Title

Transcranial direct current stimulation effects in late life depression: a meta-analysis of individual participant data

Authors

Rachael M. Rimmer [1], Sergi, G. Costafreda [2], Julian Mutz [3], Katherine Joseph [1], Andre R. Brunoni [4], Colleen K. Loo [5], Frank Padberg [6], Ulrich Palm [6, 7], Cynthia H. Y. Fu [1,8]

Affiliations

1. School of Psychology, University of East London, London, UK
2. Division of Psychiatry, Faculty of Brain Sciences, University College London, London, UK
3. Social Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
4. Service of Interdisciplinary Neuromodulation, Institute of Psychiatry, Hospital das Clínicas da Faculdade de Medicina da USP; Department of Psychiatry and Department of Internal Medicina, Faculdade de Medicina da USP; University of São Paulo, São Paulo, Brazil
5. Department of Psychiatry & Black Dog Institute, University of New South Wales, Sydney, Australia
6. Department of Psychiatry and Psychotherapy, LMU University Hospital Munich, Germany
7. Medical Park Chiemseeblick, Hospital for Psychosomatics, Bernau-Felden, Germany
8. Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

Corresponding Author:

CHY Fu, University of East London, Arthur Edwards Building, Water Lane, London, E15 4LZ, UK

Tel: +44 (0)208 223 4119 Fax: +44(0)208 223 4937 Email: c.fu@uel.ac.uk

Abstract

Background: Late life depression (LLD) refers to major depressive disorder (MDD) in adults over 65 years. LLD is associated with high morbidity and poor treatment outcomes. Transcranial direct current stimulation (tDCS) is a novel treatment for MDD. Efficacy in LLD though is unclear. Our aim was to investigate tDCS efficacy by pooling randomised controlled trials (RCT) in an individual participant data meta-analysis.

Methods: Databases were searched for sham controlled RCTs of tDCS in MDD and bipolar depression. Individual participant data (IPD) were requested. Primary outcome was change in depressive symptoms. Bayesian multilevel modelling meta-analysis was conducted with individual participants nested within studies.

Results: 6 RCTs were eligible, consisting of 43 participants (22 women), mean age 69.2 years. Active anodal tDCS over left dorsolateral prefrontal cortex (n=19) was associated with an improvement in depressive severity, effect size 0.14 (95% credible interval [-0.44;0.15]) as compared to sham tDCS, which was not statistically significant. There was an 82% probability that tDCS treatment has a modest but non-null effect in improving depressive symptoms. Acceptability was high with no significant differences in discontinuation rates between active and sham groups.

Limitations: The total sample size was small, limiting power.

Discussion: In LLD, tDCS demonstrates a modest but non-null effect in improving depressive symptoms. Acceptability was high as measured by discontinuation rates. tDCS is a potential novel treatment option in LLD, though large scale RCTs in LLD are required to investigate this important clinical application.

Keywords

transcranial direct current stimulation; late life depression; geriatric depression; major depressive disorder; individual participant data; meta-analysis

Introduction

Late life depression (LLD) refers to major depressive disorder (MDD) in adults 65 years or older (Lebowitz et al., 1997). LLD is typically associated with comorbid neurological, medical and psychiatric disorders and shows a poorer clinical response relative to younger age groups (Tham et al., 2016). Aetiological mechanisms in LLD are multiple and complex, involving age- and disease-related processes, including immunological dysregulation, genetic liability and cerebrovascular changes (Alexopoulos, 2019). The most common treatments are antidepressant medication and psychotherapy. Psychotherapy has demonstrated efficacy in LLD with comparable effect sizes to antidepressants (Cuijpers et al., 2006; Huang et al., 2015). However, antidepressant adherence rates are low in LLD, in which 11-21% do not start treatment and 33-38% discontinue treatment early (Holvast et al., 2019). Antidepressants are also associated with increased rates of adverse effects, including anticholinergic effects, such as diarrhoea, nausea, and dizziness, and might be contraindicated with other medications taken in this age group (Krause et al., 2019).

Transcranial direct current stimulation (tDCS) is a novel treatment for MDD (Woodham et al., 2021). tDCS applies a weak electrical current which modulates cortical tissue excitability, facilitating neuronal depolarization and leading to polarity-dependent neuroplasticity. The effect can extend beyond the site of stimulation to deeper brain structures, including anterior cingulate and amygdala, and is associated with changes in resting state networks (Palm et al., 2016). tDCS has demonstrated efficacy and acceptability in MDD with a course of active tDCS treatment is associated with a fourfold increased rate of clinical response (OR = 4.32, 95% CI [2.02; 9.29]) and a threefold increased rate of clinical remission (OR = 3.07, 95% CI [1.58; 5.99]) as compared to sham tDCS (Mutz et al., 2018). While age has not been found to have an impact on treatment effect (Razza et al., 2020), these meta-analyses had examined aggregate data. An individual participant data (IPD) meta-analysis synthesizes the raw

individual-level data from each study, which can improve quality and reliability statistically as well as clinically, and is considered the gold standard for meta-analyses (Riley et al., 2010).

We sought to investigate efficacy and acceptability of tDCS treatment in LLD in an individual participant data meta-analysis. We examined sham-controlled RCTs of tDCS in MDD and bipolar depression and approached authors to contribute their trial data in adults aged 65 years and over.

Methods

Registration

The protocol was registered with PROSPERO (No: CRD42019137488) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplementary Figure S1).

Eligibility criteria

A systematic literature search was conducted using PsycINFO (EBSCO), MEDLINE (PubMed) and PsychSource (EBSCO) databases from the first available date to 20 October 2021, key words: ((“bipolar disorder” OR “bipolar depression” OR “major depression” OR “unipolar depression” OR “unipolar disorder”) AND (“transcranial direct current stimulation” OR “tDCS”)). References of reviews and included papers were checked for additional publications.

Inclusion criteria: (i) adults aged 65 years or older; (ii) current major depressive episode with diagnosis of MDD or bipolar disorder according to DSM or ICD criteria; (iii) sham-controlled tDCS RCT; (iv) clinician-administered depressive symptom rating scale, e.g., Hamilton Depression Rating Scale (HDRS) or Montgomery-Åsberg Depression Rating Scale (MADRS);

(v) being published in English. Exclusion criteria: (i) primary diagnosis other than MDD or bipolar disorder e.g., postpartum depression, psychotic depression, or secondary to a medical illness; (ii) co-initiation of any other form of treatment e.g., pharmacotherapy or cognitive control training.

Study selection and data extraction

Abstracts were independently assessed (KJ, RR), and differences were resolved by consensus with review (CF). Study level data were extracted, and authors were contacted for non-identifiable IPD and any information not available from the publication. Data consistency and completeness were checked (RR) and reviewed (CF).

Risk of bias assessment in individual studies

Methodological quality was assessed using Cochrane risk of bias tool (Higgins et al., 2021), which evaluates on basis of selection, performance, detection, attrition and reporting biases (Supplementary Figures S2-3).

Specification of outcomes

Outcome measures were: (1) continuous measure of depressive symptoms, estimated as difference in z-scaled mood scored from baseline to study end; (2) categorical measure of clinical response, defined as a 50% or greater improvement in depressive symptoms from baseline to study end; (3) categorical measure of clinical remission, defined as MADRS ≤10, 17-item HDRS ≤7, 21-item HDRS ≤8, 24-item HDRS ≤9 at study end (Keller, 2003); (4) acceptability, defined as number of participants who did not complete either active or sham tDCS treatment arms.

For studies which had used two or more depression rating scales, the scale used as the primary outcome was selected (Loo et al., 2010, Brunoni et al., 2013; Brunoni et al., 2017) (Supplementary Table S1). For studies with multiple treatment arms, only active and sham tDCS treatments arms were included. For studies with a crossover design, only the first phase parallel between-participants data were used.

Data analysis

A one-stage IPD Bayesian hierarchical model was conducted as the primary analysis. Hierarchical meta-analysis allows for modelling of individual-level covariates (age, sex, illness duration) and their potential interaction with treatment effects, while accounting for clustering of individual patients within a study (Higgins et al., 2021). One-stage Bayesian methods are recommended for meta-analysis of small trials with few participants and when heterogeneity is expected across trials, as uncertainty in estimates can be fully incorporated in the modelling (Lunn et al., 2013).

Individual study data sets were combined into a merged data set, with participants nested within studies. As studies used different rating scales (2 HDRS versions and MADRS), depression scores were standardised across studies by transforming them into z-scores. For variables of interest, 4 participants had missing follow-up mood outcome, and 1 participant had missing disease duration. To maintain the intention-to-treat nature of the analysis, we assumed data were missing at random, and we imputed missing disease duration and depression scores at follow-up using a well-established multivariate imputation algorithm (van Buuren and Groothuis-Oudshoorn, 2011), resulting in multiple (n=200) datasets with imputed missing values.

Mixed effects models with random trial-specific intercepts, treatment effects and co-variates were fitted to these data sets, with results combined into an average fitted model (Bürkner,

2017). Trial-specific treatment effects were assumed to follow a normal distribution, with the mean of this distribution representing pooled population-averaged treatment effect. We used weakly informative prior distributions so information in the dataset would be reflected in final posterior distributions. In particular, we used a weakly informative normal distribution (centred at zero and with a standard deviation of 1) as prior distribution of pooled treatment effect estimate, and similarly weakly informative half-Cauchy prior (scale parameter of 0.5) was used for between study variability. We used a Markov chain Monte Carlo algorithm to draw samples from the posterior distribution of parameters of interest (Bürkner, 2017).

Bayesian IPD meta-analysis was used to predict final depression score with adjustment for baseline score, age and sex. Additional analyses explored effect of disease duration and presence of treatment-resistant depression, defined by having persistent depressive symptoms despite at least 2 adequate treatment trials, and duration of illness. We considered fitting additional logistic regression models to predict planned categorical outcomes of treatment response and remission, however this was not possible due to the very limited number of participants with these outcomes (n=6 clinical response; n=3 remission).

Posterior distributions obtained from Bayesian model fitting allow for direct probability statements, and we report the probability of a beneficial treatment effect of tDCS, along with point estimates and 95% credible intervals for parameters of interest. Sensitivity analysis on average pooled tDCS treatment effect, as main parameter of interest, was conducted using a two-step approach with trial-level estimates of treatment effect estimated and pooled in a second level frequentist meta-analysis, and last observation carried forward instead of imputation of missing values (Viechtbauer, 2010). All analyses were conducted using R (R Core Team, 2018).

Results

Total of 4336 records were assessed, and 9 studies met inclusion and exclusion criteria. Present analysis consists of 6 studies, 43 participants (22 women) (mean age 69.3 ± 4.2 years, range 65 – 81 years), mean illness duration 145.33 ± 151.48 months, from total sample of 617 participants (Loo et al., 2010; Loo et al., 2012; Palm et al., 2012; Brunoni et al., 2013; Brunoni et al., 2017; Loo et al., 2018) (Supplementary Figure S1). Majority had unipolar depression 76.7% (n=33), and 62.7% met criteria for treatment resistant depression (n=27) (Table 1, Supplementary Table S1). There were no significant differences in demographics between tDCS (n=19) and sham control (n=24) treatment groups. There were no cases of treatment-emergent mania. Risk of bias was low for all studies (Supplementary Figures S2-S3). Authors from remaining studies had not replied to requests or were unable to share individual participant data.

Using Bayesian multilevel modelling for IPD meta-analysis, treatment with tDCS was associated with a reduction of SMD = -0.14 (95% credible interval [-0.44; 0.15]) in depression scores, relative to sham tDCS, which was not statistically significant.

Based on estimated posterior distribution of the average effect of tDCS across the studies, there is an 82% probability that tDCS treatment has at least a small effect (change in symptoms score < 0) in improving depressive symptoms in LLD. There was no evidence of significant main effects of age (change per year in SMD = 0.00 95% credible interval [-0.02;0.02]), sex (male sex SMD = -0.09 95% credible interval [-0.27;0.10]), or their interactions with treatment, though samples sizes were small. There was no evidence of significant main effect of treatment resistance or illness duration. Sensitivity analysis using a two-step IPD frequentist meta-analysis with last observation carried-forward showed similar results, with tDCS treatment associated with a reduction of -0.12 (95% confidence interval [-0.34; 0.12]) (Figure 1).

Most participants completed treatment (n=39; 90.7%). Discontinuation rates were 15.8% (3/19) for active tDCS and 4.2% (1/24) for sham tDCS, which was not statistically significant (OR = 4.3, 95% CI 0.41- 45.28, p=0.31).

Discussion

The present IPD meta-analysis demonstrates a modest but non-null effect for tDCS improving depressive symptoms in LLD. While the effect was low and did not reach statistical significance in the present IPD sample, the sample size was small, and many participants had a more treatment resistant form of depression. As tolerability and acceptability are significant limitations of current treatments in LLD, tDCS offers a potential novel treatment option. tDCS efficacy has shown an overall effect size that is low to moderate across all ages (Mutz et al., 2018; Moffa et al., 2020; Zhang et al., 2021), and full efficacy might become evident over a longer term, from 3 - 6 months (Brunoni et al., 2017). In the present analysis, outcomes were assessed immediately following the treatment period, which consisted of 5 - 22 sessions (Loo et al., 2010; Loo et al., 2012; Palm et al., 2012; Brunoni et al., 2013; Brunoni et al., 2017; Loo et al., 2018), and it is possible that improved outcomes might been seen with a longer follow up. Moreover, dose has been identified as a significant and independent predictor (Brunoni et al., 2016). We also considered that treatment resistant depression might contribute to efficacy, although this was underpowered in the present sample (Moffa et al., 2020).

A limitation of this meta-analysis is the small sample size, which limited power to detect an effect. IPD were collated from large RCTs of all ages, but there has not yet been a large scale RCT in LLD. There is emerging evidence for tDCS as an adjunct treatment in hard-to-treat vascular LLD and using novel montages such as high definition-tDCS in LLD (Wong et al., 2019; Zanardi et al., 2021).

In summary, the present IPD meta-analysis demonstrates that tDCS has a modest but non-null effect in improving depressive symptoms in LLD. However, the sample was small, and large-scale RCTs are required to investigate efficacy of tDCS in LLD. Acknowledging these shortcomings and the modest statistical effects, the findings provide support for further investigation into the efficacy of tDCS as a treatment for LLD and vascular depression.

Acknowledgements

We would like to thank the participants and research team members in the clinical trials.

Funding

This work was supported by the Rosetrees Trust [A1950] to CF. RR received funding support from UEL PhD Excellence studentship.

Figure Legends

Figure 1. Standardised mean difference of depressive scores are presented for each study, with negative scores indicating a benefit from treatment and favouring tDCS over sham.

References

Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. *Translational Psychiatry*, *9*(1), 1-16. https://doi.org/10.1038/s41398-019-0514-6

Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., ... & Loo, C. K. (2016). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *British Journal of Psychiatry*, *208*(6), 522-531. https://doi.org/10.1192/bjp.bp.115.164715

Brunoni, A. R., Moffa, A. H., Sampaio-Junior, B., Borrione, L., Moreno, M. L., Fernandes, R. A., … Benseñor, I. M. (2017). Trial of electrical direct-current therapy versus escitalopram for depression. *New England Journal of Medicine*, *376*(26), 2523–2533. https://doi.org/10.1056/NEJMoa1612999

Brunoni, A. R., Valiengo, L., Baccaro, A., Zanao, T. A., de Oliveira, J. F., Goulart, A., ... & Fregni, F. (2013). The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry*, *70*(4), 383-391. https://doi.org/10.1001/2013.jamapsychiatry.32

Bürkner, P. C. (2017). brms: An R package for Bayesian multilevel models using Stan. *Journal of Statistical Software*, *80*(1), 1-28. https://doi.org/10.18637/jss.v080.i01

Cuijpers, P., van Straten, A., & Smit, F. (2006). Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. *International Journal of Geriatric Psychiatry, 21*(12), 1139-1149. https://doi.org/10.1002/gps.1620

Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li T, Page, M. J., & Welch, V. A., (editors, 2021). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2. *The Cochrane Collaboration*: 33-49. Available from: www.training.cochrane.org/handbook

Holvast, F., Oude Voshaar, R. C., Wouters, H., Hek, K., Schellevis, F., Burger, H., & Verhaak, P. F. (2019). Non-adherence to antidepressants among older patients with depression: a longitudinal cohort study in primary care. *Family Practice*, *36*(1), 12-20. https://doi.org/10.1093/fampra/cmy106

289 Huang, A. X., Delucchi, K., Dunn, L. B., & Nelson, J. C. (2015). A systematic review and
290 meta-analysis of psychotherapy for late-life depression. *The American Journal of Geriatric*
291 *Psychiatry*, *23*(3), 261-273. https://doi.org/10.1016/j.jagp.2014.04.003
292 Keller, M. B. (2003). Past, present, and future directions for defining optimal treatment
293 outcome in depression: remission and beyond. *JAMA*, *289*(23), 3152-3160.
294 https://doi.org/10.1001/jama.289.23.3152
295 Krause, M., Gutsmiedl, K., Bighelli, I., Schneider-Thoma, J., Chaimani, A., & Leucht, S.
296 (2019). Efficacy and tolerability of pharmacological and non-pharmacological interventions in
297 older patients with major depressive disorder: A systematic review, pairwise and network
298 meta-analysis. *European Neuropsychopharmacology*, *29*(9), 1003-1022.
299 https://doi.org/10.1016/j.euroneuro.2019.07.130
300 Lebowitz, B. D., Pearson, J. L., Schneider, L. S., Reynolds III, C. F., Alexopoulos, G. S.,
301 Bruce, M. L., ... & Parmelee, P. (1997). Diagnosis and Treatment of Depression in Late Life:
302 Consensus Statement Update [Consensus Statement]. *JAMA*, *278*(14), 1186-1190.
303 https://doi.org/10.1001/jama.1997.03550140078045
304 Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., & Sachdev, P. (2012).
305 Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled
306 trial. *British Journal of Psychiatry*, *200*(1), 52-59. https://doi.org/10.1192/bjp.bp.111.097634
307 Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., ... & Mitchell, P.
308 (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the
309 treatment of depression. *International Journal of Neuropsychopharmacology*, *13*(1), 61-69.
310 https://doi.org/10.1017/S1461145709990411
311 Loo, C., Husain, M., Mcdonald, W., Aaronson, S., O'Reardon, J., Alonzo. A., … Lisanby, S.
312 (2018). International randomized-controlled trial of transcranial Direct Current Stimulation in
313 depression. *Brain Stimulation*, *11*(1), 125-133. https://doi.org/10.1016/j.brs.2017.10.011
314 Lunn, D., Barrett, J., Sweeting, M., & Thompson, S. (2013). Fully Bayesian hierarchical
315 modelling in two stages, with application to meta-analysis. *Journal of the Royal Statistical*
316 *Society. Series C, Applied Statistics*, *62*(4), 551-572. https://doi.org/10.1111/rssc.12007

Moffa, A. H., Martin, D., Alonzo, A., Bennabi, D., Blumberger, D. M., Benseñor, I. M., ... & Brunoni, A. R. (2020). Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *99*, 109836. https://doi.org/10.1016/j.pnpbp.2019.109836

Mutz, J., Edgcumbe, D. R., Brunoni, A. R., & Fu, C. H. (2018). Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. *Neuroscience & Biobehavioral Reviews*, *92*, 291-303. https://doi.org/10.1016/j.neubiorev.2018.05.015

Palm, U., Hasan, A., Strube, W., & Padberg, F. (2016). tDCS for the treatment of depression: a comprehensive review. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(8), 681-694. https://doi.org/10.1007/s00406-016-0674-9

Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., ... & Padberg, F. (2012). Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. *Brain Stimulation*, *5*(3), 242-251. https://doi.org/10.1016/j.brs.2011.08.005

Razza, L. B., Palumbo, P., Moffa, A. H., Carvalho, A. F., Solmi, M., Loo, C. K., & Brunoni, A. R. (2020). A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. *Depression and Anxiety*, *37*(7), 594-608. https://doi.org/10.1002/da.23004

Riley, R. D., Lambert, P. C., & Abo-Zaid, G. (2010). Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*, *340*(c221).https://doi.org/10.1136/bmj.c221

Tham, A., Jonsson, U., Andersson, G., Söderlund, A., Allard, P., & Bertilsson, G. (2016). Efficacy and tolerability of antidepressants in people aged 65 years or older with major depressive disorder–a systematic review and a meta-analysis. *Journal of Affective Disorders*, *205*, 1-12. https://doi.org/10.1016/j.jad.2016.06.013

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(3), 1–67. https://doi.org/10.18637/jss.v045.i03

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*, *36*(3), 1-48. https://doi.org/10.18637/jss.v036.i03

Woodham, R., Rimmer, R. M., Mutz, J., & Fu, C. H. (2021). Is tDCS a potential first line treatment for major depression?. *International Review of Psychiatry*, *33*(3) 1-16. https://doi.org/10.1080/09540261.2021.1879030

Wong, H. L., Chan, W. C., Wong, Y. L., Wong, S. N., Yung, H. Y., Wong, S. M. C., & Cheng, P. W. C. (2019). High-definition transcranial direct current stimulation—An open-label pilot intervention in alleviating depressive symptoms and cognitive deficits in late-life depression. *CNS Neuroscience & Therapeutics*, *25*(11), 1244-1253. https://doi.org/10.1111/cns.13253

Zanardi, R., Poletti, S., Prestifilippo, D., Attanasio, F., Barbini, B., & Colombo, C. (2020). Transcranial direct current stimulation: A novel approach in the treatment of vascular depression. *Brain Stimulation*, *13*(6), 1559-1565. https://doi.org/10.1016/j.brs.2020.08.013

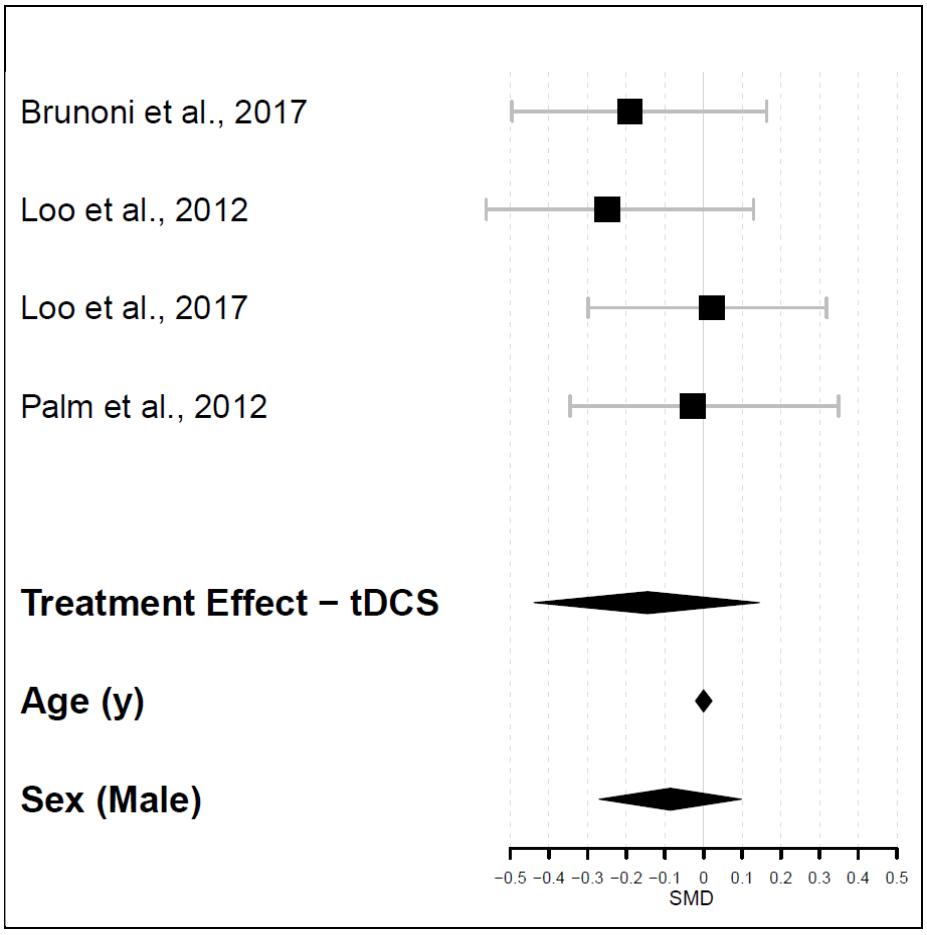
Zhang, R., Lam, C. L., Peng, X., Zhang, D., Zhang, C., Huang, R., & Lee, T. M. (2021). Efficacy and acceptability of transcranial direct current stimulation for treating depression: A meta-analysis of randomized controlled trials. *Neuroscience & Biobehavioral Reviews*, *126*, 481-490. https://doi.org/10.1016/j.neubiorev.2021.03.026

Table 1. Clinical and demographic characteristics

	Average	**Loo (2010)**	**Loo (2012)**	**Palm (2012)**	**Brunoni (2013)**	**Brunoni (2017)**	**Loo (2017)**
Total sample size	43 (22)	1 (0)	5 (2)	7 (5)	4 (2)	7 (3)	19 (10)
Age (yrs)	69.3 (4.22)	65.0	70.2 (5.17)	70 (4.83)	65.0 (0.00)	68.3 (3.45)	70.4 (4.29)
Age range	65-81	65	65-78	65-79	65	65-73	65-81
Education (yrs)	16.72 (3.57)	NR	NR	NR	NR	14.3 (3.62)	18 (2.89)
Unipolar depression	33	1	4	7	4	6	11
Medication (n)	15	0	1	7	0	2	5
Duration of illness (months)	145.33 (151.48)	6	64 (81.28)	219.4 (110.57)	11 (9.42)	87.17 (169.68)	213.89 (166.00)
Treatment resistant depression (TRD)	27	0	1	7	0	3	16

Number of participants is presented with number of female participants in parenthesis. Mean values are presented for each variable with standard deviation in parenthesis. As there was one participant from Loo et al. (2010), there is no standard deviation for age and no age range.

Figure 1.


Brunoni et al., 2017
Loo et al., 2012
Loo et al., 2017
Palm et al., 2012
Treatment Effect − tDCS
Age (y)
Sex (Male)
−0.5 −0.4 −0.3 −0.2 −0.1 0 0.1 0.2 0.3 0.4 0.5
SMD

Supplementary Table S1

Table S1. Summary of the included studies

Study	**Loo et al (2010)**	**Loo et al (2012)**	**Palm et al (2012)**	**Brunoni et al (2013)**	**Brunoni et al (2017)**	**Loo et al (2017)**
Study design	RCT	RCT	RCT, crossover	4-arm RCT	3-arm RCT	RCT
Main inclusion	MDD	MDD ≥3 years	MDD	MDD, low suicide risk, AD free	MDD	MDD
Depression cut off	MADRS ≥ 20	MADRS ≥ 20	HDRS-24 ≥ 18	HDRS-17 ≥ 17	HDRS-17 ≥ 17	MADRS ≥ 20
Bipolar disorder	Excluded	Allowed	Excluded	Excluded	Excluded	Allowed
Main exclusion criteria	Other Axis I disorders, Failure of ECT, neurological disorders	Other Axis I disorders, ECT failure, neurological disorders	Other Axis I disorders, suicidality, neurological disorders	Other Axis I disorders, Axis II disorders, neurological disorders	Other Axis I disorders, Axis II disorders, neurological disorders (Anxiety not excluded)	Other Axis I disorders, >3 failed meds, ECT failure, neurological disorders
Primary outcome measure	MADRS	MADRS	HDRS-24	MADRS	HDRS-17	MADRS
Age range, years	18-65	23-78	36-79	18-65	18-75	18-81
Total Sample Size (n)	40	60	22	120	245	130
<u>tDCS characteristics</u>						
Device	Eldith DC	Eldith DC	Eldith DC	Chattanooga lonto	Soterix	Customised device
Anode	F3	pF3	F3	F3	F3	F3
Cathode	RSO	F8	FP2	F4	F4	F8
Frequency, No sessions	5	15	10	10	22	20
Weeks, stimulation	2	3	2*	4	10	4
Current density	0.29	0.57	0.28-0.57	0.8	0.8	0.83
Session duration (mins)	20	20	20	30	30	30
Total charge (mA)	1	2	1-2	2	2	2.5

AD= antidepressant, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale; all studies completed an intention-to-treat analysis, *crossover +2.

Figure S1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

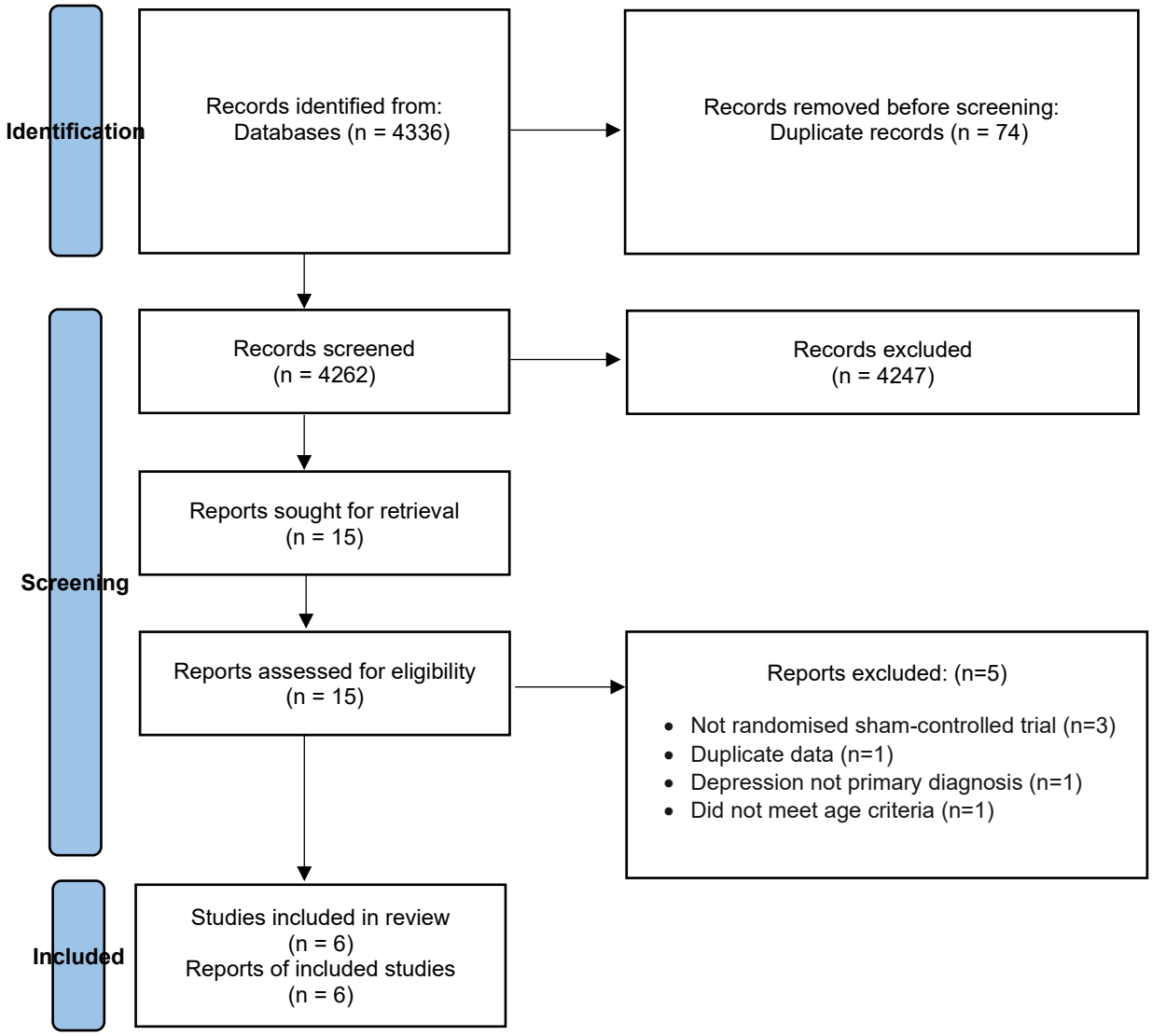


Figure S2. Cochrane Risk of Bias Graph

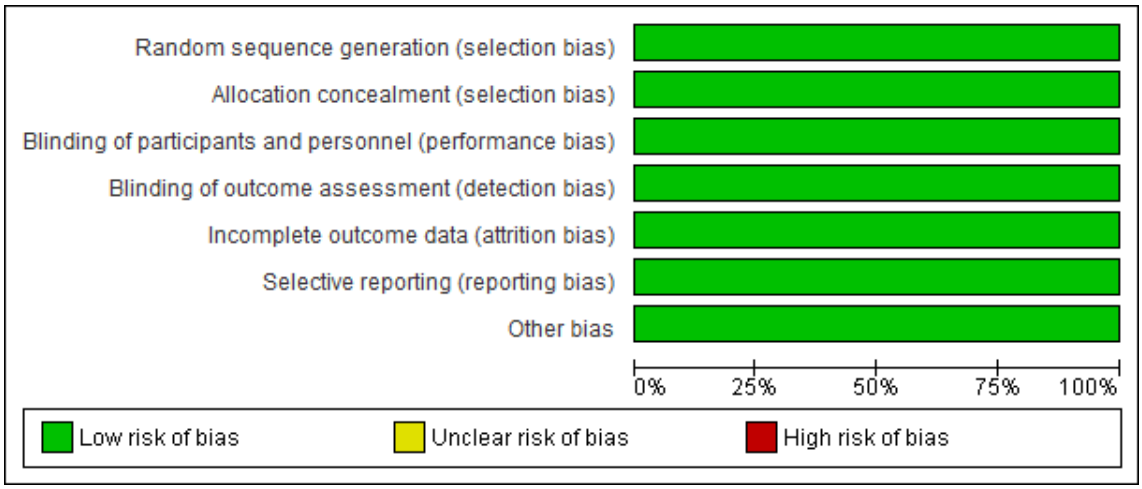
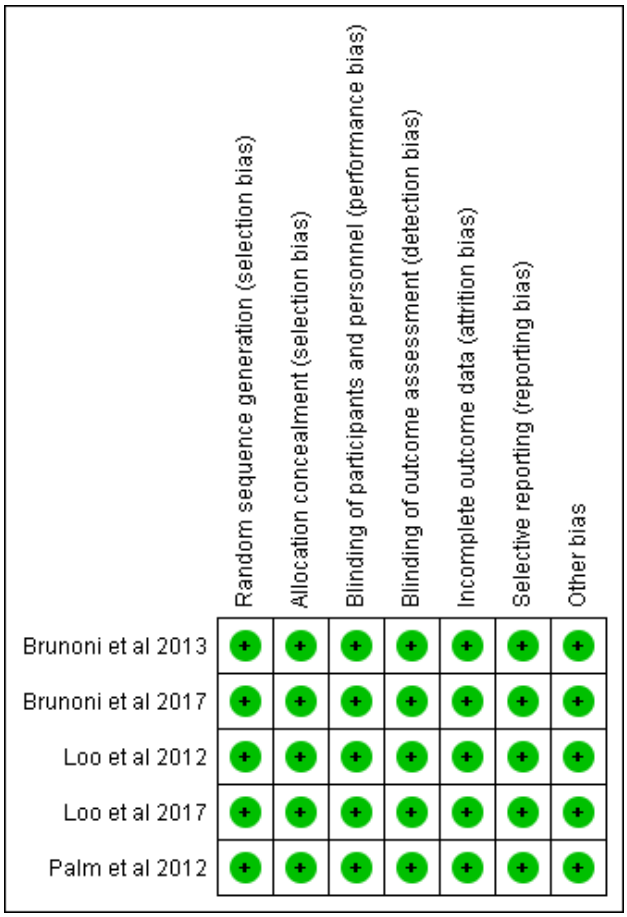


Figure S3. Risk of Bias Summary



Cochrane Risk of Bias Tool – Supporting evidence

Brunoni et al., 2017

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: 'patients were randomly assigned in a 2:3:3 ratio, with the use of a permuted-block design'
Allocation concealment (selection bias)	Low Risk	quote: using 'a computer-generated list, to receive one of three regimens'
Blinding of participants and personnel (performance bias)	Low Risk	Comment: double blind study: Quote: 'used fully automated devices that perform active or sham tDCS according to a randomized stimulation code'
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: 'Patients correctly guessed their trial-group assignment to escitalopram but not to active tDCS'.
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: 'Patients correctly guessed their trial-group assignment to escitalopram but not to active tDCS'.
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: 'missing data will be handled using an ITT approach
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	Low Risk	Quote: missing data will be handled using an ITT approach
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Loo et al., 2017

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: 'Participants were randomly assigned by a computer-generated random number sequence to active or sham tDCS with permuted-block randomization. Randomization was stratified according to . . .[diagnosis]'
Allocation concealment (selection bias)	Low Risk	Quote: 'Participants were randomly assigned by a computer-generated random number sequence to active or sham tDCS with permuted-block randomization. Randomization was stratified according to . . .[diagnosis]'
Blinding of participants and personnel (performance bias)	Low Risk	Quote: 'All participants, tDCS treaters… were blinded to the participants' tDCS group allocation in the RCT phase. The blinding was

		maintained until the entire study was completed'.
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: 'All participants … were blinded to the participants' tDCS group allocation in the RCT phase. The blinding was maintained until the entire study was completed'.
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: 'All … study raters were blinded to the participants' tDCS group allocation in the RCT phase'
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: 'using a mixed effects repeated measures (MERM) analysis. . . more appropriately handle missing data relative to more traditional repeated measures analytical methods'
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	Low Risk	Quote: 'using a mixed effects repeated measures (MERM) analysis. . . more appropriately handle missing data relative to more traditional repeated measures analytical methods'
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Brunoni et al., 2013

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: "A assistant not directly involved in other aspects of the trial performed a 1:1:1:1 permuted block randomization."
Allocation concealment (selection bias)	Low Risk	Quote: '"...the allocation was concealed using a central randomization method."
Blinding of participants and personnel (performance bias)	Low Risk	Quote: "...patients were blinded to the treatment"; "..., because the nurses were not blinded to the intervention, their interaction with the participants was minimal"
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: " The raters and patients were blinded to the treatment"
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: " The raters and patients were blinded to the treatment"
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: "Analyses were conducted in the intention-to-treat sample according to last observation carried forward through the time points. Missing data were considered to be at random" Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	work focused in the efficacy of tDCS during the acute phase of the major depressive episode

Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Palm et al., 2012

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: “patients were randomized in two groups.”
Allocation concealment (selection bias)	Low Risk	Quote: “...using a PC-generated random number list”. Concealment confirmed by the authors.
Blinding of participants and personnel (performance bias)	Low Risk	“double blind”; “Two indistinguishable CE-certified programmable constant current DCStimulator were used for active and placebo tDCS. ” Personnel blinding confirmed by authors
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: “double blind”.
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: “rating scales and cognitive tests were administered by experienced raters blind to treatment conditions..."
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: “Twenty patients completed the study, two dropped out because of personal reasons. The data of all 22 subjects were included in the analysis (last observation carried forward)."
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Loo et al., 2012

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: “participants were stratified by gender and age and randomly assigned by a computergenerated random sequence”
Allocation concealment (selection bias)	Low Risk	Quote: “The treatment assignment was indicated by a code on study treatment sheets, which were concealed from raters.”
Blinding of participants and personnel (performance bias)	Low Risk	Quote: “ ...participants(...) masked to group allocation.”
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: “"...participants (...) masked to group allocation."
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: “... raters masked to group allocation

Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote:" Intention-to-treat last observationcarried-forward scores were used for the analyses". Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Loo et al., 2010

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: “Subjects were stratified by age and gender and then randomly assigned to active or sham treatment groups
Allocation concealment (selection bias)	Low Risk	Comment: allocation concealment confirmed by the authors
Blinding of participants and personnel (performance bias)	Low Risk	Quote: “with (...) subjects blind to treatment group assignment.”; Quote: “The switching on and off of the current was programmed into the stimulator and did not require intervention by the operator. The machine was placed behind the subjects’ heads so that they were unable to see the readout on the front panel of the stimulator..” Personnel blinding confirmed by the authors
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote:" with (...) subjects blind to treatment group assignment."
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: "All ratings were conducted by a psychiatrist who was blinded to treatment condition..."
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: “Intention-to-treat last-observation carried-forward scores were used for the analyses" Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	Comment: work focused on the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.