost, tolerability and availability⁷. In particular, there are important differences between tDCS and
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35 repetitive transcranial magnetic stimulation (rTMS) in terms of adverse effect profiles, focality of stimulation, and
36
37 also in the cost, availability and portability of equipment⁷. Trans-cranial direct current stimulation (tDCS) is a novel
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39 treatment modality for depression, which may represent an alternative to pharmacological or psychological
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41 treatments. tDCS is a non-invasive brain stimulation modality, which changes cortical tissue 'excitability' as a
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43 result of applying a weak (0.5–2mA) direct current via scalp electrodes overlying targeted cortical areas. In
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45 contrast to other neurostimulation modalities, tDCS does not directly trigger action potentials in neuronal cells,
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47 but instead changes overall tissue excitability, and therefore may be more aptly regarded as a 'neuro-modulatory'
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49 rather than a neuro-stimulatory approach ⁷. Cortical tissue underlying the anode (positive electrode) becomes
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51 hypo-polarized, and therefore hyper-excitable; areas underlying the cathode (negative electrode) become less
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53 excitable as the average resting potential becomes more polarized. The magnitude of these membrane
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55 polarization changes is not in itself sufficient to directly cause neurons to fire ⁸. These effects continue after
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57 electrical stimulation ceases, and a single application can be associated with tissue excitability changes lasting
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59 more than 60 minutes ^{9,10}. These findings suggest tDCS is likely to be associated not only with transient membrane
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61 polarization changes, but also with longer-lasting synaptic changes ¹¹.
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4 The body of research describing the efficacy, safety and tolerability of tDCS in depression is growing. Three earlier
5 meta-analyses have been published¹²⁻¹⁴, these used different methodologies and produced inconsistent findings.
6 We therefore performed a systematic review and meta-analysis of the efficacy and tolerability of tDCS in
7 depression, using a comprehensive set of meta-analytic tools, and incorporating all published randomised
8 controlled trials to date.
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15 2. METHOD

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17 A literature search and meta analysis were conducted following the recommendations of the Cochrane
18 collaboration¹⁵ and the *PRISMA* guidelines¹. Two authors (DM and NH) performed the systematic review and data
19 extraction. All discrepancies were resolved by consensus.
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24 2.1 LITERATURE REVIEW

25 We searched the PubMed database using the following search strategy:

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27 ((((((“direct”[Title/Abstract]) AND “stimulation”[Title/Abstract])) OR “tdcs”[Title/Abstract])) AND
28 (“rand*”[Title/Abstract]) OR “control*”)) AND “depress*”[Title/Abstract]. The date range extended up to April 30th,
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30 2015. We also scrutinized the reference lists in published meta-analyses of tDCS in depression and articles listed
31 as citing these meta-analyses¹²⁻¹⁴.
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35 Inclusion criteria used were: English language publications; Randomised, sham-controlled trials. Including data
36 enabling calculation of effect size for depression rating scale change, and/or response/remission rates. Patient
37 population with depressive disorders. tDCS as monotherapy or augmentation therapy for treatment of depression.
38 Exclusion criteria used were: Studies in animals. Non-controlled or non-randomised trials. Case reports / case
39 series. Trials of treatments for disorders other than depression. Trials of interventions other than tDCS. Duplicated
40 data-sets.
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48 2.2 DATA EXTRACTION

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50 The following data were extracted: Population demographics including sample size. Diagnosis (unipolar/bipolar
51 depression). tDCS characteristics (including number of sessions, montage, current used, inter-session intervals,
52 sham stimulation characteristics). Efficacy outcome measures and outcomes (Including rating scale score changes
53 and response/remission rates). Acceptability (using dropout numbers as a proxy measure).
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4 Outcome measures included both continuous depression rating scale scores, and categorical response/remission
5 rates – we included both types of outcome for the following reasons: First, previous meta-analyses utilised
6 continuous outcome measures ¹², categorical outcome measures ¹³, or both ¹⁴, which may explain the inconclusive
7 and at times contradictory nature of their findings. Second, whereas continuous outcome measures may offer
8 superior sensitivity, their specificity is considered inferior to that of categorical outcome measures. Third, while
9 categorical response/remission rates may be more clinically ‘meaningful’, they require larger sample sizes, and as
10 all studies included in our meta-analysis utilised continuous primary outcome measures, they may have lacked
11 sufficient statistical power to reliably test hypotheses based on categorical outcomes.
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21 We therefore extracted the following data: for continuous outcomes we meta-analysed depression rating scale
22 scores at randomised blinded treatment endpoint, using the study primary outcome measure rating scale; for
23 categorical outcomes, we meta-analysed remission and response rates for active and sham groups at randomised
24 blinded treatment endpoint. Response was defined as $\geq 50\%$ reduction in depression rating scale score from
25 baseline to endpoint; we used the specified remission criteria provided by each study.
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32 2.3 META ANALYSIS

33 Our adopted meta-analytic approach makes several important contributions to the literature (Table 2). We:

- 34 1. increase the number of included RCTs and subjects, compared to previous meta-analyses.
- 35 2. use a methodology combining continuous outcome measures (rating scale scores) with possibly more
36 clinically relevant dichotomous measures (i.e. response and remission rates).
- 37 3. perform moderator analyses to clarify the effect of putative moderators identified in narrative analysis.
- 38 4. perform power and precision analyses to inform future research in terms of sample size planning.
- 39 5. identify important gaps in knowledge and suggest new directions for future research, methodological
40 improvements and improved reporting standards.
- 41 6. Examine the use of tDCS in conjunction with antidepressant medication and with Cognitive Control
42 Training (CCT)
- 43 7. clarify in which conditions tDCS might be clinically useful.
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57 The primary effect size index used to quantify the continuous treatment effect was Hedge’s g – the difference in
58 the reduction in depression severity rating scale scores (MADRS and/or HDRS) between the two groups (active
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4 tDCS – sham tDCS). This was calculated by subtracting the Hedge's g for the difference in depression ratings
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6 between groups before treatment from the corresponding difference immediately after treatment. A positive value
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8 of g represents a larger decrease in depression severity rating in the treatment group, relative to the control
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10 group. Our choice of standardizer for g was the pooled within-groups SD (SD_{pooled}), as this has more degrees of
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12 freedom (since it is derived from two groups) than other standardisers and is thus likely to be the most precise
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14 estimate of the population SD . We chose the "bias corrected" Hedges g since it provides superior point estimates
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16 over Cohen's d which inflates point estimates for small samples. However, following best practice, our confidence
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18 intervals were uncorrected, since simulations show that confidence intervals on d provide more accurate interval
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20 estimates¹⁶. For each study, we computed g and 95% confidence intervals by using a combination of means,
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22 standard deviations, independent samples t , p and F statistics using the R programming language. In practice,
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24 these were the same routines implemented by the widely used Comprehensive Meta Analysis Software (CMA:
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26 Biostat, Englewood, NJ).

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28 We performed two additional meta-analyses to quantify the overall treatment effect in terms of categorical
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30 response and remission rates⁴. In both cases, we compared the differences between treatment and control groups
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32 by using the log odds ratio as an effect size index. A positive score represents a higher likelihood of response or
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34 remission in the treatment (active tDCS) group, relative to the control (sham tDCS) group. Response was defined as
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36 50% reduction in depression rating scale score from baseline to endpoint. We used the remission criteria provided
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38 by each study.

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41 As previous meta-analyses have indicated considerable heterogeneity in effect size estimates between studies¹²,
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43 we made an *a priori* decision to analyse our effect size data using a random effects model, due to its tolerance of
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45 heterogeneous effect sizes and conservative nature of estimation^{16,17}. The random effects model assumes that
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47 each study estimates different values from a distribution of population parameters, rather than assuming studies
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49 are direct replications of each other. We assessed heterogeneity across effect sizes by using Cochran's Q and I^2
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51 statistics. Unless reported otherwise, parameter estimates were obtained via restricted maximum likelihood
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53 estimation, due to its accuracy relative to other estimators with smaller numbers of studies¹⁸. Statistical tests of
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55 model coefficients were computed via Wald-type chi squared tests. We additionally used a pseudo- R^2 statistic to
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57 assess the amount of heterogeneity between effects explained by including moderators¹⁹. R^2 estimates the
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59 proportional reduction in heterogeneity after including moderators. For interpretation, it is important to note that
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61 this pseudo- R^2 does not include sampling variability, meaning that it is possible to get very large R^2 values, even
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4 when there are discrepancies between the model and the observed effects (provided these are not larger than
5 expected by sampling variability). Model comparisons were conducted via likelihood ratio tests. All meta analyses
6 were performed using the "metafor" package in R²⁰.
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11 To account for heterogeneity across treatment effects, we assessed the impact of potential categorical and
12 continuous moderators of the treatment effect. The moderators we examined are listed in table 1. Moderator data
13 for each study were recorded in a structured fashion. Where the information was reported, we recorded both
14 categorical moderators and continuous moderators. Two experienced authors (NH, DM) acted together as coders,
15 and no disagreements on coding decisions were encountered.
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Potential moderator	Units	Descriptive Statistics
Current	mA (Boolean)	<i>k</i> = 11 1mA (<i>k</i> = 2) 2mA (<i>k</i> = 9)
Course delivered	Number of sessions	<i>k</i> = 11 <i>M</i> = 9.55 <i>SD</i> = 3.50 Range = 5-15
Session duration	Minutes per session (Boolean)	<i>k</i> = 11 20 mins (<i>k</i> = 7) 30 mins (<i>k</i> = 4)
Total tDCS time	Number of sessions x session duration (minutes)	<i>k</i> = 11 <i>M</i> = 229.09 <i>SD</i> = 87.80 Range = 100- 300
Total current delivered	mA x number of sessions x session duration	<i>k</i> = 11 <i>M</i> = 430.91 <i>SD</i> = 210.97 Range = 100- 600
Inter-session intervals	Days (Boolean)	<i>k</i> = 11 1 day (<i>k</i> = 9) 2 days (<i>k</i> = 2)
Diagnosis		<i>k</i> = 11 unipolar (<i>k</i> = 9) unipolar and bipolar (<i>k</i> = 2) <i>k</i> = 11
Concurrent anti-depressant medications (ADMs)		Concurrent ADMs (<i>k</i> = 8) No-concurrent ADMs (<i>k</i> = 3)
Concurrent cognitive control therapy (CCT)		<i>k</i> = 11 Concurrent CCT (<i>k</i> = 2) No concurrent CCT (<i>k</i> = 9)
Treatment resistance level	Number of previous courses of antidepressants failed in current episode	<i>k</i> = 9 (see table 3)

Table 1: variables examined as potential moderators of tDCS outcomes in depression. These include both participant-related and tDCS-related factors, with a view to enable meta-analytical examination of the variables found to be associated with tDCS outcomes in the narrative analysis.

Additional analyses: publication bias, precision and power

To assess the impact of the so-called "file drawer problem", whereby unpublished null results can distort meta-analytic estimates, we performed 'fail-safe N ' analyses using the methods developed by Orwin²¹ and Rosenthal²². This allowed estimation of the total number of unpublished studies averaging null effects that would be required to reduce the reported treatment effect size to target levels²¹ or to statistical non-significance²². Despite the existence of other meta-analyses estimating the magnitude of tDCS efficacy, to date there has been no formal, explicit attempt to use these parameter estimates to inform future research planning. We hence addressed this issue from both an Accuracy In Parameter Estimation (AIPE), and power analytic perspective. The AIPE analyses were used to estimate the appropriate sample size for future trials such that the expected width of the confidence interval meets a desired level of precision¹⁶. Unlike power analysis, this approach negates the need to invoke a null hypothesis significance test, and instead is solely concerned with precision in parameter estimation. This was achieved by using the non-central t method described by Kelley²³, implemented in the "MBESS" package in R²⁴. To provide an assessment of the statistical power of individual studies, we estimated the power of each study to detect the summary effect estimated in the meta-analysis at a nominal level of significance ($p=.05$). By extension, for future sample size planning, we calculated the minimum N required to achieve adequate (80%) power to detect the estimated summary effect.

3. RESULTS: EFFICACY

3.1 Randomized Controlled Trials (RCTs): We identified ten randomized controlled trials of tDCS in depression using PRISMA methodology (Figure 1a), and quality-assessed the each trial using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials²⁵ – this yielded an acceptable profile of Risk of Bias across the RCTs included in the meta-analysis (Figure 1b). Due to the diversity of study designs, we made the following decisions about the analysis of individual studies: 1. Boggio et al. (2008)²⁶ randomised participants to 3 groups: active tDCS over left DLPFC, sham tDCS over left DLPFC, and active occipital tDCS; we chose to exclude the occipital group from our meta-analysis. 2. In analyzing the Brunoni et al. 2013 trial²⁷, we separated the data from participants who received sertraline and those who received placebo medication – this created two separate effects (hence although we included 10 RCTs, we analyzed $k=11$ effects). 3. Segrave et al (2014)²⁸ randomised participants to 3 groups: 1.tDCS + Cognitive Control Training (CCT), or 2.sham tDCS + CCT, or 3. tDCS + sham CCT – For the purpose of this meta-analysis, we included only 2 of the 3 study arms – comparing tDCS+CCT vs. sham tDCS+CCT. 4. Several studies reported primary outcomes at endpoints which included a follow-up period after the

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4 end of active treatment course. For the sake of consistency, we analysed all available data at the point when active
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6 blinded treatment ceased.

7 8 9 **3.1.1 Fregni 2006²⁹.**

10 Study. A randomised double blind sham controlled trial in which 18 outpatients with (unipolar) MDD who had not
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12 been prescribed antidepressant medication for at least three months prior to inclusion were randomised to 2
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14 treatment arms: either active tDCS, in which the anodal electrode was placed over F3 (10–20 International EEG
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16 System), and the cathode over the right supra-orbital area, a current of 1mA being applied for 20 minutes on 5
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18 alternate days; or sham tDCS with similar settings, but the stimulator being switched off after 5 seconds. Outcome
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20 measures involved a battery of neuropsychological rating scales; mood was assessed with the HDRS. The active
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22 treatment group showed a significantly greater improvement in mood, mean Hamilton Depression Rating Scale
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24 (HDRS) scores reduced by 58.5% (+/-20.4%) vs. 13.1% (+/-23.4%) in the sham tDCS group [$F(1,16)=19.2$,
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26 $p<0.001$]. tDCS was generally well tolerated, and no complications were reported. The active tDCS group improved
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28 on all cognitive tests, compared to their baseline scores. There was no significant cognitive improvement in the
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30 sham tDCS group. Improvement in cognitive function in the treatment group was not correlated with the
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32 improvement in mood, suggesting that cognitive and affective changes were mediated by different mechanisms.

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35 Comment. Although involving a small number of participants, this study found evidence for antidepressant
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37 efficacy and tolerability of tDCS in MDD. The sample baseline characteristics were well defined, with moderate-to-
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39 marked baseline depressive severity (mean HDRS scores of 23.56+/-5.03 in the active tDCS group and 25.89+/-
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41 4.26 in the sham group), significant number of patients had recurrent or persistent illness.

42 43 44 **3.1.2 Boggio 2008²⁶.**

45 Study. Following this pilot study, the same group conducted a parallel-group, double-blind, initial clinical trial of
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47 tDCS in patients with unipolar depression who had not been prescribed antidepressants for at least two months
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49 prior to trial entry. Exclusion criteria included neurological disorders, comorbid Axis I disorders, substance abuse
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51 within three months of study participation, psychotic features, bipolar disorder and Axis II disorders. Forty
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53 patients were randomized into three treatment arms (using a 2:1:1 randomization strategy): active treatment, with
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55 anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) – anode over F3 on the 10–20 International EEG
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57 System, cathode over right supraorbital region ($N=21$); active control, with anodal tDCS of the occipital cortex –
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59 anode 2cm above Inion on the midline, cathode over right supraorbital region ($N=9$); or sham control with sham
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4 tDCS over left DLPFC, and cathode over the right supraorbital region, the stimulator being active for an initial 30
5 seconds only, with ramp-up and ramp-down to mask shamming ($N=10$). Patients received 10 sessions of tDCS on
6 consecutive working days (no treatment being given at weekends), the current was set at 2mA for 20 minutes in
7 each session. The primary outcome measure was the 21-item HDRS, the BDI being the secondary outcome
8 measure. Patients were rated at baseline, at end of treatment and at 15 and 30 days after treatment. tDCS was well
9 tolerated, reported adverse effects being mild (headache, itching or redness at electrode site) and not significantly
10 associated with group assignment. At the end of treatment, there was a significant difference between the active
11 treatment group and the active control group ($p=0.009$) and the sham control group ($p=0.0018$) in HDRS score;
12 but the control groups did not separate from each other ($p=0.6$). The active group maintained separation from the
13 sham control at the 30-day follow-up ($p=0.04$). BDI outcomes showed a similar pattern, with the active group
14 separating from the sham group at the end of treatment ($p=0.0045$, effect size (Cohen's d) = 1.11), and at 30-day
15 follow-up ($p=0.03$). There were 8 responders (HDRS scores reduced by at least 50% from baseline) in the active
16 treatment group, compared with 2 in the active control and none in the sham control groups ($p=0.019$). There
17 were 5 patients in remission (HDRS < 8) in the active treatment group, but none in the other two groups ($p=0.02$).
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32 Comment. This study was larger than previous studies of tDCS in depression and demonstrated both acute efficacy
33 and an effect lasting 30 days after treatment was stopped. The findings provide support for the use of left DLPFC
34 anodal stimulation. This was the first study to indicate that the therapeutic effect in depression is related to the
35 anodal effect at left DLPFC rather than to the cathodal effect at the right supra-orbital area. The tolerability of
36 active tDCS was not significantly different to sham stimulation.
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43 3.1.3 Loo (2010) ³⁰

44 This double-blind, sham-controlled trial of left prefrontal tDCS in depression involved 40 outpatients with DSM-IV
45 MDD with baseline MADRS (Montgomery-Åsberg Depression Rating Scale) score of 20 or more. Exclusion criteria
46 included diagnosis of bipolar disorder, drug or alcohol dependence or abuse, other Axis-I disorders, and
47 neurological disorders; or the failure to respond to ECT during the index episode. Subjects were either
48 medication-free, or had continued on the antidepressant drug to which they had not previously responded at a
49 stable dose, unaltered for at least 4 weeks prior to study enrolment (some patients were prescribed antipsychotic
50 drugs, and 1 patient was prescribed lamotrigine: none were prescribed benzodiazepines). Subjects were
51 randomised to: [i] active tDCS with anodal tDCS over left DLPFC (pF3 on the 10/20 EEG International System), the
52 cathode being placed over the right lateral orbital area: 1 mA of current was used for 20 minutes, with 30 seconds
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4 of ramping-up at onset; [ii] sham tDCS with a similar montage, the current being ramped down over 30 seconds
5 immediately after initial ramping up. Subjects in both arms underwent treatment three times weekly for five
6 treatment sessions. All subjects then received active tDCS for another five sessions (at the same frequency). After
7
8 10 sessions, the blind was broken and patients who had received sham tDCS in sessions 1–5 were then offered
9 another 5 sessions of active tDCS – bringing the total number of active tDCS sessions offered to all participants
10 (regardless of treatment arm assignment) to 10. The primary mood outcome measure was the MADRS, and
11 secondary outcome measures included the 17-item HDRS and Clinical Global Impression of Severity (CGI-S), the
12 patient-rated BDI and Patient Global Impression Scale of Improvement (PGI-I). Subjects were assessed at baseline,
13 after sessions 5, 10 and 15, and at 1-week and 1-month follow-up. Over the sham-controlled phase (sessions 1–
14 5) there were no significant between-group differences in mood outcomes ($p=0.87$ for MADRS). There were
15 statistically significant differences on all measures comparing baseline mood to mood after session 10, but no
16 significant differences between groups. There were 6 responders (MADRS score reductions of at least 50%) and 5
17 remitters (MADRS<11) in the active tDCS group, compared to 4 responders and 3 remitters in the sham group.
18 One patient in the sham tDCS group committed suicide on the day following his first active tDCS session: the
19 authors felt this was unlikely to have been related to the treatment this patient received (the patient had been
20 noted to have suicidal thoughts for some months prior to his death, the suicide occurred on the first instance
21 when he was briefly left on his own, and there were no emotional or clinical changes noted following the session
22 of active tDCS that he had received). Adverse effects reported by the active tDCS group included redness, itchiness
23 and tingling at electrode (mainly anode) sites; mild headaches, lightheadedness and ringing in the ears; visual
24 changes including blurring, brighter/illuminated vision; and mild euphoria, transient hypomania ($N=1$), nausea,
25 insomnia and anxiety. After session 10, subjects were asked to indicate whether they thought they had received
26 active or sham tDCS, there being no significant in the accuracy of identification between the two groups.
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47 Comment. This study used similar stimulation parameters to those used by Fregni et al 2006^{29,31} (five 20 minute
48 sessions at 1mA on alternate days with similar electrode montage,) but did not show a statistically significant
49 separation between active and sham tDCS groups. The efficacy of active treatment over 10 sessions was
50 comparable to that demonstrated by Boggio et al.²⁶ who used tDCS at higher intensity (2mA, 5 times weekly for 10
51 sessions). The main difference between this study and the earlier trials was the greater degree of improvement in
52 the sham tDCS group. Factors which may have contributed to this difference included the participation of patients
53 taking antidepressants and patients with co-morbid Axis II (personality) disorders. The degree of treatment
54 resistance in this cohort was only 'moderate' (mainly stage 0–III on the Thase & Rush system³², which may explain
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4 the magnitude of sham tDCS effects in this trial. The authors acknowledge that main weaknesses in this study,
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6 namely its short duration and the small number of treatments in the sham-controlled phase: they state that a
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8 longer sham-controlled phase would have been necessary to demonstrate a difference between active and sham
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10 tDCS. They suggest that future studies utilise tDCS at higher intensities (>1mA), with daily treatment sessions,
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12 over longer periods, in more treatment-resistant patients.
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15 **3.1.4 Palm (2011)** ³³

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17 This randomized double-blind placebo-controlled cross-over trial of tDCS in treatment resistant depression
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19 included 22 outpatients (14 women, 8 men: mean age 57 years): 20 with unipolar depression (17 with recurrent
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21 depression, and 3 with first-episode depression), and 2 patients with bipolar depression. All participants had
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23 failed to respond to at least two trials of antidepressants from different classes. Antidepressant medication was
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25 kept unchanged for at least 3 weeks before starting tDCS, and no medication changes were made during the
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27 study. Patients were randomized to two arms: [i] 10 sessions of active tDCS followed by 10 sessions of sham tDCS;
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29 [ii] 10 sessions of sham tDCS followed by 10 sessions of active tDCS. The anode was placed over left DLPFC (F3 on
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31 the 10-20 EEG international system), and cathode over right supraorbital region. The first 10 patients received
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33 stimulation sessions of 20 minutes at 1mA; the current setting was increased to 2mA for the subsequent 12
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35 patients. All patients received 20 tDCS treatments over 4 weeks. The sham stimulation included 15-second ramp-
36
37 up and ramp-down periods to simulate active tDCS sensations. Electrodes were soaked in tap-water for the initial
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39 15 participants, but this was changed to normal saline solution, due to skin lesions at stimulation sites. The
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41 primary outcome measure was the HAMD-24 at 2 weeks and 4 weeks, secondary outcome measures included the
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43 BDI, CGI, PANAS and a series of cognitive tests. Twenty patients completed the trial: no significant differences
44
45 were found between active and sham tDCS on the primary outcome measure – although modeling the HAMD
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47 course via mixed model analysis showed that active tDCS was superior to sham tDCS in weeks 1 and 2 ($p=0.0492$).
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49 Subjective mood ratings showed a significant advantage for active over sham tDCS in positive emotions on the
50
51 PANAS-pos and a trend for reduced negative emotions on the PANAS-neg. There were no significant between
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53 group differences in cognitive measures. Six of the 15 patients undergoing treatment involving use of tap-water
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55 soaked electrodes developed crusty skin lesions at the cathode site, but after normal saline solution was
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57 substituted, no further lesions were reported. Other adverse effects reported were minor, including slight
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59 headache and skin itchiness during treatment. Blinding integrity was not significantly different between groups.
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4 **Comment.** The failure of active tDCS to separate from sham tDCS in this study may have been influenced by the
5 small sample size, the change in treatment (from 1mA to 2mA) during the study, the cross-over design without an
6 intervening no-treatment period, the higher degree of treatment resistance (average failed antidepressant trials
7 2.9 vs. 1.0–2.6 in previous trials), the older age of patients (56 years, compared to 46–54 years in previous
8 studies), and the use of concomitant antidepressant medication.
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15 **3.1.5 Loo (2012)** ³⁴

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17 This randomised sham-controlled trial included 64 outpatients with DSM-IV defined major depressive episode
18 (MDE) in the context of both unipolar and bipolar depression, with baseline MADRS score of 20 or more. Exclusion
19 criteria included the presence of other Axis I mental disorders, excessive alcohol/drug use, neurological disorders,
20 metal implants, history of heart or neurological disease, failure to respond to ECT in the index episode, pregnancy,
21 and treatment with medications known to modulate tDCS effects (including benzodiazepines, anticonvulsants,
22 dextromethorphan and pseudoephedrine). Subjects were either antidepressant medication-free for the duration of
23 the trial, or continued on the antidepressants to which they had previously failed to respond (with no dose
24 changes for at least 4 weeks before starting tDCS). Subjects were randomized to receive either active tDCS at 2mA
25 for 20 minutes, with ramp-up and ramp-down for 30 seconds, or sham tDCS at 1mA for 30 seconds, with ramp-
26 up and ramp-down for 10 seconds. The anode was placed over left DLPFC (pF3 on the 10–20 EEG international
27 system), the cathode lateral to the right orbit (F8 on the 10–20 EEG international system). Treatments were carried
28 out five days per week for three weeks; each subject subsequently being offered another 15 sessions of open-
29 label active tDCS. Treatment responders (i.e. those whose MADRS scores reduced by at least 50% from baseline)
30 were offered further weekly sessions of tDCS during the 1-month follow-up period. The primary outcome measure
31 was the MADRS, assessed at baseline, after sessions 8, 15, 23 and 30, and at weeks 1 and 4 after trial completion.
32 Other measures included the IDS, CGI-S, QIDS-C, QIDS-SR, CORE and a set of neuro-cognitive assessment tools. A
33 significant interaction between group and time was seen on the primary outcome measure (MADRS scores), active
34 tDCS being associated with lower MADRS scores during the sham-controlled phase ($p=0.04$; effect size 0.49), but
35 there was no significant separation on other mood outcome measures. At 1-week follow-up, 16 out of 26 subjects
36 in the active tDCS group met criteria for response (reduction in MADRS of at least 50% from baseline) compared to
37 6 out of 26 in the sham tDCS group. The NNT for response at 3 weeks of active vs. Sham tDCS was 16.7; the NNT
38 for response at 6 weeks of active tDCS vs. 3 weeks of sham tDCS was 2.6. There was one reported case of
39 transient hypomania in the open phase of the trial (the patient had bipolar depression), other adverse effects were
40 transient and mild to moderate in intensity, including skin redness, burning sensation, tingling and itchiness at
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4 electrode sites, headache, dizziness and nausea. A blinding integrity test found no significant differences between
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6 groups.

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10 Comment. This trial included more participants and employed more robust treatment parameters (in terms of
11 number of sessions, duration of blinded treatment, current settings, and follow-up period) than previous tDCS
12 trials. Using the *a priori* primary outcome measure, this study confirmed that active tDCS has significantly greater
13 antidepressant effects than sham tDCS over the 3-week sham-controlled phase. The magnitude of antidepressant
14 effects (28% reduction in MADRS) was lower than in some previous studies^{26,31} but patients in those trials were
15 medication-free and the scope for tDCS-related improvement may have been greater in the absence of
16 medication: a meta-analysis of treatment with rTMS with and without concomitant medication showed a similar
17 finding³⁵. The number of responders after six weeks of treatment was superior to the responder rate reported in
18 the STAR*D trial (28.5%)⁴. The authors suggest that extending the treatment duration to 6 weeks may be associated
19 with additional gains (though it is unclear whether the benefit is associated with a higher number of treatments, or
20 with the extended duration of treatment). The study findings suggest a broadly equivalent effect size to that
21 observed with antidepressant medication, despite selection of patients with a moderate degree of treatment
22 resistance, many of whom were already taking antidepressant medication. The results suggest that more robust
23 tDCS treatment parameters, in terms of current, number of sessions and overall duration of treatments, may be
24 associated with better outcomes in depression.
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39 **3.1.6 Blumberger (2012)**³⁶

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43 This study explored the potential utility of tDCS in treatment-resistant depression. A total of 24 outpatients with a
44 diagnosis of DSM-IV defined major depressive episode (MDE), a baseline HDRS score greater than 20, and fulfilling
45 Stage II criteria (or above) on the Thase Scale for treatment resistance (i.e. failure to achieve remission or tolerate
46 at least two trials of antidepressants from different classes) were recruited. Adjuvant medication (including
47 antidepressants, antipsychotics and benzodiazepines) was permitted, providing dosage was stable for at least 4
48 weeks before study treatment started and throughout the duration of the trial. Exclusion criteria included
49 treatment with anticonvulsants, DSM-IV substance use disorder in the 6 months prior to potential trial
50 commencement, an unstable co-morbid medical condition, a history of seizures, pregnancy, and DSM-IV
51 borderline or antisocial personality disorder. Subjects were randomised to receive active ($N=13$) or sham ($N=11$)
52 tDCS. Treating clinicians were aware of treatment allocation, but patients and outcome assessors were blind to
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4 allocation. Fifteen treatment sessions were delivered on consecutive working days, over 3 weeks. The anode was
5 placed over the left DLPFC (F3 according to the 10–20 EEG system), the cathode over the right DLPFC (F4 according
6 to the 10–20 EEG system). Active treatment was delivered at 2mA for 20 minutes, the sham treatment included an
7 initial 30 second period of stimulation at 2mA, and the current was then turned off. The primary outcome measure
8 was change in HDRS from baseline to endpoint, secondary outcome measures including the proportion achieving
9 symptom remission (HDRS<8) or response to treatment (50% reduction in severity). There was no significant
10 difference between active and sham tDCS in the change in HDRS score ($p=0.80$): none of the subjects met HDRS
11 remission criteria, and only 1 subject in each group met response criteria; and there were no significant between-
12 group differences in MADRS change or in BDI-II change. No serious adverse events were reported during the trial,
13 though four subjects in each group reported skin tingling. Headache was reported by three subjects in the active
14 group and by none of the sham group subjects: 1 participant in the sham group withdrew due to scalp irritation.
15 The majority (73.7%) of subjects correctly guessed their treatment allocation at trial endpoint (60% in active group
16 and 88.9% in the sham group).
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30 Comment. This sample had a higher degree of antidepressant treatment resistance when compared to participants
31 in previous tDCS trials (the mean number of failed antidepressant trials was larger than 4, 46.2% of the active
32 group and 18.2% of the sham group had a history of treatment with ECT; 23% of the active group and 9.1% of the
33 sham group had failed a trial of ECT in the current episode of depression). This was the first study to focus on use
34 of tDCS in treatment resistant unipolar depression in patients taking a wide variety of concomitant medication. The
35 study limitations include small sample size, and probable under-powering (the power calculation required 48
36 subjects, but only 24 were recruited): recruitment was stopped on ethical grounds after an interim analysis found
37 no difference between treatment groups. The degree of treatment resistance in this cohort may have been too
38 great to permit a detectable effect; and blinding may have been sub-optimal. Subjects who started antidepressants
39 four weeks prior to the trial may have experienced antidepressant drug-related treatment effects during the trial.
40 The active stimulation group was more treatment-resistant and more were taking benzodiazepines (which may
41 impair the effects of neurostimulation).
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54 **3.1.7 Brunoni (2013)** ²⁷

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56 This study explored the comparative safety and efficacy of tDCS, the antidepressant sertraline, and placebo, as
57 well as their combinations in the treatment of Major Depressive Disorder. A total of 120 subjects with DSM-IV
58 defined major depressive disorder (MDD), a baseline HDRS₁₇ score greater than 17, and a low suicide risk, took
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4 part in this double-blind randomized controlled trial. All subjects were free of antidepressant, antipsychotic and
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6 anticonvulsant medication for at least 5 half-lives of the drug, before onset of trial. Adjuvant benzodiazepines
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8 were permitted. Exclusion criteria included: other axis-I disorders (co-morbid anxiety disorders were permitted),
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10 substance use disorders, axis-II disorders, previous neurological conditions, severe axis-III disorders and specific
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12 contra-indications to tDCS (e.g. metallic implants in the head). Subjects who were prescribed sertraline in the
13
14 current depressive episode were excluded. Subjects were randomized to one of four groups: Active tDCS +
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16 sertraline, tDCS + placebo medication, sham tDCS + sertraline, sham tDCS + placebo medication. Participants and
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18 assessors were blinded to treatment allocation; the treating clinicians were aware of allocation, but their
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20 interaction with participants was kept to a minimum. Medication and tDCS were initiated concurrently. tDCS was
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22 delivered using a bi-frontal montage, with the anode placed over the Left DLPFC (F3 according to the 10-20 EEG
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24 system), and the cathode over Right DLPFC (F4 according to the 10-20 EEG system). Twelve tDCS sessions were
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26 delivered - 10 sessions on consecutive week days (Monday to Friday) and two subsequent sessions at fortnightly
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28 intervals. Active tDCS was delivered using a current setting of 2mA, for 30 minutes per session; sham tDCS was
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30 delivered by switching the stimulator off after 1minute. Sertraline was administered at a fixed dose of 50mg per
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32 day. The primary outcome measure was change in MADRS score at 6 weeks; secondary outcomes were clinical
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34 response (defined as >50% reduction of the baseline MADRS score), clinical remission (defined as a MADRS score
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36 ≤ 10), and scores on the HDRS17, Global Impression-Severity of Illness scale, and Beck Depression Inventory). At
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38 the main end point (6 weeks), there was a significant difference in MADRS scores when comparing the combined
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40 treatment group (sertraline/active tDCS) vs. sertraline + sham tDCS (mean difference, 8.5 points; 95% CI, 2.96 to
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42 14.03; $p=.002$), tDCS + placebo (mean difference, 5.9 points; 95% CI, 0.36 to 11.43; $p=.03$), and placebo/sham
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44 tDCS (mean difference, 11.5 points; 95% CI, 6.03 to 17.10; $p<.001$). Analysis of tDCS + placebo medication vs.
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46 sertraline + sham tDCS demonstrated comparable efficacies (mean difference, 2.6 points; 95% CI, -2.90 to 8.13;
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48 $p=.35$). Use of tDCS + placebo medication (but not sertraline + sham tDCS) was superior to placebo + sham tDCS.
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50 Common adverse effects did not differ between interventions, except for skin redness on the scalp in active tDCS
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52 ($p=.03$).

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54 Active vs. sham tDCS was significantly superior for all outcomes (Odds Ratios for response and remission were,
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56 respectively, 1.63; 95% CI = 1.26-2.12 and 2.50; 95% CI = 1.26-2.49). There were 7 episodes of treatment-
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58 emergent mania or hypomania, five of which occurred in the combined treatment group.

59 Comment.

60 This is largest trial to date of tDCS in depression; the factorial (2X2) design enables the authors to address issues
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62 of monotherapy vs. co-initiation of tDCS and antidepressant medication. The combination of sertraline and tDCS
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4 (initiated simultaneously) was associated with better outcomes than in other arms of the trial, this may be a
5 pointer to particular efficacy of co-initiated combination therapy. The choice of primary outcome endpoint at 6
6 weeks differs from all previous tDCS RCTs in depression, as it encompasses both the 2 week intensive treatment
7 phase, and 2 fortnightly add-on tDCS sessions.
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10 11 12 13 **3.1.8 Bennabi (2014)³⁷**

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15 This study examined the utility of tDCS in treatment resistant depression. A total of 24 patients meeting diagnostic
16 criteria for DSM-IV criteria for Major Depressive Disorder, with a baseline MADRS score greater than 24, and
17 meeting stage II criteria (or above) for treatment resistance. All patients received a constant dose of escitalopram
18 (10–20mg/d) over 4 weeks prior to tDCS treatment initiation. Concomitant treatment with benzodiazepine and/or
19 second generation antipsychotics was allowed. Exclusion criteria included bipolar depression, psychotic features,
20 neurological/ severe organic disease or treatment with First Generation Antipsychotics. Subjects were randomised
21 to receive active ($N=12$) or sham ($N=12$) tDCS. Both subjects and clinicians were blinded to allocation. Ten
22 treatment sessions were delivered over five consecutive days (two treatments per day). The anode was placed over
23 the Left DLPFC, and the cathode over the Right supraorbital area. Active tDCS was delivered using 2mA intensity
24 for 30 minutes per session. Sham tDCS was delivered using identical settings, but the current was gradually
25 ramped down to zero mA. Depression severity was assessed using the HDRS21 (primary outcome measure),
26 MADRS, and BDI. Response was defined as a decrease of at least 50% from baseline HDRS score, remission was
27 defined as a HDRS score of 8 or less. There was no significant difference between active and sham tDCS in the
28 change in HDRS score ($p=0.69$): immediately after the course ended, in the active tDCS group there were 3
29 subjects who responded and 2 who met criteria for remission. In the sham tDCS group there was 1 responder and
30 no remitters. The authors comment that one subject developed mania and withdrew from the study, but they do
31 not mention the group allocation for this subject. There were no other serious adverse events. The authors do not
32 supply information about the degree of blinding integrity.
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50 Comment. This study is limited by the small number of subjects. There is considerable level of treatment
51 resistance, and similarly to the Blumberger study³⁶, subjects started a new antidepressant 4 weeks prior to the
52 trial, and may have experienced medication-related effects.
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58 **3.1.9 Segrave (2014)²⁸**

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4 This was the first study to examine the use of tDCS in conjunction with Cognitive Control Training (CCT), a type of
5 neurocognitive training, which like tDCS is aimed at activating the DLPFC. The rationale for combining both
6 modalities is that there is evidence to suggest that there are more pronounced functional outcomes when tDCS is
7 applied to active brain regions, rather than to areas at rest.³⁸⁻⁴⁰. CCT is a novel therapeutic modality for depression,
8 aimed at activation of the DLPFC through two targeted cognitive activities designed in reference to functional
9 imaging data, to activate the DLPFC²⁸: the first, a modified Wells Attentional Training (WAT) paradigm is a guided
10 auditory process, directing attention through phases of focused attention, switching attention and divided
11 attention; the second, is a modified Paced Serial Addition Task (PASAT), a mental arithmetic task. 27 subjects with
12 DSM-IV Major Depressive Episode, whose baseline MADRS score was greater than 18 took part in this study.
13 Exclusion criteria included: Lifetime history of neurological illness, mania, hypomania PTSD or psychosis, and
14 substance use disorders in the year prior to study initiation. Subjects were either not prescribed antidepressant
15 medication, or were stable on the same dose for at least 4 weeks prior to study initiation. Subjects were
16 randomised to receive five sessions of either: 1.tDCS + CCT ($N=9$), or 2.sham tDCS + CCT ($N=9$), or 3. tDCS +
17 sham CCT($N=9$). Participants and raters were blinded to allocation, but the operator was aware of allocation.
18 Sessions were delivered on 5 consecutive working days. Active tDCS was delivered for 24 minutes per session
19 using current setting of 2.0 mA. Sham tDCS was delivered using a 2minute fade out period. CCT started 2 minutes
20 after initiation of tDCS session. The anode was placed over Left DLPFC (F3 according to the 10–20 EEG system), the
21 cathode over the lateral aspect of the Right orbit (F8 according to the 10–20 EEG system). Results: there were no
22 drop-outs during the course of treatment, tDCS was well tolerated and no serious adverse events were reported.
23 There was a significant difference between the three arms in respect of the change in MADRS scores over time
24 $F_{(4,48)}=4.63$ ($p=0.03$). Post-hoc analysis demonstrates significant reduction in MADRS scores for subjects in the
25 sham-tDCS+CCT group ($p=0.02$), and in the tDCS+sham-CCT group ($p=0.04$); there was a trend towards
26 significance in the tDCS+CCT group ($p=0.06$). At 3-week follow-up, only the tDCS+CCT group showed significant
27 difference from baseline MADRS scores ($p<0.001$). There were no significant differences in response rates
28 immediately following the 5 treatment course ($p=0.08$). At 3 week follow up, there was a significant difference in
29 response rates ($p=0.04$): tDCS+CCT 44%, sham tDCS+CCT 11%, tDCS+sham CCT 0%. For the purpose of this
30 meta-analysis, we included only 2 of the 3 study arms - comparing tDCS+CCT vs. sham tDCS+CCT.
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56 Comment. An interesting finding was the delayed onset of maximal therapeutic efficacy of the tDCS+CCT
57 combination. This is not consistent with a previous study of the tDCS+CCT combination in healthy individuals⁴¹.
58 This finding supports the inclusion of follow-up phases in future tDCS studies.
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3.1.10 Brunoni (2014)⁴²

This is the second study examining the combination of tDCS and CCT for the treatment of depression. Subjects fulfilled criteria for DSM-IV major depressive episode, with a baseline HDRS score > 21; the age range was 18–65. Exclusion criteria included: 1. Bipolar disorder, substance use disorders, schizophrenia, personality disorders, and other co-morbid psychiatric disorders apart from anxiety disorders. 2. Neurological conditions. 3. Patient prescribed antipsychotics or tricyclic antidepressants. All subjects were taking antidepressant medication (SSRI or SNRI) with no dose changes for at least six weeks prior to Study initiation. Subject were randomised to 10 treatments on consecutive working days, consisting of either: 1. CCT+sham tDCS (n=17) or 2. CCT+tDCS (N=20). The primary endpoint was 4 weeks post initiation (2 weeks of active treatment and 2 weeks of follow-up). tDCS parameters used were: 30 minutes per session at 2mA current setting, Anode over Left DLPFC (F3 according to the 10–20 EEG system), Cathode over Right DLPFC (F4 according to the 10–20 EEG system). Sham tDCS used 30 sec ramp-in, 30 sec active stimulation and 15 sec ramp-out. The CCT intervention included only the modified PASAT, and was delivered during the final 15 minutes of each tDCS session. Results; tDCS was well-tolerated and no adverse effects were reported. There was 1 drop out from the active tDCS+CCT and 3 drop outs from the sham tDCS+CCT groups during the active treatment phase. There were no statistically significant differences between the groups in respect of the primary outcome measure. Both groups demonstrated similar reductions of HDRS scores at week 2 ($p=0.91$) and at week 4 ($p=0.71$). There were no statistically significant differences in categorical response and remission rates at week 2 or at week 4. Older subjects demonstrated a stronger additional effect of tDCS when combined with CCT. There were no additional improvement in depressive symptoms during the 2-week follow-up period (in contrast to the findings in the previous CCT+tDCS study²⁸).

Comment. This study demonstrated no statistically significant differences between active vs. sham tDCS, when added to a course of CCT in subjects with unipolar depression. The lack of significant difference at the end of the active treatment phase is consistent with the previous CCT+tDCS study²⁸; however, in this study there was also no difference after a 2 week follow-up period.

3.2 Published meta-analyses

Our search of the literature identified 3 published meta-analyses of tDCS in depression. Their main design features and those of our own meta-analysis are summarised in table 2.

Meta analysis	Date range	Trials	<i>N</i> subjects	Power to detect “small” effect ($g=0.30$)	Precision (pooled confidence interval width)	Outcome measures	Other analyses
Kalu et al., 2012	01/01/1998-05/2011	6	Active tDCS: 96 Sham tDCS: 80	0.50	1.06	Continuous- mean change in depression rating scale scores	Publication bias
Berlim et al., 2013	01/07/ 1998-20/08/2012	6	Active tDCS: 103 Sham tDCS: 97	0.55		Categorical- reponse and remission rates	Publication bias
Shiozawa et al., 2014	2006-31/01/2014	7	Active tDCS: 167 Sham tDCS: 152	0.76	0.66	Both categorical and continuous outcome measures	Publication bias
This meta-analysis	01/01/1995-30/04/2015	10 (43% increase)	Active tDCS: 206 Sham tDCS: 187 (23% increase)	0.84 (11% increase)	0.52 (21% increase)	Both categorical and continuous outcome measures	Publication bias Power analyses Precision analyses

Table 2: Comparison of previously published and current meta-analyses of tDCS in depression

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3.2.1 Kalu et al (2012)¹²

The first systematic review and meta-analysis of tDCS in the treatment of depression included randomized parallel or cross-over studies of active tDCS vs. sham tDCS controls, double blind allocation to treatment, and outcome measures including a clinician-rated depressive symptom severity scale (HDRS or MADRS), and an account of the change (%) in symptom severity. Six randomized controlled trials including a total of 96 patients in active tDCS arms and 80 patients in sham tDCS arms were included^{26,29-31,33,34}. Depressive symptom severity was reduced by a weighted mean of 28.9% (14.6-60%). A weighted mean of 21.8% (range: 0-80%) of RCT participants receiving active tDCS experienced categorical response (50% symptom severity reduction), and 6.1% (range 0-23%) experienced symptomatic remission (HDRS score < 8 or MADRS score <11). The wide variability between studies may have reflected differing levels of treatment resistance, concomitant medication use, and variability in delivery of tDCS between trials. The pooled estimate of effect size (Hedges' *g*) for depressive severity reduction between active and sham tDCS was 0.74 ($Z=2.76$, $p=0.006$, 95% confidence interval 0.21-1.27). All four studies which included 1-month follow-up data reported that the reduction in symptom severity with treatment was maintained (and in 2 studies increased in magnitude) at follow-up. No significant correlations were found with baseline symptom severity, concomitant antidepressant use, stimulation current strength or total number of sessions. The most common adverse effects in both active and sham tDCS study-arms were headaches, and local itchiness and/or redness at electrode sites. Skin-lesions were associated with the use of tap-water instead of saline solution for electrode preparation. Four cases of tDCS-associated hypomania were reported - 3 in published trials^{30,34,43} and one in an ongoing trial⁴⁴. The authors conclude that tDCS is a potentially effective treatment for depression, but acknowledge limitations such as the small number of available studies, small number of participants, and heterogeneity in participant populations and treatment parameters. The authors called for large-scale studies with longer follow-up periods in more representative participant groups.

3.2.2 Berlim et al (2013) meta analysis¹³

The second meta-analysis of tDCS in the treatment of MDD investigated the utility of tDCS using response and remission rates as outcome measures. Systematic review searched for publications which fulfilled the following inclusion criteria: randomised, sham-controlled, double-blind, parallel or cross-over design with at least 5 subjects randomised to each study arm; participants aged 18-75, with a primary diagnosis of DSM-IV or ICD-10 Major Depressive Episode (MDE) of a unipolar or bipolar nature; treated with at least 5 sessions of tDCS, at an intensity of at least 1mA, with the anode over the left DLPFC, tDCS being administered as either monotherapy or

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4 32 augmentation strategy; publications in the English language. Exclusion criteria included enrolment of subjects with
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6 33 subsets of depression (e.g. post-partum or vascular depression); contemporaneous initiation of tDCS and another
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8 34 treatment for depression (e.g. antidepressant medication); and studies, which did not report response and/or
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10 35 remission rates. The literature search yielded 6 RCTs, including 5 of the 6 trials incorporated by Kalu et al.¹² in
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12 36 their meta-analysis^{26,30,31,33,34}; together with a more recent RCT³⁶. Overall, the dataset included 200 subjects with
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14 37 MDE, 103 of whom were randomised to active tDCS. Subjects received a 10.8 +/- 3.76 sessions of tDCS. The
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16 38 cohort had failed to respond to a mean of 2.36 +/- 1.19 trials of antidepressants. There was no significant
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18 39 difference in baseline depression severity between the active and sham tDCS groups ($p=0.66$). Using drop-out
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20 40 rates to assess overall treatment acceptability, there were no significant differences in drop-out rates between
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22 41 active (4.8%) and sham (5.1%) tDCS ($p=0.86$). There was no significant difference in blinding integrity between
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24 42 active and sham tDCS ($p=0.41$); 44.1% of active tDCS participants correctly guessed treatment allocation at study
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26 43 end, vs. 53.7% of sham tDCS participants. The overall rates of response and remission were not significantly
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28 44 different between the active and sham tDCS groups: response rates were 23.2% for active tDCS vs. 12.4% for sham
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30 45 tDCS, pooled $OR = 1.97$ (95% CI = 0.85–4.56; $p=0.11$); and remission rates were 12.2% for active tDCS vs. 5.4% for
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32 46 sham tDCS, pooled $OR = 2.13$ (95% CI = 0.64–7.06; $p=0.22$). Active tDCS significantly out-performed sham tDCS
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34 47 when used as a monotherapy for MDE: $OR = 7.54$ (95% CI = 1.63–34.8; $p=0.01$). There was no association
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36 48 between number of treatment sessions (5 vs. 10 treatments) or electrical current used (1 vs. 2 mA) and treatment
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38 49 efficacy. The authors highlighted limitations, including small sample sizes, little or no follow-up after treatment
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40 50 protocol is ended, and no differentiation between effects in unipolar and bipolar depression.

41 52 3.2.3 Shiozawa et al (2014)¹⁴

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43 53 This meta-analysis aimed to improve on previous meta-analyses by addressing two main areas: First, previous
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45 54 meta-analyses had utilised different methodologies for calculating effect size: the Kalu meta-analysis¹² used
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47 55 continuous depression severity scores, whereas the Berlim meta-analysis¹³ used categorical response/remission
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49 56 rates. Second, previous meta-analyses had not includes data from the biggest tDCS for depression trial to date²⁷.
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51 57 The inclusion criteria were: randomised, sham-controlled trials, providing data including continuous depression
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53 58 scores and categorical response + remission rates. The meta-analysis includes 7 RCTs^{26,27,29,30,33,34,36}, ($N=259$
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55 59 participants). Active tDCS significantly outperformed sham-tDCS on continuous depression scores ($g=0.37$; CI
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57 60 0.04–0.7). Odds Ratios for response and remission were respectively 1.63; 95% CI=1.26–2.12 and 2.50; 95%
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59 61 CI=1.26–2.49.

63 3.2.4 Discussion of previous meta-analyses

64 The three published meta-analyses of tDCS for depression present inconsistent conclusions, possible due to a
65 number of factors. First, choice of outcome measures for calculating effect sizes – the 2012 meta-analysis¹² used
66 percentage change in depressive rating scale scores from baseline to endpoint, whereas the 2013 meta-analysis¹³
67 used categorical response and/or remission rates, dichotomous outcomes which effectively raise the threshold for
68 demonstrating differential effects between active and sham interventions. The 2014 meta-analysis¹⁴ utilises both
69 approaches: its conclusions are aligned with previous findings in respect of continuous depression rating scale
70 data¹², but are at odds with previous conclusions¹² regarding response/remission rates¹³ – this may be due to the
71 different studies included in this meta-analysis (in particular, the inclusion of the large 2013 trial²⁷). Second, the
72 2013 meta-analysis includes a study which recruited participants with highly treatment-resistant depression
73 (including those whose depression failed to respond to ECT, who were excluded from earlier trials). Third, there
74 was an increased proportion of studies involving tDCS augmentation vs. Monotherapy in the 2013 meta-analysis:
75 tDCS trials in which participants are allowed to continue antidepressant medication. This may limit the apparent
76 effectiveness available to be demonstrated by tDCS, as the scope for active tDCS to increase the response and/or
77 remission rates may be reduced when subjects are concurrently treated with antidepressant medication; some
78 medications (for instance anticonvulsants) may actually reduce the efficacy of tDCS; and there may be an increased
79 degree of treatment refractoriness in patients recruited to these trials. The 2014 meta-analysis¹⁴ included large
80 RCT²⁷ in which ADM and tDCS were co-initiated – this group outperformed other arms of the trial (as well as
81 giving rise to most manic switches), which may indicate a particular increase in antidepressant efficacy when tDCS
82 & Sertraline are co-initiated.

84 3.3 Narrative analysis of recent randomized controlled trials and meta-analyses of tDCS in depression

85 The body of evidence examining the use of tDCS in depression has grown significantly in recent years, to include
86 10 RCTs and 3 meta-analyses.

87 As regards efficacy, RCTs have yielded mixed results: 4 RCTs²⁹ show a statistically significant advantage for active
88 tDCS over sham tDCS ('positive RCTs'), Whereas 6 RCTs^{28,33,36,37,42} failed to demonstrate a significant separation
89 between active and sham treatments ('failed RCTs') (Table 3).

91 Factors associated with these differential outcomes can be divided into participant-related factors and tDCS-
92 related factors (table 3)

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4 94 Participant-related factors include treatment-resistance level, and concurrent treatment with medication or with
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6 95 CCT. Using the mean number of antidepressant medication trials before starting tDCS as a measure of the mean
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8 96 level of treatment resistance in each cohort, it seems that 4 RCTs^{28,33,36,37} recruited patients with higher levels of
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10 97 treatment resistance. The mean number of failed ADM trials in these studies was greater than 2 (compared to
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12 98 1.0–1.7 in all other RCTs for which data was available). All these studies found no advantage of active over sham
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14 99 tDCS, whereas 3: out of 4 RCTs in which tDCS was used for less treatment-resistant depression found evidence for
15 100 superiority of active over sham tDCS^{26,27,34}. The available data suggest that active tDCS is more likely to outperform
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17 101 sham tDCS in patients who have failed less than two trials of ADM, than in those who have failed more than two
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19 102 trials of ADM. It is notable that a similar pattern is seen in antidepressant drug RCTs: compared to patients who
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21 103 have not been treated or who have failed one ADM trial, patients who have not responded to more than 2 trials of
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23 104 ADM demonstrate a significantly lower response rate to subsequent ADM trials⁴⁵. As regards concurrent
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25 105 medication usage, 2 out of 10 RCTs did not permit concurrent ADM use during the trial, both found significant
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27 106 superiority of active over sham tDCS^{26,29,42}. The potential for additional improvement with tDCS in patients who are
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29 107 already prescribed an antidepressant or undergoing CCT may be limited, in comparison with patients who are
30 108 receiving tDCS monotherapy. Antidepressants may also directly interfere with tDCS efficacy.
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34 110 TDCS-related factors include current settings, number of tDCS sessions and session duration, as well as electrode
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36 111 placement. Of the 4 positive RCTs, three used the higher (2mA) rather than the lower (1mA) current setting. By
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38 112 contrast, of the six failed RCTs, two used the lower current setting (1mA) in all participants³⁰, or in some of them
39 113³³. Palm et al.³³ compared the outcomes for participants who received tDCS at 1mA vs. 2mA and found there was no
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41 114 significant difference ($p=0.38$) between groups: however, this trial recruited participants with treatment resistant
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43 115 depression, in whom the difference in efficacy between current levels may not have been sufficiently great to be
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45 116 associated with significantly different treatment outcomes. As regards the number of sessions, the number of
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47 117 sessions used in RCTs ranges from 5 to 15. Of the four positive RCTs, one involved 5 treatment sessions, two
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49 118 involved 10 treatment sessions, and a single trial involved 15 sessions. The negative RCTs include 2 trials
50 119 involving 5 sessions, three involving 10 sessions, and one involving 15 sessions.
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54 121 Of course, it may be that these factors influence the efficacy of tDCS in an additive fashion: among the 6 failed
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56 122 RCTs, 4 trials recruited participants with higher levels of treatment-resistance. The only failed RCT which reported
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58 123 recruiting participants with lower levels of treatment-resistance mean number of failed ADM courses <2)³⁰,
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60 124 combined a short course of tDCS (5 treatment sessions), with a low current setting (1mA).
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Name	Diagnosi s	N active, sham	Age (S.D.)	Gender % Female	Rating Scale	tDCS Curren t (mA)	tDCS Session Duration (min)	tDCS Montage: anode, cathode	Number of tDCS Sessions	Treatment resistance level	Con- current ADM	Con- current CCT	Depression outcome
Fregni 2006 ²⁹	Unipolar	9,9	48.2 (10)	No data	MADRS	1.0	20	F3 , FP2	5	no data	No	No	Active>Sham
Boggio 2008 ²⁶	Unipolar	21,10	49 (7.4)	67.5%	HDRS	2.0	20	F3 , FP2	10	1.7	No	No	Active>Sham
Loo 2010 ³⁰	Unipolar	20,20	47.3 (11.3)	55%	MADRS	1.0	20	F3 , FP2	5	Active 1.0 Sham 1.7	Yes	No	Active=Sham
Palm 2011 ³³	Unipolar & bipolar	11,11	57 (12)	50%	HDRS	1.0 or 2.0	20	F3 , FP2	10	Active 2.9 Sham 2.91	Yes	No	Active=Sham
Loo 2012 ³⁴	Unipolar & bipolar	33,31	48.2 (12.5)	46.6%	MADRS	2.0	20	F3, F8	15	Active 1.71 Sham 1.79	Yes	No	Active>Sham
Blumberger 2012 ³⁶	Unipolar	13,11	42.7 (11.6)	45.6%	HDRS	2.0	20	F3, F4	15	Active 4.3 Sham 4.1	Yes	No	Active=Sham
Brunoni 2013 ²⁷	Unipolar	30,30	42 (12)	68%	MADRS	2.0	30	F3, F4	10+2	1.7	Yes	No	Active>Sham
Bennabi2014 ³⁷	Unipolar	12,12	61.8 (16.3)	75%	HDRS	2.0	30	F3 , FP2	10 (5 days twice daily)	100% > 2	Yes	No	Active=Sham
Segrave 2014 ²⁸	Unipolar	9,9	40.4 (14.5)	37%	MADRS	2.0	24	F3, F8	5	3.0	Yes	Yes	Active=Sham
Brunoni 2014 ⁴²	Unipolar	20,17	18-65	70.2%	HDRS	2.0	30	F3, F4	10	35-41% > 2	Yes	Yes	Active=Sham

Table 3: Participant-related factors, tDCS-related factors and tDCS trial depression outcomes: RCTs of tDCS in depression listed in chronological order. Depression outcome is a categorical statement as to whether active tDCS out-preformed sham tDCS in terms of depression outcome measures ($p \leq 0.05$), at the end of active treatment course. ADM = Antidepressant Medication. CCT=Cognitive Control Training. The degree of treatment resistance is indicated by the number of ADM trials failed prior to starting tDCS.

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131 **3.4 Analysis of published meta-analysis efficacy factors**

132 Consideration of the 3 published meta-analyses, provides the following efficacy-related insights:

133 3.4.1 Kalu et al. 2012¹². This meta analysis utilised continuous outcome measures and showed that active tDCS

134 was associated with significant reduction in symptom severity compared with sham tDCS. It found that meta-

135 regression with participant related factors (baseline severity, concurrent treatment with antidepressant

136 medication), and with tDCS-related factors (number of sessions, current settings) did not yield any significant

137 correlations.

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139 3.4.2 Berlim et al. 2013¹³. This meta-analysis utilised categorical response and remission outcome measures, and

140 concluded that there was insufficient evidence to support tDCS as superior to placebo in achieving response or

141 remission from depression. Neither participant-related, nor treatment-related factors were significantly correlated

142 with differential treatment outcomes.

143

144 3.4.3 Shiozawa et al. 2014¹⁴. This meta-analysis utilised both continuous and categorical outcome measures, and

145 found that tDCS with statistically superior to sham tDCS in the treatment of depression in both outcome domains.

146 Meta-regression of both categorical and continuous outcome measures did not yield any statistically significant

147 correlation between participant-related or treatment-related factors and treatment outcomes.

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149 **1.5 Published meta-analysis safety and tolerability findings:**

150 The three published meta-analyses contribute the following insights into safety and tolerability:

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152 1. Kalu et al. 2012¹². The most common adverse effects reported by studies included in the systematic review

153 were of a minor nature including headaches, itchiness and redness of skin underlying the electrodes. Skin lesions

154 reported by Palm et al. 2011⁴⁶ were not observed once the electrodes were soaked in saline solution rather than

155 tap water. The authors note that although adverse effects were more commonly reported in the active tDCS than

156 in sham tDCS groups, the differences were not statistically significant. There were several reports of 'treatment

157 emergent' hypomanic episodes.

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159 2. Berlim et al. 2013¹³. Dropout rates at study end did not demonstrate a statistically significant difference

160 between active and sham tDCS groups. The authors did not comment on safety aspects.

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162 3. Shiozawa et al. 2014¹⁴. No statistically significant differences were found between acceptability (as measured by
163 dropout rates) of active versus sham tDCS.

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166 **4. CURRENT META-ANALYSIS: Continuous Treatment effects**
167 Across all studies the combined treatment effect was significant and consistent with a small effect size ($k=11$,
168 $g=0.30$, 95% CI=[0.04, 0.57], $p= .027$)(see Figure 2a). The 'probability of superiority' metric ³⁰ indicated a 62%
169 chance that a randomly sampled individual receiving active tDCS would have a greater reduction in depressive
170 symptoms than a randomly sampled individual receiving sham tDCS 95% CI [52% 72%]. A 'leave one out' analysis
171 revealed that removing Boggio et al (2008) ²⁶, Loo et al (2012)³⁴, or the concurrent Sertraline group of Brunoni et al
172 (2013)²⁷ would reduce the effect to non-significance (largest $p = .078$, smallest $g = 0.23$). The meta-analytic
173 combination of effects yielded a valuable increase in precision. From the earliest study to the most recent, the
174 margin of error (width of one arm of the confidence interval: MOE) decreased from 1.18 to 0.26. The test for
175 heterogeneity was significant ($Q(10) = 19.27$, $p= .037$) and the I^2 statistic indicated that 40% of the heterogeneity
176 between studies could not be accounted for by sampling variability, justifying the use of a random effects model.

177
178 **4.1 Fail-safe N analyses**
179 The "fail safe N" calculation using the Rosenthal approach ²², revealed that 27 unpublished studies averaging null
180 results would be required in order for the treatment effect to dip below significance ($\alpha=.05$). Additionally, we used
181 the Orwin fail-safe N calculations ²¹ to estimate the number of unpublished studies averaging null results that
182 would be required to reduce the effect size to a range of target levels, this data is plotted in Figure 2b.

183
184 **4.2 Publication bias**
185 A funnel plot of the outcomes is shown in Figure 2c. To examine the sensitivity of the data to publication bias we
186 employed the nonparametric "trim and fill" method ⁴⁷. The procedure estimated that one study (on the left of the
187 summary effect) could have been suppressed due to publication bias. Imputing this missing study and repeating
188 the analyses marginally reduced the effect size ($k=12$, $g=0.22$, 95% CI=[-0.11, 0.56], $p = .195$).

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190 **4.3 Precision and power analyses**

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4 191 By using our interval of effect size estimates ($g=0.30$, 95% CI [0.04 0.57]) as a plausible population estimate of the
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6 192 treatment effect, we estimated the sample size required for future trials to yield target levels of precision,
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8 193 expressed in terms of the maximum confidence interval width for g . All analyses were performed to provide a level
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10 194 of 99% assurance that the confidence interval would be sufficiently narrow. This data is plotted in Figure 2d.

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13 196 For sample size planning, we estimated that for an individual study to detect the summary effect estimated by our
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15 197 meta analysis at the $p = .05$ level with 80% power, an N of at least 346 (173 in each group, assuming equal
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17 198 allocation) would be required in both the treatment and control group (with the total N required to detect the
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19 199 upper and lower bound being 49 and 12693 respectively) . These estimates by far exceed the mean sample size of
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21 200 the studies included in the meta analysis ($N=36$). These analyses suggest that the studies included in the analysis
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23 201 do not meet the criterion for adequate statistical power.

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26 203 **4.4 Moderator analysis for continuous outcomes**
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28 204 A summary of the one-moderator models is shown in table 4. Treatment resistance level was removed due to the
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30 205 inconsistent reporting (for separate groups, or for all participants combined, or no exact values) which prevented a
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32 206 useful and informative component of this analysis. Meta regression did not detect any significant moderators of
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34 207 the treatment effect - no one-moderator model provided a better fit to the data than an empty (no moderator
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36 208 model). In a multiple regression model, we calculated the proportional contribution of each moderator to the
37
38 209 overall R^2 , collapsed across orderings of regressors. This revealed that concurrent Antidepressant Medication
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40 210 (ADMs) and concurrent Cognitive Control Training (CCT) were the most important predictors, both impacted
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42 211 negatively on the treatment effect and accounted for 47% and 36% of the total variation explained respectively
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44 212 (Figure 2e). Closer examination of these factors revealed that samples who were not taking concurrent ADMs
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46 213 ($g=0.71$, 95% CI [0.12 1.29], $p=.019$) had a larger treatment effect than those who were ($g=0.18$, 95% CI [-0.16
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48 214 0.51], $p=.302$). Similarly, samples that did not receive concurrent CCT ($g=0.39$, 95% CI [0.13 0.65], $p=.004$) had a
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50 215 larger treatment effect than those who did ($g=-0.20$, 95% CI [-0.82 0.41], $p=.517$). No interactions between
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52 216 moderators could be tested, due to empty cells in the model matrices.

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Moderator	k	df	Q_0	p	R^2	b_0	b_1
Current	11	1	0.50	.481	0.0	0.57	-0.30
Number of sessions	11	1	0.00	.964	0.0	0.28	0.00
Session length	11	1	0.14	.705	0.0	0.35	-0.11
Total tDCS time	11	1	0.07	.791	0.0	0.43	-0.00
Total current	11	1	0.41	.783	0.0	0.41	-0.00
ISI	11	1	0.50	.481	0.0	0.26	0.30
Diagnosis	11	1	0.00	.995	0.0	0.31	-0.00
Concurrent ADMs	11	1	2.35	.125	0.0	0.70	-0.53
Concurrent CCT	11	1	3.03	.082	41.2	0.39	-0.59

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Table 4: A summary of the calculated one-moderator models and associated significance levels. Q_0 is the Wald-type chi squared value for the omnibus test of model coefficients. R^2 is the pseudo R^2 . b_0 and b_1 are the slope and intercept respectively. (ISI=inter-session interval in days, ADM = Antidepressant Medication)

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223 5 CURRENT META-ANALYSIS: Categorical treatment effects (Response and Remission rates)

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226 Data for response rates were available from 9 of the 11 effects (Figure 3a). The pooled LOR for response was
227 positive, but did not reach significance ($k= 9$, LOR = 0.36, 95% CI[-0.16, 0.88], $p = .176$), Heterogeneity between
228 studies did not exceed that expected by chance ($Q(8) = 6.18$, $p= .627$) and the I^2 statistic indicated that only
229 0.86% of the heterogeneity could not be explained by sampling error. Cumulative meta-analysis revealed that the
230 meta-analytic combination of effects yielded an increase of precision from an MOE of 1.71 to 0.52. Data for
231 remission rates were available from 9 of the 11 effects (Figure 3b). Consistent with response rates, the pooled LOR
232 for remission was positive, but did not reach significance ($k= 9$, LOR = 0.25, 95% CI [-0.42, 0.91], $p = .468$),
233 Heterogeneity between studies did not exceed that expected by chance ($Q(8)=4.68$, $p= .791$) and the I^2 statistic
234 indicated that all heterogeneity could be attributed to sampling error. Cumulative meta-analysis revealed that the
235 meta-analytic combination of effects yielded an increase of precision from an MOE of 2.97 to 0.66.

235

236 5.1 Fail safe N analyses

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238 Owing to the non-significant summary effects for response and remission, we did not compute fail-safe N
239 analyses based on a nominal significance level. Instead, we used the Orwin method to assess the impact of
publication bias on effect size. These data are plotted in Figure 3c.

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241 5.2 Publication bias

242 Analyses revealed that no studies were trimmed and filled on the opposite side of zero in either the response or
243 remission meta-analyses. Furthermore, both funnel plots were broadly symmetrical, suggesting a low risk of
244 publication bias (figure 3d & 3e).

245

246 5.3 Moderator analysis for categorical outcomes

247 Meta regression revealed no statistically significant moderators of either response or remission rates.

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249 6 CURRENT META-ANALYSIS: SAFETY AND TOLERABILITY:

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Dropout rates were available from 9 studies (table 5) and were analysed in a random effects model using
the log odds ratio as an effect size measure (effect sizes greater than 0 indicate a greater likelihood of dropout in
the active relative to the sham tDCS group). The analysis revealed no significant differences in drop out rates ($k= 9$
 $LOR = 0.05$, 95% CI= [-1.0, 1.10], $p = .928$).

Study	<i>N</i> - active	drop out rate due to adverse effects - active tDCS	<i>N</i> - control	drop out rate due to adverse effects - sham tDCS	<i>p</i>
Fregni 2006 ²⁹	9	0	9	0	1
Boggio 2008 ²⁶	21	0	19	0	1
Loo 2010 ³⁰	20	0	20	0	1
Palm 2011 ³³	11	0	11	0	1
Loo 2012 ³⁴	33	1	31	1	.964
Blumberger 2012 ³⁶	13	1	11	0	.558
Brunoni 2013 ²⁷	60	3	60	1	.347
Brunoni 2014 ⁴²	20	1	17	3	.245
Segrave 2014 ²⁸	9	0	9	0	1

Table 5 : Drop out rates due to adverse events in blind phase of tDCS depression RCTs

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261 7. DISCUSSION

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We carried out a meta analysis of 10 RCTs comparing active tDCS to sham tDCS, including 393 participants with major depressive episodes in the context of unipolar or bipolar disorders. tDCS was used as mono therapy or as adjunctive treatment for depression in conjunction with medication and/or Cognitive Control Training (CCT).

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Analysis of continuous outcomes – depression rating scale scores, demonstrates clear superiority of active tDCS over sham tDCS in the treatment of MDE. The combined treatment effect was significant and consistent with a small effect size ($k=11$, $g=0.30$, 95% CI=[0.04, 0.57], $p=.027$) (Figure 2).

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It is important to highlight the findings from our precision and power analyses: These indicate that for an individual study to detect the summary effect ($g=0.30$) at the $p=.05$ level at 80% power, a total (combined treatment and control) N of at least 346 would be required. The mean total sample size of the studies included in the meta analysis is 36 – it is therefore likely that the RCTs included lacked sufficient statistical power. Given that an N of 346 is of considerable size, future studies may wish to focus on enhancing the precision of their interval based estimates within practical and financial constraints, rather than placing too much stock in conclusions based on null hypothesis significance testing. In this context, *a priori* power and precision analyses (and explicit reporting of the associated values) are recommended to enhance interpretation of data relating to tDCS efficacy in future RCTs. It is, of course, worth noting that power is not simply a function of sample size. Correspondingly, enhancements in the design of RCTs, including rigorous eligibility criteria and optimizing a sensitive study design and endpoint may decrease the number of participants required to detect an effect. The issues surrounding power, in turn, also go some way towards providing a possible explanation for the lack of statistically significant differences between active and sham tDCS in the categorical response and remission analyses that we carried out.

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Categorical outcome measures are more robust and clinically meaningful, but require a larger sample size to demonstrate an effect. We found that both response and remission rates showed a positive pooled LOR but failed to reach statistical significance at the $p=.05$ level. These findings are consistent with the findings from earlier

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meta-analyses: Kalu et al. (2012)¹² used continuous outcome measures and found a significant superiority of active over sham tDCS; whereas Berlim et al. (2013)¹³, used categorical outcome measures and failed to

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demonstrate significant differences. The more recent meta analysis Shiozawa et al (2014)¹⁴ used both types of

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outcome measures and demonstrated significant superiority of active over sham tDCS in both continuous and

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categorical outcome measures. This difference in findings is likely to be mainly due to the way we analyzed data

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from the largest tDCS trial to date²⁷ – we decided to analyze the outcomes at week 2, immediately following the

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4 291 daily tDCS treatment phase – in contrast to analyzing the outcomes at 6 weeks (the primary outcome measure for
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6 292 the trial), following 2 fortnightly “top-up” sessions. The rationale for our choice being that most other RCTs we
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8 293 included in the meta-analysis used an endpoint at the termination of the intensive tDCS treatment phase. The
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10 294 outcomes at week 6 demonstrate an added degree of separation between active and sham tDCS. Repeating our
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12 295 analyses with week 6 as an endpoint revealed that this is sufficient to provide overall statistical significance to the
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14 296 categorical analysis (response: LOR = 0.81, [0.28, 1.34], $p = .003$, remission: LOR = 0.73, [0.13 1.33], $p = .017$)
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16 297 and slightly increase the magnitude of the continuous effect. ($g=0.37$, [0.09, 0.65], $p = .008$) This accords with
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18 298 the findings from other tDCS trials^{28,34,48}, indicating that at follow up, participants’ depression rating scales score
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20 299 continued to improve. We also decided to separately analyze the data from participants who received sertraline
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22 300 and those who received placebo medication in the Brunoni et al. 2013 trial²⁷ – this created two separate effects
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24 301 (hence although we included 10 RCTs, we analyzed $k=11$ effects). Moderator analysis demonstrated that although
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26 302 no moderators reached statistical significance at the level of $p=.05$, concurrent use of antidepressant medication,
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28 303 and concurrent use of Cognitive Control Training were the most important predictors, accounting for 47% and 36%
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30 304 of the total variation explained respectively (Figure 2e). Notably, these moderators remained the most important
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32 305 when outcomes for the Brunoni et al. 2013 trial²⁷ trial were analyzed at week 6, with the concurrent ADMs factor
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34 306 reaching significance ($R^2 = 24.15$, $Q(1)=4.94$, $p=.026$).
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36 307 Our moderator analyses revealed that samples who were not taking concurrent ADMs ($g=0.71$, 95% CI[0.12 1.29],
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38 308 $p=.019$) had a larger treatment effect than those who were ($g=0.18$, 95% CI[-0.16 0.51], $p=.302$). Similarly,
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40 309 samples that did not receive concurrent CCT ($g=0.39$, 95% CI[0.13 0.65], $p=.004$) had a larger treatment effect
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42 310 than those who did ($g=-0.20$, 95% CI[-0.82 0.41], $p=.517$). It is of note, that the largest trial to date²⁷ included a
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44 311 group of participants, in whom tDCS and pharmacological antidepressant therapy were *concurrently initiated* – the
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46 312 authors report that this group did particularly well in terms of depression outcomes, and go on to postulate that
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48 313 simultaneous initiation of tDCS and ADM may confer added benefits in patients with MDE. One should note that
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50 314 these participants were treated with a low dose of antidepressant medication (sertraline 50mg daily). Insufficient
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52 315 data prevented us from conclusively analyzing the effect of treatment-resistance level as a moderator of tDCS
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54 316 outcomes. More trials are needed in order to improve the precision of moderator analyses; this is currently limited
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56 317 due to small k . The evidence suggests tDCS has a good safety and acceptability profile, with only mild adverse
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58 318 effects reported in most trials. There were no statistically significant differences in the drop-out rates between
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60 319 active and sham tDCS groups in any of the RCTs. The only serious adverse event recorded in published tDCS RCTs
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62 320 was a case of suicide, which was considered by the authors as unlikely to be directly related to tDCS³⁰. Early
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64 321 reports of tDCS trials included descriptions of burns to the skin underlying scalp electrodes, but this has not been
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4 322 reported since researchers started using physiological saline rather than water to soak electrodes prior to use ⁴⁹.
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6 323 Several cases of tDCS-associated hypomanic episodes have been reported in the literature ^{12,14,27}.
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8 324 This meta-analysis offers several improvements compared to previous publications (Table 2): The literature search
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10 325 extends up to April 2015, and therefore captures 3 new RCTs (43% increase), which were not included in previous
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12 326 meta-analyses. This enabled us to increase the number of subjects by 23%. We were able to assess the effect of
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14 327 adding tDCS to CCT; this was not previously meta-analytically addressed. The power to detect “small” effects is
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16 328 increased, as is the precision (21% improvement in pooled confidence interval width). We also performed power
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18 329 and precision analyses to directly inform future research in terms of sample size planning.
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20 330 Limitations: The main limitation of this meta analysis is the low number of participants in most trials included. As
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22 331 demonstrated by our precision and power calculations, all but one of these trials ²⁷ are probably underpowered.
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24 332 This is likely to explain the lack of separation between active and sham tDCS in terms of categorical response and
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26 333 remission outcomes; as well as limiting the number of moderators reaching statistical significance. There is a lack
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28 334 of evidence regarding longer-term outcomes of tDCS in the acute and maintenance treatment of depression.

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32 336 **8. Conclusions:**
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36 338 Based on current evidence, the following conclusions may be drawn: First, tDCS may represent an effective
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38 339 treatment option for patients presenting with major depressive episodes. Second, tDCS offers a generally
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40 340 acceptable tolerability profile, which may make it a useful alternative to antidepressant medication in patients who
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42 341 do not wish to take medication and for those who cannot tolerate antidepressant medication. Third, the current
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44 342 body of evidence does not support the use of tDCS in treatment resistant depression. Fourth, the current body of
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46 343 evidence does not support the use of tDCS as an add-on augmentation treatment for depressed patient who are
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48 344 already taking an antidepressant or undergoing Cognitive Control Training (CCT). However, there may be an
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50 345 advantage for concurrently initiating treatment with an antidepressant and tDCS. Further research is needed, in
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52 346 particular, involving larger sample sizes over longer periods of treatment.

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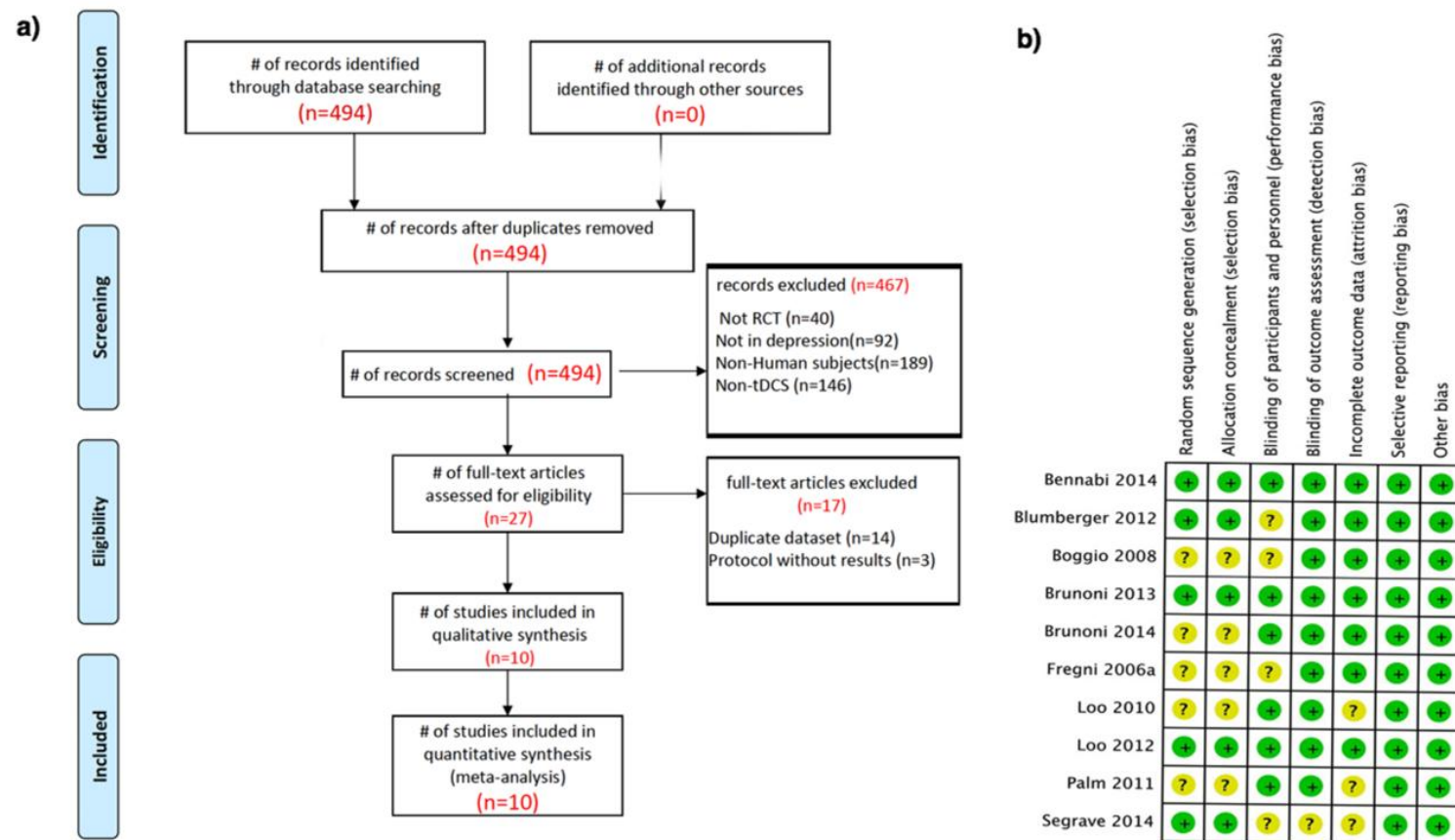
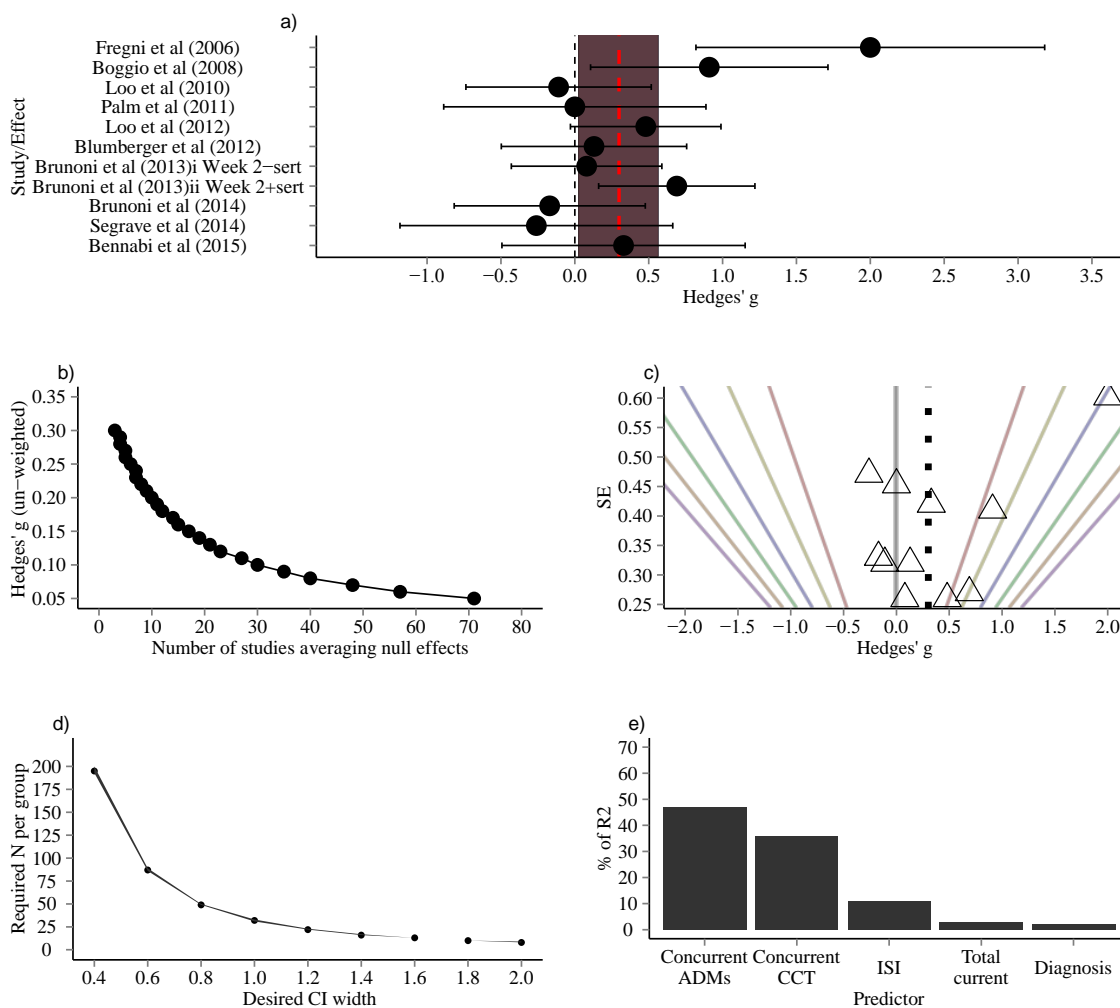
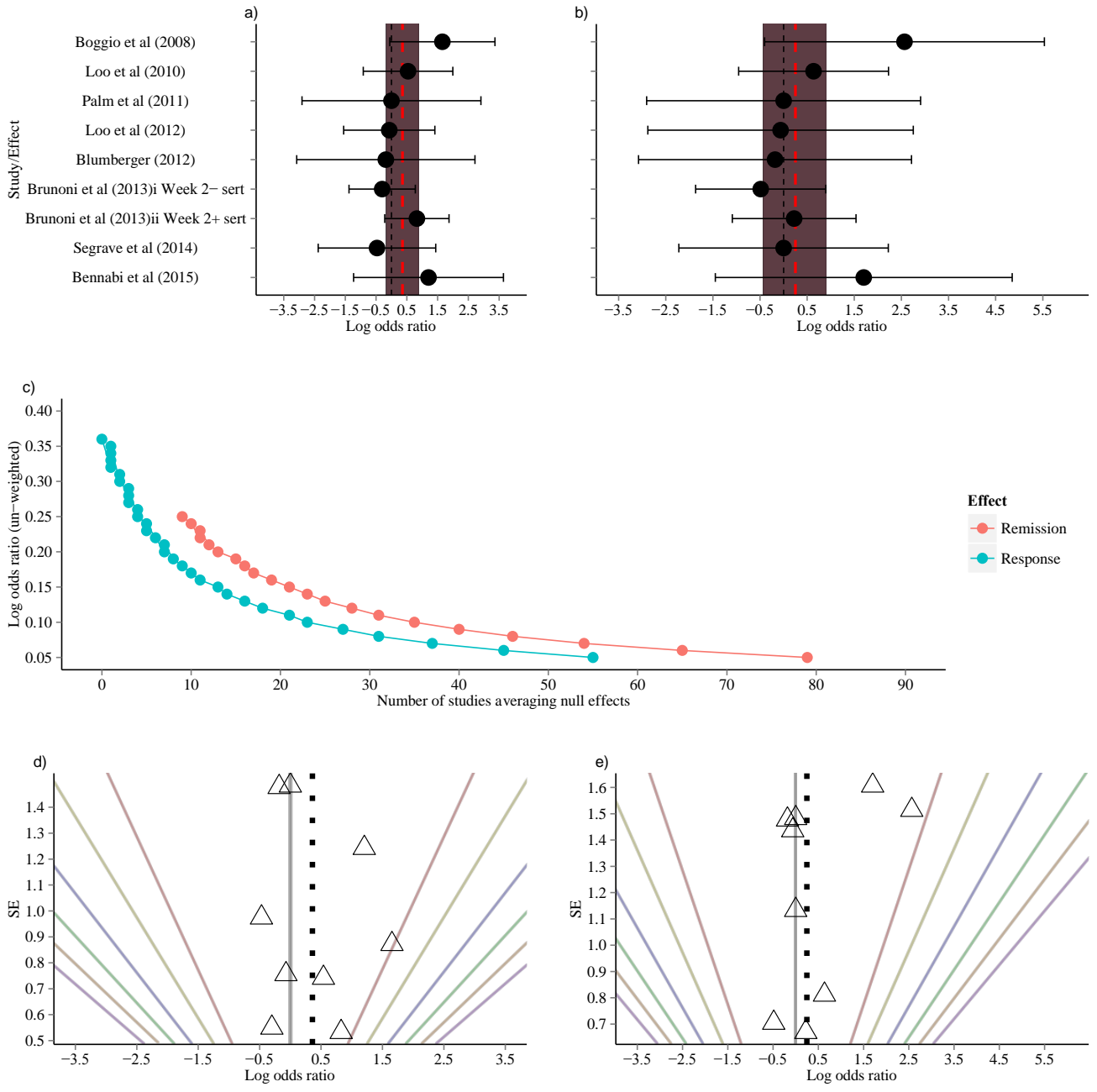


Figure 1 Study selection and quality assurance: (a) PRISMA¹ study-selection flowchart for our systematic review and meta-analysis. RCT = Randomised Controlled Trial. (b) Summary of risk of bias in line with the Cochrane Collaboration's tool for assessing risk of bias in randomised trials²⁵. Green circles represent low risk; yellow circles represent unclear risk of bias. The summary was generated using Cochrane's Review Manager software (RevMan5.3) –<http://tech.cochrane.org/revm>



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355 **Figure 2.** (a) Forest plot of effect sizes for active versus sham treatment. Error bars are 95% confidence intervals.
356 Dotted red line depicts pooled effect. Shaded red region is 95% confidence interval. (b) Orwin fail-safe N analyses
357 (c) Funnel plot. Dotted line is the pooled effect size, colored lines are p values (e.g. red=.05, yellow = .01, blue=
358 .001). (d) Outcome of precision analyses. For instance, to have 99% assurance that a 95% CI will be less than 0.8,
359 approximately 50 participants per group would be required. (e) Relative importance of each moderator. Note that
360 total TDCS time, amplitude, session length and number of sessions were removed due to multi-collinearity. Total
361 current is instead included to summarize these variables.

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4 **363** Figure 3. (a) Forest plot of effect sizes for active versus sham treatment: response rates. (b) Forest plot of effect
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6 **364** sizes for active versus sham treatment: remission rates. Error bars are 95% confidence intervals. Dotted red line
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8 **365** depicts pooled effect. Shaded red region is 95% confidence interval. (c) Orwin fail-safe N analyses (d) Funnel plot:
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10 **366** response rates. (d) Funnel plot: remission rates. Dotted line is the pooled effect size, colored lines are p values
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12 **367** (e.g. red=.05, yellow = .01, blue= .001).

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16 508 Conflict of Interest disclosures:

18 509

- 20 510 • None declared

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26 513 Funding sources:

28 514 None declared

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Potential moderator	Units	Descriptive Statistics
Current	mA (Boolean)	<i>k</i> = 11 1mA (<i>k</i> = 2) 2mA (<i>k</i> = 9)
Course delivered	Number of sessions	<i>k</i> = 11 <i>M</i> = 9.55 <i>SD</i> = 3.50 Range = 5-15
Session duration	Minutes per session (Boolean)	<i>k</i> = 11 20 mins (<i>k</i> = 7) 30 mins (<i>k</i> = 4)
Total tDCS time	Number of sessions x session duration (minutes)	<i>k</i> = 11 <i>M</i> = 229.09 <i>SD</i> = 87.80 Range = 100- 300
Total current delivered	mA x number of sessions x session duration	<i>k</i> = 11 <i>M</i> = 430.91 <i>SD</i> = 210.97 Range = 100- 600
Inter-session intervals	Days (Boolean)	<i>k</i> = 11 1 day (<i>k</i> = 9) 2 days (<i>k</i> = 2)
Diagnosis		<i>k</i> = 11 unipolar (<i>k</i> = 9) unipolar and bipolar (<i>k</i> = 2)
Concurrent anti-depressant medications (ADMs)		<i>k</i> = 11 Concurrent ADMs (<i>k</i> = 8) No-concurrent ADMs (<i>k</i> = 3)
Concurrent cognitive control therapy (CCT)		<i>k</i> = 11 Concurrent CCT (<i>k</i> = 2) No concurrent CCT (<i>k</i> = 9)
Treatment resistance level	Number of previous courses of antidepressants failed in current episode	<i>k</i> = 9 (see table 3)

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2 Table 1: variables examined as potential moderators of tDCS outcomes in depression. These include both

3 participant-related and tDCS-related factors, with a view to enable meta-analytical examination of the variables

4 found to be associated with tDCS outcomes in the narrative analysis.

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Meta analysis	Date range	Trials	<i>N</i> subjects	Power to detect “small” effect ($g=0.30$)	Precision (pooled confidence interval width)	Outcome measures	Other analyses
Kalu et al., 2012	01/01/1998-05/2011	6	Active tDCS: 96 Sham tDCS: 80	0.50	1.06	Continuous- mean change in depression rating scale scores	Publication bias
Berlim et al., 2013	01/07/ 1998-20/08/2012	6	Active tDCS: 103 Sham tDCS: 97	0.55		Categorical- reponse and remission rates	Publication bias
Shiozawa et al., 2014	2006-31/01/2014	7	Active tDCS: 167 Sham tDCS: 152	0.76	0.66	Both categorical and continuous outcome measures	Publication bias
This meta-analysis	01/01/1995-30/04/2015	10 (43% increase)	Active tDCS: 206 Sham tDCS: 187 (23% increase)	0.84 (11% increase)	0.52 (21% increase)	Both categorical and continuous outcome measures	Publication bias Power analyses Precision analyses

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8 Table 2: Comparison of previously published and current meta-analyses of tDCS in depression

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Name	Diagnosi s	N active, sham	Age (S.D.)	Gender % Female	Rating Scale	tDCS Curren t (mA)	tDCS Session Duration (min)	tDCS Montage: anode, cathode	Number of tDCS Sessions	Treatment resistance level	Con- current ADM	Con- current CCT	Depression outcome
Fregni 2006 ²⁹	Unipolar	9,9	48.2 (10)	No data	MADRS	1.0	20	F3 , FP2	5	no data	No	No	Active>Sham
Boggio 2008 ²⁶	Unipolar	21,10	49 (7.4)	67.5%	HDRS	2.0	20	F3 , FP2	10	1.7	No	No	Active>Sham
Loo 2010 ³⁰	Unipolar	20,20	47.3 (11.3)	55%	MADRS	1.0	20	F3 , FP2	5	Active 1.0 Sham 1.7	Yes	No	Active=Sham
Palm 2011 ³³	unipolar & bipolar	11,11	57 (12)	50%	HDRS	1.0 or 2.0	20	F3 , FP2	10	Active 2.9 Sham 2.91	Yes	No	Active=Sham
Loo 2012 ³⁴	unipolar & bipolar	33,31	48.2 (12.5)	46.6%	MADRS	2.0	20	F3, F8	15	Active 1.71 Sham 1.79	Yes	No	Active>Sham
Blumberger 2012 ³⁶	Unipolar	13,11	42.7 (11.6)	45.6%	HDRS	2.0	20	F3, F4	15	Active 4.3 Sham 4.1	Yes	No	Active=Sham
Brunoni 2013 ²⁷	Unipolar	30,30	42 (12)	68%	MADRS	2.0	30	F3, F4	10+2	1.7	Yes	No	Active>Sham
Bennabi2014 ³⁷	Unipolar	12,12	61.8 (16.3)	75%	HDRS	2.0	30	F3 , FP2	10 (5 days twice daily)	100% > 2	Yes	No	Active=Sham
Segrave 2014 ²⁸	Unipolar	9,9	40.4 (14.5)	37%	MADRS	2.0	24	F3, F8	5	3.0	Yes	Yes	Active=Sham
Brunoni 2014 ⁴²	Unipolar	20,17	18-65	70.2%	HDRS	2.0	30	F3, F4	10	35-41% > 2	Yes	Yes	Active=Sham

10 Table 3: Participant-related factors, tDCS-related factors and tDCS trial depression outcomes: RCTs of tDCS in depression listed in chronological
11 order. Depression outcome is a categorical statement as to whether active tDCS out-preformed sham tDCS in terms of depression outcome
12 measures ($p \leq 0.05$), at the end of active treatment course. ADM = Antidepressant Medication. CCT=Cognitive Control Training. The degree of
13 treatment resistance is indicated by the number of ADM trials failed prior to starting tDCS.

Moderator	k	df	Q_0	p	R^2	b_0	b_1
Current	11	1	0.50	.481	0.0	0.57	-0.30
Number of sessions	11	1	0.00	.964	0.0	0.28	0.00
Session length	11	1	0.14	.705	0.0	0.35	-0.11
Total tDCS time	11	1	0.07	.791	0.0	0.43	-0.00
Total current	11	1	0.41	.783	0.0	0.41	-0.00
ISI	11	1	0.50	.481	0.0	0.26	0.30
Diagnosis	11	1	0.00	.995	0.0	0.31	-0.00
Concurrent ADMs	11	1	2.35	.125	0.0	0.70	-0.53
Concurrent CCT	11	1	3.03	.082	41.2	0.39	-0.59

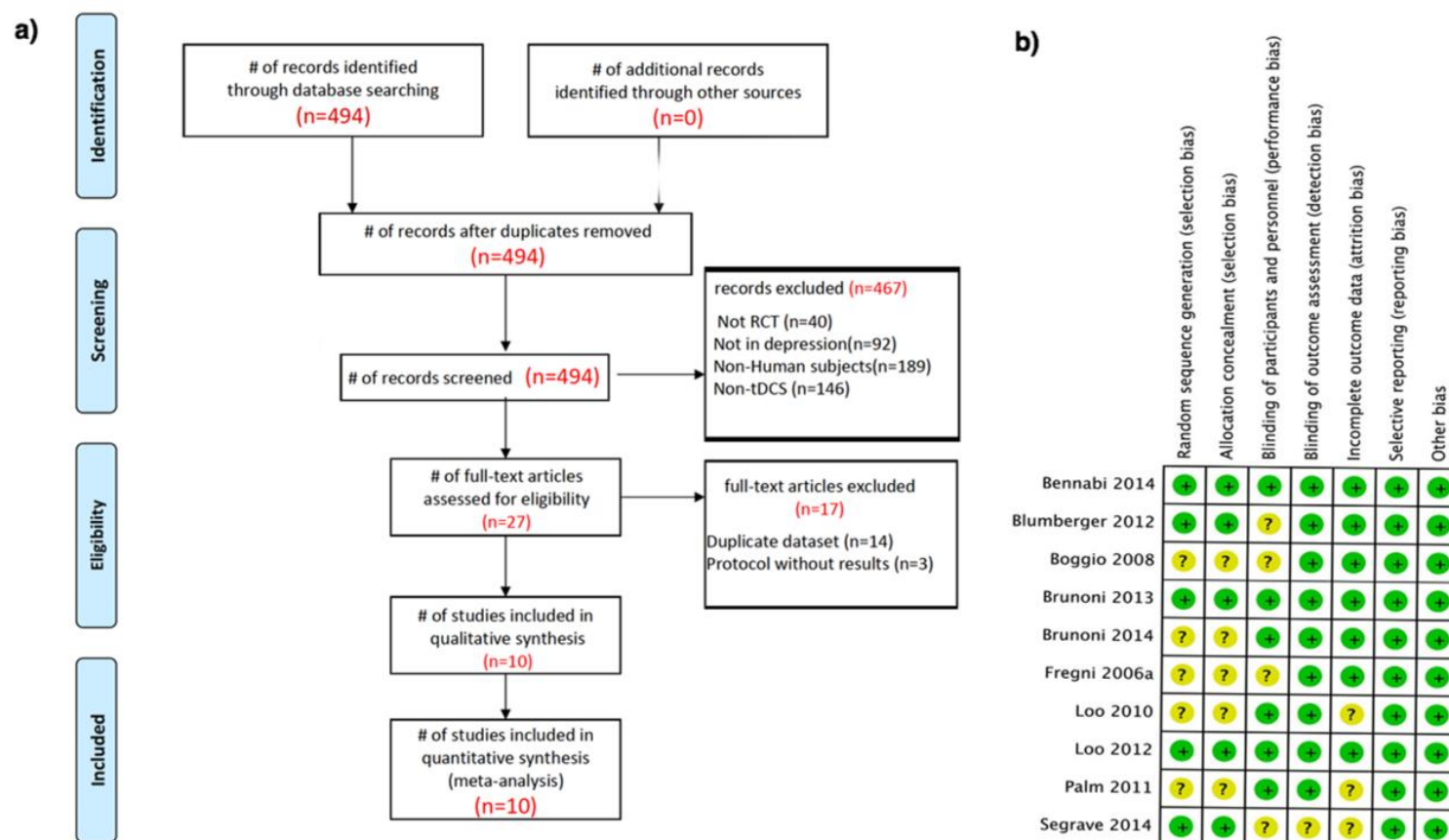
Table 4: A summary of the calculated one-moderator models and associated significance levels. Q_0 is the Wald-type chi squared value for the omnibus test of model coefficients. R^2 is the pseudo R^2 . b_0 and b_1 are the slope and intercept respectively. (ISI=inter-session interval in days, ADM = Antidepressant Medication)

Study	n- active	drop out rate due to adverse effects - active tDCS	n- control	drop out rate due to adverse effects - sham tDCS	<i>p</i>
Fregni 2006 ²⁹	9	0	9	0	1
Boggio 2008 ²⁶	21	0	19	0	1
Loo 2010 ³⁰	20	0	20	0	1
Palm 2011 ³³	11	0	11	0	1
Loo 2012 ³⁴	33	1	31	1	.964
Blumberger 2012 ³⁶	13	1	11	0	.558
Brunoni 2013 ²⁷	60	3	60	1	.347
Brunoni 2014 ⁴²	20	1	17	3	.245
Segrave 2014 ²⁸	9	0	9	0	1

Table 5 : Drop out rates due to adverse events in blind phase of tDCS depression RCTs

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4 Figure 1 Study selection and quality assurance: (a) PRISMA¹ study-selection flowchart for our systematic review and meta-analysis. RCT =
 5 Randomised Controlled Trial. (b) Summary of risk of bias in line with the Cochrane Collaboration’s tool for assessing risk of bias in
 6 randomised trials²⁵. Green circles represent low risk, yellow circles represent unclear risk of bias. The summary was generated using
 7 Cochrane’s Review Manager software (RevMan5.3) –<http://tech.cochrane.org/revm>

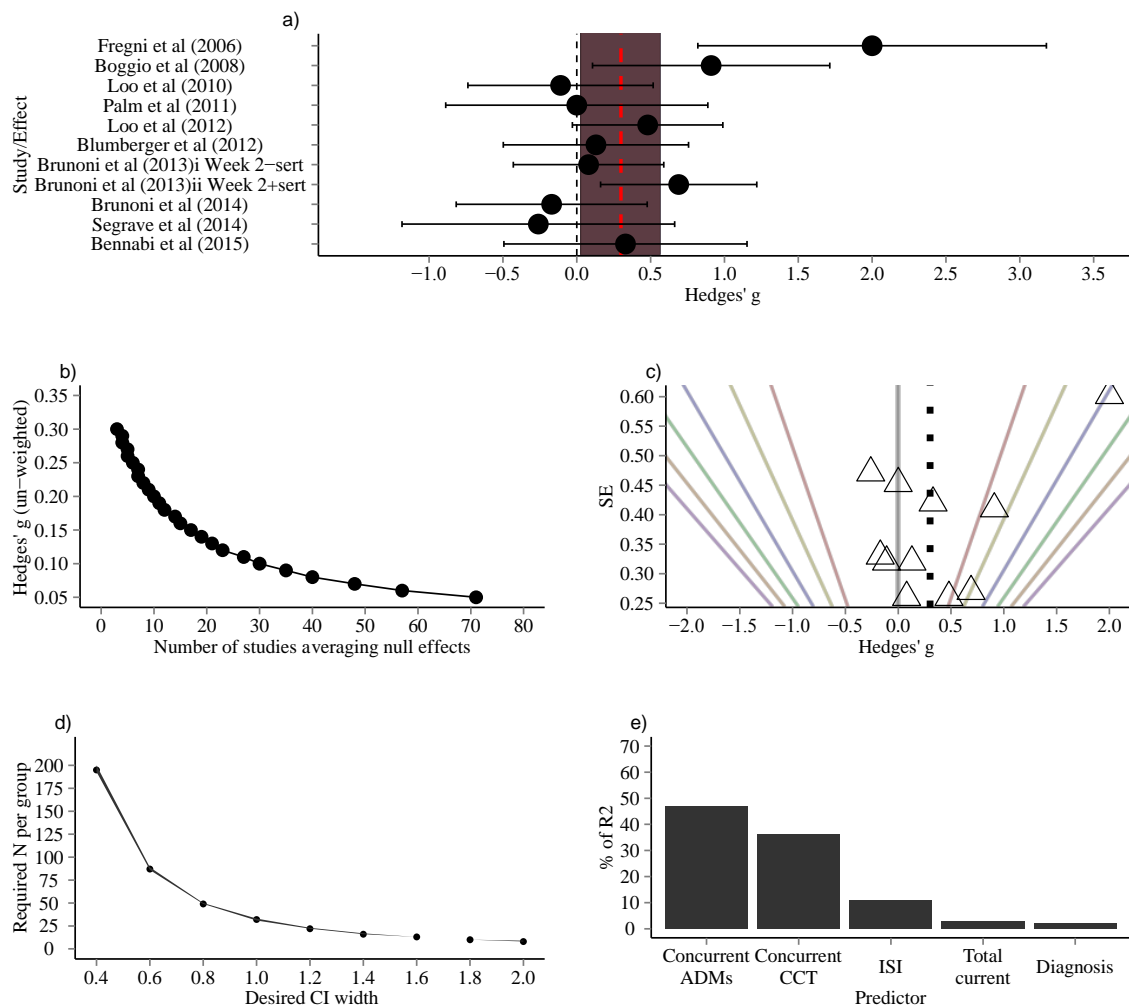


Figure 2. (a) Forest plot of effect sizes for active versus sham treatment. Error bars are 95% confidence intervals. Dotted red line depicts pooled effect. Shaded red region is 95% confidence interval. (b) Orwin fail-safe N analyses (c) Funnel plot. Dotted line is the pooled effect size, colored lines are p values (e.g. red=.05, yellow = .01, blue= .001). (d) Outcome of precision analyses. For instance, to have 99% assurance that a 95% CI will be less than 0.8, approximately 50 participants per group would be required. (e) Relative importance of each moderator. Note that total TDCS time, amplitude, session length and number of sessions were removed due to multi-colinearity. Total current is instead included to summarize these variables.

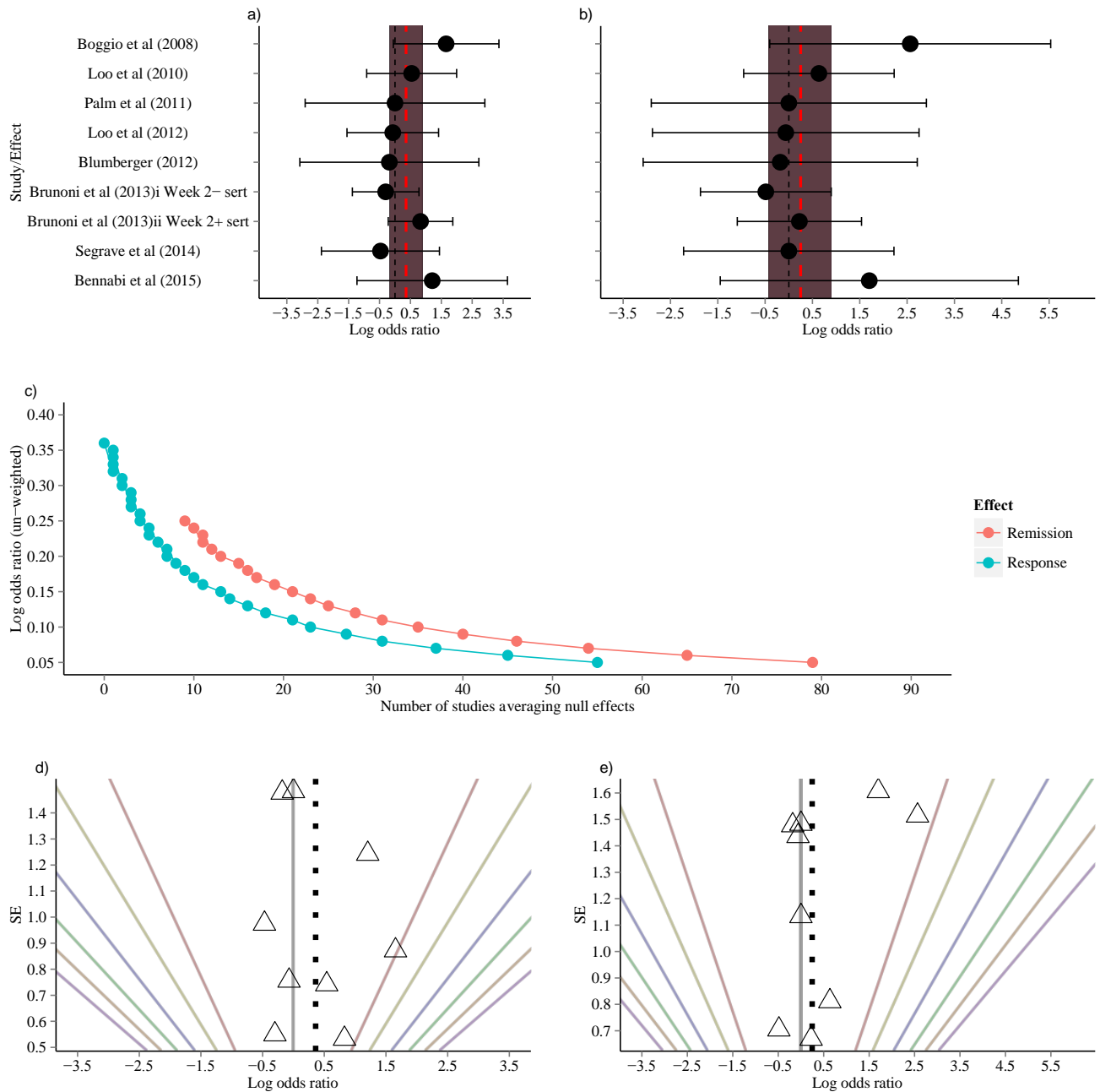


Figure 3. (a) Forest plot of effect sizes for active versus sham treatment: response rates. (b) Forest plot of effect sizes for active versus sham treatment: remission rates. Error bars are 95% confidence intervals. Dotted red line depicts pooled effect. Shaded red region is 95% confidence interval. (c) Orwin fail-safe N analyses (d) Funnel plot: response rates. (d) Funnel plot: remission rates. Dotted line is the pooled effect size, colored lines are p values (e.g. red=.05, yellow = .01, blue= .001).