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Transcranial direct current stimulation for the treatment of major depressive disorder: A meta-analysis of randomized controlled trials

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ABSTRACT

Major depressive disorder (MDD) is a common and refractory mental disorder. Although antidepressant drugs may be effective for treating MDD, a number of patients do not improve with pharmacologic treatment. Novel therapeutic strategies which are safer and more effective are of great significance in the treatment of MDD. Transcranial direct cranial stimulation (tDCS) is a promising intervention for treating MDD, and it has demonstrated antidepressant effects and beneficial effects on cognitive function. The aim was to assess the efficacy of tDCS as a treatment for MDD.

Four databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI) and Wanfang database were searched for articles related to tDCS and major depression. The mean difference (MD) and 95% confidence interval (CI) were calculated in this study.

A significant difference between tDCS compared with the control group in Montgomery-Asberg depression rating scale (MADRS) was found. There was a significant statistical difference between tDCS and the control group in Hamilton Depression Rating Scale, 17-items (HDRS-17).

This study demonstrated that the intervention of active tDCS was superior to the use of sham tDCS in improving MDD. Furthermore, tDCS might be an effective treatment for MDD.

1. Introduction

Major depressive disorder (MDD) is one of the most prevalent and morbid psychiatric disorders worldwide which does not only cause great suffering of individuals, but results in a growing economic burden as well (Greenberg et al., 2015). About 20–40% of patients do not benefit sufficiently from the existing antidepressant interventions including trials of medication and psychotherapy (Greden, 2001). In addition, approximately one third of MDD patients do not achieve remission after using 3 or more antidepressants, and about 80% of them present recurrence (Nemeroff, 2007). Therefore, novel therapeutic strategies which are safer and more effective are of great significance in the treatment of MDD.

MDD is a complex and severe mental disorder, which is characterized by a persistent low mood and usually accompanied by alterations of cortical excitability. In recent years, brain stimulation techniques have been found to have antidepressant effects by regulating neural plasticity (Huang et al., 2017). Noninvasive brain stimulation techniques, which are widely seen as promising treatment alternatives (Brunoni and Fregni, 2011), such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation, are increasingly being used to treat neurological and mental disorders, particularly major depression. In tDCS, a weak, direct current of low intensity is injected into the brain through electrodes placed over the scalp, and the current then modulates cortical excitability by changing the resting membrane potential of neurons (Nitsche and Paulus, 2000). In recent years, tDCS has been investigated for the treatment of MDD, and this simple but powerful technique of brain modulation has demonstrated some antidepressant effects and beneficial effects on cognitive function. In addition, tDCS is convincing since it is low-cost, simple to handle (Zhao et al., 2017), portable, and especially well tolerated by subjects due to its mild side effects (Brunoni et al., 2011). This novel brain stimulation technique has been used for several years for treating depression (Bennabi and Haffen, 2018). However, little is known of the effects of tDCS in improving distinct symptoms of depression. Besides, results from trials and meta-analyses are mixed. Thus, it is of great significance not only to increase the knowledge of the effects of tDCS, but also to guide its potential use in clinical practice. This meta-analysis was conducted to evaluate the effects of tDCS applied for the treatment of MDD .

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2. Methods

2.1. Literature search

Four databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI) and Wanfang database were searched for articles published from inception to December 2018. MeSH terms/keywords related to tDCS and major depression were used.

2.2. Inclusion/exclusion criteria

Qualified studies had to satisfy the following criteria:

1 Study design: randomized controlled trial(RCT).
2 Subjects were required to have a diagnosis of MDD, or the participants had a major depressive episode.
3 tDCS alone or in combination with other treatments compared with placebo tDCS or sham tDCS.
4 The outcomes related to MDD were reported.
5 The results were reported in the form of mean and standard deviation or necessary data could be obtained after calculation.

Meanwhile, duplicate studies, abstracts and reviews were excluded.

2.3. Outcomes

The primary outcome was Montgomery–Asberg depression rating scale (MADRS). It is a clinical interview to assess depression severity which has good responsiveness to the effect of antidepressant treatments. The secondary outcome was Hamilton Depression Rating Scale, 17-items (HDRS-17).

2.4. Data extraction

For each study included, the following information was extracted carefully: the first author, year of publication, country, study design, sample size, sex ratio (male/female), mean age of subjects, intervention characteristics of the trial groups and control groups, and the outcomes. If outcomes were presented from the studies at different time points, the results were extracted from the endpoints of the qualified treatment sessions.

2.5. Risk of bias

The risk of bias of RCTs was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2008). The tool classifies the studies as having low, moderate, or high risk of bias across six domains: sequence generation, allocation concealment, blinding, missing data, selective reporting, and other biases.

2.6. Statistical analysis

A random-effects model was used since it took into consideration the fact that the true treatment effects had likely varied in the RCTs included. The mean difference (MD) and the 95% confidence interval (CI) were calculated in this research. All of the analyzes were performed using RevMan version 5.3, and p values ≤ 0.05 were considered significant.

3. Results

3.1. Study inclusion

There were 132 relevant studies in the primary literature search. 27 studies from them were excluded because of the duplication. After the titles and abstracts being screened, 33 studies were excluded since they failed to meet the inclusion criteria. After the full text of the remaining 72 articles being read, 49 studies were excluded as a result of not having sufficient information. Furthermore, 14 studies were eliminated because they were not RCTs. Ultimately, 9 qualified studies were included in the meta-analysis (Loo et al., 2012; Blumberger et al., 2012; Brunoni et al., 2013, 2014, 2015, 2016, 2018; Salehinejad et al., 2017; Mayur et al., 2018). The detailed study procedures are shown in Fig. 1.

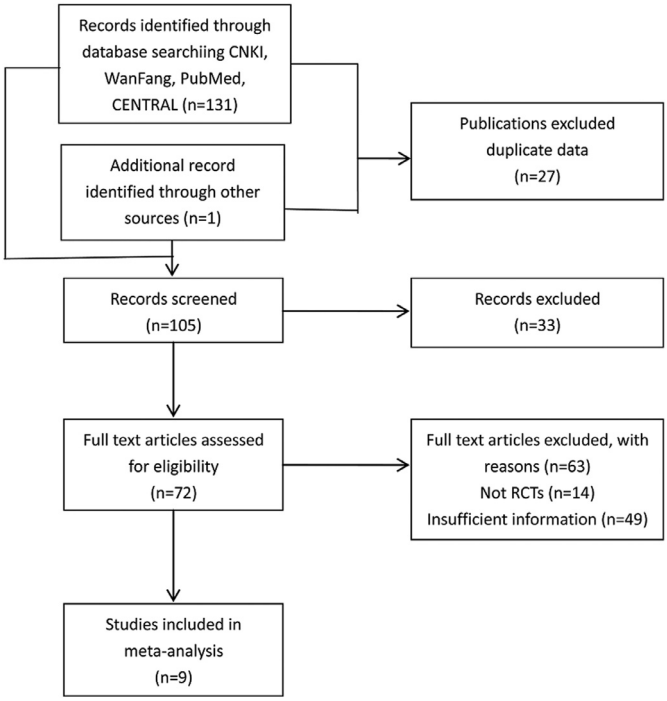

Fig. 1. The flow diagram of the selection of the studies.

3.2. Study characteristics

The basic characteristics of the 9 included studies are summarized in Table 1. The 9 selected studies contained 623 patients. 331 patients of them received tDCS and 292 patients received sham tDCS. The number of participants in each study included in the meta-analysis ranged from 16 to 149. In terms of outcomes, three studies utilized the HDRS-17, and the MADRS was observed in seven studies.

3.3. Study quality

The risk of bias of each study is described in Fig. 2, and the proportions of trials with low risk, unclear risk, and high risk of bias in each of the domains are shown in Fig. 3. All included studies claimed randomization, and four articles described the method of random sequence generation. Two studies gave information that allowed the assessment of whether an adequate concealment of allocation procedure was applied. As to the blinding of participants and personnel, one study had a high risk, two studies were unclear, and six articles reported the blinding of participants and personnel. Seven studies included reported the blinding of outcome assessment while two articles were unclear. All studies reported the complete outcome data. One study was unclear about selective reporting while no selective reporting was found in other included studies.

3.4. Meta-analyses

Seven studies reported the MADRS as the outcome measure. The

Table 1
Characteristics of studies included in the meta-analysis.

Study	Country	Design	Sample size (n)	Age (years) Gender Male/Female (n)		Intervention		Outcome measure
				Trial	Control	Trial	Control	
Blumberger et al. (2012)	Canada	RCT	24	45.3 ± 11.6 3/10	49.7 ± 9.4 1/10	Active tDCS over the left DLPFC; 2 mA, 15 treatments for 3 weeks	Sham tDCS	1. MADRS
Brunoni et al. (2013)	Brazil	RCT	94	41.2 ± 12 40.7 ± 12.7 5/18 6/19	46.4 ± 13.7 40.8 ± 11.9 9/14 11/12	One group: active tDCS over the (EEG 10–20) F3 area - placebo pill, another group: active tDCS over the (EEG 10–20) F3 area - sertraline	One group: sham tDCS - placebo pill, another group: sham tDCS - sertraline	1. MADRS
Brunoni et al. (2014)	Brazil	RCT	102	41.4 ± 12 11/42	44.9 ± 13 22/27	Active tDCS over the (EEG 10–20) F3 area; 2 mA, 30-min 10-daily sessions and two additional fortnight sessions over 6 weeks	Sham tDCS	1. MADRS
Brunoni et al. (2015)	Brazil	RCT	34	41 ± 12 5/10	50 ± 12 7/12	Active tDCS over the left DLPFC; 10 consecutive weekday sessions of tDCS, followed by two extra tDCS sessions delivered every other week	Sham tDCS	1. MADRS 2. HDRS-17
Brunoni et al. (2016)	Brazil	RCT	120	41 ± 12 41 ± 13 9/21 6/24	46.4 ± 14 41 ± 12 10/20 13/17	One group: active tDCS over the left DLPFC - placebo, another group: active tDCS over the left DLPFC - sertraline	One group: sham tDCS - placebo, another group: sham tDCS - sertraline	1. MADRS
Salehinejad et al. (2017)	Iran	RCT	24	26.8 ± 7.1 5/7	25.5 ± 4.6 4/8	Active tDCS over the (EEG 10–20) F3 area; 2 mA, 20-min active stimulation per day for 10 consecutive days	Sham tDCS	1. HDRS-17
Mayur et al. (2018)	Australia	RCT	16	47.00 ± 12.570 6/2	42.88 ± 16.643 4/4	Active tDCS over the left DLPFC; 2 mA, 10 tDCS sessions, 5 days a week over 2 weeks, tDCS + electroconvulsive therapy	Sham tDCS + electroconvulsive therapy	1. MADRS
Brunoni et al. (2018)	Brazil	RCT	149	44.6 ± 11.9 30/61	41.1 ± 12.9 19/39	Active tDCS over the left DLPFC; 2 mA, 15 sessions in the first 3 weeks, patients received 1 session from Monday to Friday, and 7 sessions from week3 to week10, once a week	Sham tDCS	1. HDRS-17
Loo et al. (2012)	Australia	RCT	60	47.8 ± 12.5 17/14	48.6 ± 12.6 15/14	Active tDCS to the left prefrontal cortex; 2 mA, 15 sessions over 3 weeks	Sham tDCS	1. MADRS

RCT, randomized controlled trial; tDCS, transcranial direct current stimulation; DLPFC: dorsolateral prefrontal cortex; MADRS, Montgomery-Asberg depression rating scale; HDRS-17, Hamilton Depression Rating Scale, 17-items.

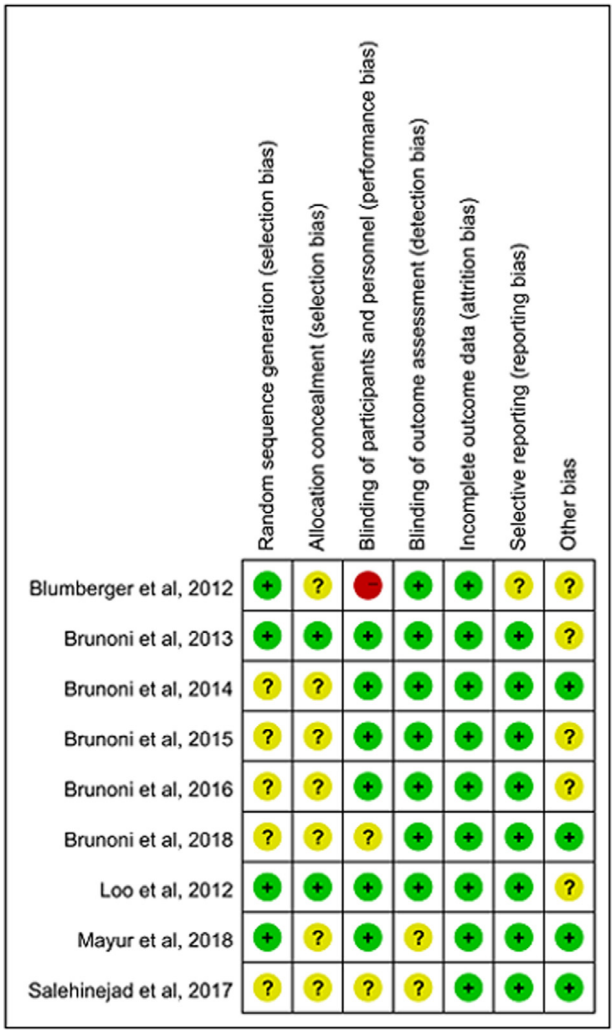

Fig. 2. Risk of bias summaries for individual studies.

effect sizes of tDCS and the control group for the MADRS are summarized in Fig. 4. An obviously significant difference between tDCS compared with the control group was found in this analysis ($p < 0.00001$, MD = −5.18, 95% CI: −7.13 to −3.23; heterogeneity test: $Tau^2 = 1.61$, $Chi^2 = 9.77$, $p = 0.28$, $I^2 = 18\%$). Besides, the result showed clearly that tDCS was more effective than the control group in most of the studies which were analyzed.

Three studies reported the HDRS-17. The effect sizes of tDCS and the control group for HDRS-17 are summarized in Fig. 5. There was a significant statistical difference between tDCS and the control group ($p < 0.00001$, MD = −3.95, 95% CI: −5.58 to −2.32; heterogeneity test: $Tau^2 = 0.00$, $Chi^2 = 0.03$, $p = 0.99$, $I^2 = 0\%$). Furthermore, tDCS was observed to be more useful than the control group in all the studies which were analyzed.

4. Discussion

The objective of this meta-analysis was to evaluate the effectiveness of tDCS for the treatment of MDD. In this meta-analysis of 9 studies involving 623 patients, a significant difference was found between tDCS and the control group in MADRS ($p < 0.00001$). In addition, compared with the control group, a significant effect of active tDCS in improving the HDRS-17 was revealed ($p < 0.00001$). Therefore, tDCS may be quite effective to treat MDD and to improve the condition of MDD patients. Furthermore, tDCS can be a relatively safe method which has few adverse effects.

Different stimulation parameters among the studies included might be a potential factor to explain the differences observed in the results. The density, current intensity, the number of sessions, duration, frequency, and other details may affect the efficacy of tDCS. The lateral system, including premotor and parietal cotex and cerebellum, may be activated to produce externally driven movement through the specific objects or stimuli (Nieuwboer et al., 2009). Some previous studies showed that anodal tDCS over the left dorsolateral prefrontal cortex had a beneficial effect on executive function (Boggio et al., 2006; Doruk et al., 2014).

Studies assessing tDCS effects over the motor cortex showed that increasing the session duration or the current intensity may increase motor cortical excitability. However, a study found that a higher current intensity and more sessions than prior studies may not clearly improve the efficacy of active tDCS. Besides, some data demonstrated that the relationship between the parameters of tDCS and the measured effects was not as linear as some people thought.

Furthermore, the length of follow-up would possibly affect the results. Therefore, future RCTs should be designed to cover long follow-up periods to obtain more conclusive results. Moreover, based on the results of this study, tDCS may be a quite effective and powerful treatment for MDD.

5. Limitations

Some limitations were observed in this study. First, this meta-analysis included a limited number of studies, and the sample sizes of some studies were relatively small. Only 9 articles met the inclusion criteria, and the studies used various parameters of stimulation. Second, some of the trials included in the analysis did not report adequate information

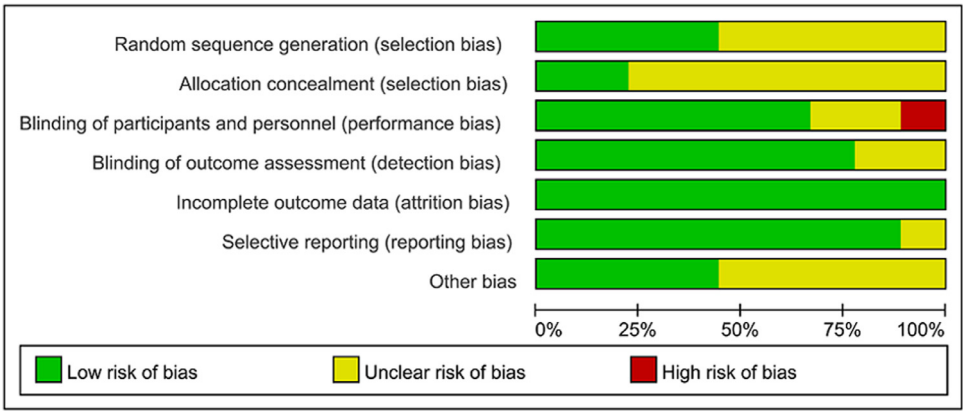

Fig. 3. Risk of bias summaries for all studies.

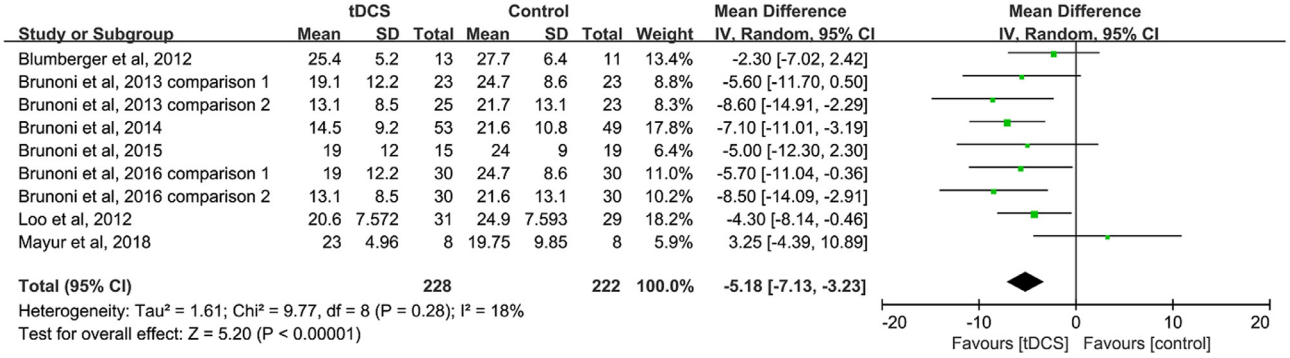

Fig. 4. The effect sizes of transcranial direct current stimulation (tDCS) and the control group for the Montgomery-Asberg depression rating scale (MADRS).

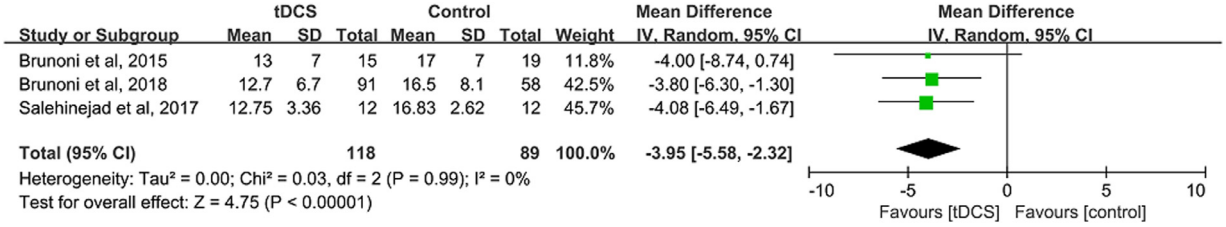

Fig. 5. The effect sizes of transcranial direct current stimulation (tDCS) and the control group for Hamilton Depression Rating Scale, 17-items (HDRS-17).

of the allocation concealment, and the validity of the results might be weakened. Due to the limitations, the results of this study should be interpreted with caution.

6. Conclusion

In summary, this study demonstrated that the intervention of active tDCS was superior to the use of sham tDCS in improving MDD. Besides, tDCS might be an effective treatment for MDD.

Conflict of interest

None.

Acknowledgment

None.

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