SYSTEMATIC REVIEW

Psychiatry and Clinical Psychopharmacology 2023;33(4):330-343
DOI:10.5152/pcp.2023.22583

Effects of Transcranial Direct Current Stimulation on Cognitive Deficits in Depression: A Systematic Review

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ABSTRACT

Background: Major depressive disorder is the leading cause of mental health-related burden globally and up to one-third of major depressive disorder patients never achieve remission. Transcranial Direct Current Stimulation is a non-invasive intervention used to treat individuals diagnosed with major depressive disorder and bipolar disorder. Since the last transcranial direct current stimulation review specifically focusing on cognitive symptoms in major depressive disorder, twice as many papers have been published.

Methods: A systematic review was conducted with 5 electronic databases from database inception until March 21, 2022. Randomized controlled trials with at least 1 arm evaluating transcranial direct current stimulation in adults (diagnosed with major depressive disorder or bipolar disorder using the Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria) aged 18 or older were included. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were adopted.

Results: A total of 972 participants were included across 14 studies (60.5% female; mean age of 47.0 years [SD=16.8]). Nine studies focused on participants with major depressive disorder and all studies used the Diagnostic and Statistical Manual of Mental Disorders to diagnose the participants. Seven out of the 14 studies showed significant improvements in at least 1 cognitive outcome measure in the active transcranial direct current stimulation group compared to the sham group. Several cognitive measures were used across studies, and 12 of the 14 studies reported mild-to-moderate side effects from treatment.

Conclusion: Current transcranial direct current stimulation literature has shown limited evidence for the treatment of cognitive impairments in major depressive disorder and bipolar disorder. Future research that applies machine learning algorithms may enable us to distinguish responders from non-responders, increasing clinical benefits of transcranial direct current stimulation.

ARTICLE HISTORY

Received: December 06, 2022
Accepted: April 23, 2023
Publication Date: July 4, 2023

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a noninvasive neuromodulation intervention that applies a low-intensity current over the scalp between 2 electrodes.[1] Unlike other noninvasive brain stimulation interventions, such as repetitive transcranial magnetic stimulation, tDCS does not directly induce action potentials due to its low voltage usage. Transcranial direct current stimulation has been increasingly used and systematically investigated over the last couple of decades.[2] The benefits of tDCS include its ease of use, safety, absence of serious adverse effects, cost-effectiveness, and the option for at-home use,[3-5] such benefits are contrasted to other therapeutics, such as electric-convulsive therapy, which not only treats depression effectively but also has cognitive and physical side effects.[6] This has led to tDCS being considered as a clinical therapeutic for the treatment of psychiatric disorders.

Major depressive disorder (MDD) is the leading cause of mental health-related burden globally,[7] and one-third of MDD patients do not achieve remission, even after using 3 or more antidepressants.[8] Recent meta-analyses demonstrate that tDCS is an effective treatment for MDD and superior in improving depressive symptoms when compared to a sham group.[9,10] Among mood disorders, bipolar disorder (BD) is

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Cite this article as: Jin J, Al-Shamali H, McWeeny R, et al. Effects of transcranial direct current stimulation on cognitive deficits in depression: A systematic review. *Psychiatry Clin Psychopharmacol.* 2023;33(4):330-343.

also of clinical interest as it refers to a group of affective disorders that involve episodes of depression and either mania or hypomania.[11] A 2017 meta-analysis found that tDCS is also capable of significantly reducing depression scores in BD patients.[12]

Emerging evidence from brain imaging studies shows a link between BD and neurocognitive impairment.[13] Moreover, a meta-analysis recently showed that cognitive deficits in the domain of selective attention, working memory, and long-term memory persist after a major depressive episode.[14] Fortunately, in response to the aforementioned challenges, tDCS is an alternative treatment that is increasingly being investigated with benefits demonstrated in improving cognitive performance, as well as depressive symptoms in patients diagnosed with MDD and BD.[1,3] Ninghetto et al[15] reported on 2 patients with MDD who received 6 sessions of tDCS treatment. Both patients showed significant improvement in their depressive symptoms as well as improved spatial attention. However, cognitive functioning only improved in the first patient and worsened in the second patient.[15] Additionally, a 2014 review puts forward that tDCS may improve some of the cognitive deficits associated with MDD.[16]

Given the overall burden of MDD and BD, as well as the potential clinical and therapeutic benefits of tDCS, the aim of this systematic review is to update the most recent reviews done for tDCS in specifically alleviating cognitive symptoms in MDD[17,18] diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. If tDCS is demonstrated to be effective, this would address a gap in treatment outcomes since cognitive dysfunction in MDD was found to be the principal mediator for occupational impairment, even in remitted states.[19]

MATERIALS AND METHODS

Guidelines from the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed in the present systematic review.[20] This review was registered with Open Science Framework (OSF) with DOI 10.17605/OSF.IO/WCH9B.

MAIN POINTS

- Transcranial direct current stimulation (tDCS) is a non-invasive, safe, and cost-effective treatment option for patients with major depressive disorder (MDD) or bipolar disorder (BD).
- Our systematic review found limited evidence that tDCS is an effective treatment for cognitive impairments in patients with MDD or BD. More high-quality research is needed.
- Machine learning applications show promise in enabling researchers and clinicians to predict which patients would respond to tDCS treatment.

Search Strategy and Information Sources

The search strategy was informed by team discussion and was created by a health sciences librarian (LD). The search combined subject headings and keywords for 2 concepts: transcranial direct current stimulation and depression. The search was not limited by publication type, but animal studies were removed wherever possible. Conference abstracts were retrieved in Embase. No limits were placed on language, country, or publication date.

The search was conducted from database inception until March 21, 2022, in MEDLINE (Ovid Interface 1946-2022), Embase (Ovid interface 1974-2022), APA PsycINFO (Ovid Interface 1806-2022) CINAHL Plus with Full Text (EBSCO host interface 1937-2022), and SCOPUS (1970-2022). Reference lists of included articles and systematic reviews were reviewed for additional studies. The full search strategy is available in the Supplementary Table 1.

Eligibility Criteria

Only randomized placebo-controlled trials with at least 1 arm evaluating tDCS in adults aged 18 or older were eligible for inclusion. Participants must have had a primary diagnosis of either current or euthymic MDD or BD as defined by the DSM or ICD criteria. The tDCS intervention needed to have stimulation amplitude of at least 1 mA, last for a minimum of 10 minutes per session, and consist of no less than 3 sessions over 2 weeks. Cognition was an outcome measured by the studies using a validated psychometric scale. Only peer-reviewed articles written in English or Arabic were included due to limited resources. The full inclusion and exclusion criteria can be found in Supplementary Table 1.

Data Screening and Extraction

All studies identified by the search were uploaded into the Covidence software (https://www.covidence.org), where duplicates were automatically removed. Two independent reviewers screened the articles, first using titles and abstracts, and then using the full-text article (Figure 1). Conflicts were resolved by a third reviewer.

The data extraction form was informed by study team discussion and created through Covidence. Data were extracted independently by 2 reviewers. The 2 reviewers resolved discrepancies through discussion and consensus. The data extracted included treated disorder, method of diagnosis, depression severity, cognitive assessments, sample size, mean age and standard deviation, percent of female participants, education level, medication status, psychotherapy status, treatment setting, tDCS device manufacturer, intervention protocol (i.e., electrode placement, stimulation duration, frequency), comparator groups, primary outcomes, dropouts, side effects, and main results.

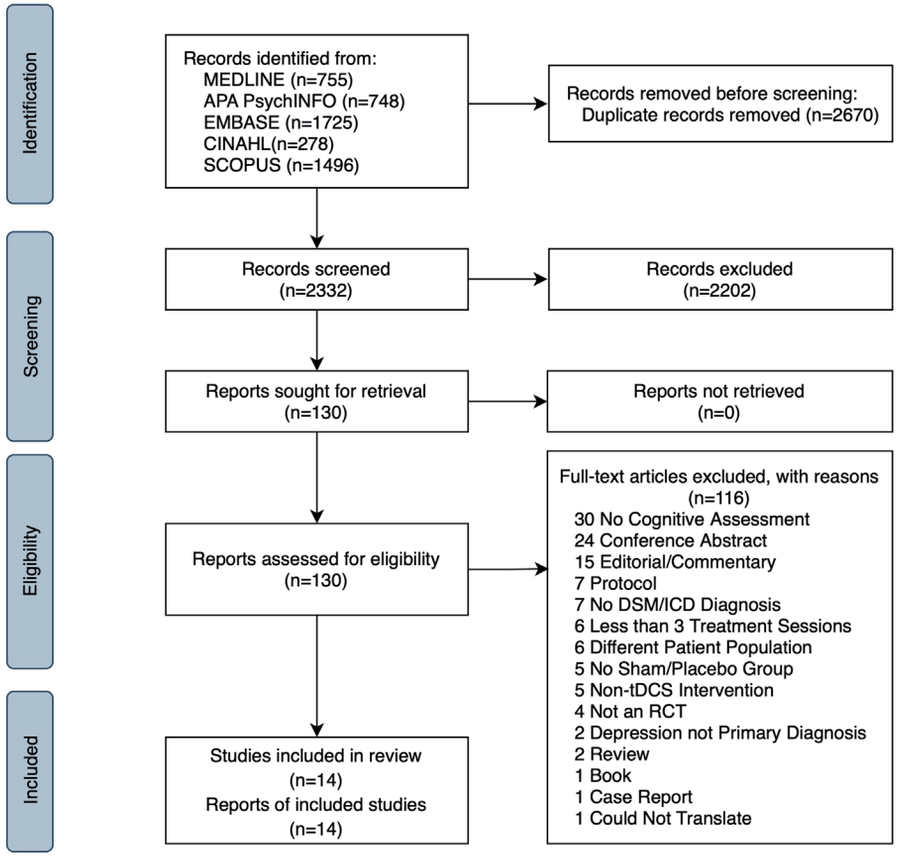

Figure 1. PRISMA 2020 flow diagram

Risk of Bias Assessment

Two independent reviewers assessed the risk of bias for the included studies. Discrepancies that arose were resolved through discussion and consensus by the 2 reviewers. Studies were not excluded based on the risk of bias. Included articles were checked against their study protocol wherever applicable.

Randomized controlled trials were assessed for bias using The Revised Cochrane Collaboration's tool for assessing the risk of bias for randomized controlled trials in the following 5 domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.[21] Each domain was graded as yes/probably yes, no/probably no, or no information. These grades were used to assess whether a study demonstrates a high, some, or low risk of bias.

Synthesis of Results

A narrative synthesis of the results was completed following the Synthesis Without Meta-analysis methodology.[22] Aggregate data was used for analysis with a focus on response to cognitive assessments and are presented in summary tables. Finally, the limitations of the synthesis are discussed.

RESULTS

A total of 5002 studies were identified through the database search and imported into Covidence where 2670 duplicates were automatically removed. The remaining 2332 studies were screened. Following the title/abstract screening phase, an additional 2202 papers were excluded. Of the remaining 130 studies assessed for eligibility, 116 were excluded. Fourteen articles were eligible for analysis (Figure 1).

Study Design and Sample Characteristics

All 14 studies were randomized controlled clinical trials published between 2010 and 2022, with a majority of studies published during 2020 (5 studies; 36%). The studies took place in 8 different countries, mostly conducted in Australia (3 studies; 21%) or Brazil (3 studies; 21%) (Table 1).

The studies included a total of 972 participants, 60.5% of whom were female, with mean ages ranging between 25.5 and 73.6 years old for a total mean age of 47.0 years [SD=16.8]. All of the studies used the DSM to

Table 1. Sample and Study Characteristics

	Number (%) of References (n=14)
Diagnosis	
MDD current	8 (57.1%)
MDD euthymic	1 (7.1%)
BD current	1 (7.1%)
BD euthymic	1 (7.1%)
MDD and BD current	3 (21.4%)
Method of diagnosis	
DSM	14 (100.0%)
ICD	0 (0.0%)
Country of publication	
Australia	3 (21.4%)
Brazil	3 (21.4%)
Canada	1 (7.1%)
France	1 (7.1%)
Germany	1 (7.1%)
Iran	2 (14.3%)
Italy	2 (14.3%)
Korea	1 (7.1%)
Year of publication	
2010	1 (7.1%)
2012	2 (14.3%)
2015	2 (14.3%)
2016	1 (7.1%)
2017	2 (14.3%)
2020	5 (35.7%)
2022	1 (7.1%)
Co-interventions	
Sham	14 (100%)
Antidepressants	3 (21.4%)
Placebo	2 (14%)

BD, bipolar disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MDD, major depressive disorder.

diagnose participants and assessed depressive and manic symptoms using the following outcome measures: Hamilton Depression Rating Scale (HDRS), Montgomery-Åsberg Depression Rating Scale (MADRS), Beck's Depression Inventory (BDI), Young Mania Rating Scale (YMRS), Perceived Deficits Questionnaire–Depression (PDQ-D), Inventory of Depressive Symptomatology (IDS), PANAS, Quick Inventory of Depressive Symptomatology–Clini cian rated (QIDS-C), and Quick Inventory of Depressive Symptomatology–Self Reported (QIDS-SR). Four studies only recruited participants with treatment-resistant depression (TRD). One of the studies defined TRD as a failure to respond to an adequate dose and duration of 1 antidepressant treatment,[23] 1 defined it as a failure to respond to 1 antidepressant treatment for 2 weeks,[24] and the other 2 papers defined it as a failure to respond to 2 or more antidepressants treatments.[25,26] All but 2 studies enrolled participants who were on antidepressants and psychotropic medications during treatment.[24,27] Other psychiatric medications used were benzodiazepines, atypical antipsychotics, typical antipsychotics, lithium, anticonvulsants (i.e., lamotrigine), mood stabilizers (i.e., prophylaxis), and anxiolytics (see Tables 1 and Supplementary Table 1 for sample characteristics).

Cognitive Measures

Forty-nine measures were used to assess the following aspects of cognition: global cognitive function, attention, processing speed, reaction time, motor speed, concentration, executive functioning, decision-making, verbal memory, visuospatial memory, working memory, language, inhibitory control, visual perception, visual scanning, verbal fluency, verbal learning, psychomotor processing speed, emotion regulation, resilience, and risk for dementia and other neurological alterations (see Supplemnatary Table 1). Of the 49 measures, 13 demonstrated significant improvement following active tDCS treatment compared to sham treatment.

Transcranial Direct Current Stimulation *Protocols and Main Outcomes*

Stimulation frequency ranged from 10 to 30 sessions of tDCS over 2 to 10 weeks. All studies administered 1 tDCS treatment session per day, except 2 studies that administered tDCS twice per day.[23,25] The intervention parameters ranged between a stimulation amplitude of 1- and 2.5 mA for a total of 20-30 minutes. All of the studies placed the anode electrodes on the left dorsolateral prefrontal cortex (DLPFC) and the majority placed the cathode electrodes on the right DLPFC (8 studies, 57%)[24,27-33] (see Table 2 Study Interventions).

Seven of 14 studies observed significant improvement in at least 1 cognitive outcome measure in the active tDCS group compared to the sham group.[23,24,27,31,34-36] The cognitive measures that demonstrated significant improvement following active tDCS treatment assessed memory, attention, processing speed, verbal fluency, psychomotor speed, and cognitive impairments. Two out of the 7 studies only recruited euthymic MDD[35] or BD[34] patients. Out of the 4 studies that only recruited TRD patients, the 2 that defined treatment resistance as failure to respond to 1 antidepressant treatment observed significant improvement in at least 1 outcome in the active tDCS group.[23,24]

Most of the reported side effects were transient and mild to moderate in intensity. The most frequently reported side effects were skin redness, blurred vision, burning sensation around the electrode site, dizziness/light-head edness, fatigue, headaches, itching, nausea, ringing in the ears, and tingling. During the course of treatment, 6 of the studies reported a total of 12 episodes of hypomania/

Table 2. Study Interventions

Study	Intervention							
				Active tDCS Protocol				
Author and Country	Treatment Setting	tDCS Manufacturer	Electrode Placement	Stimulation Amplitude (mA)	Stimulation Duration (min)	Stimulation Frequency	Sham tDCS Protocol	Other Comparators
Bennabi et al (2015), France	NR	"Eldith" Stimulator, Ilmenau, Germany	Anode: Left DLPFC Cathode: Contralateral supraorbital area	2	30	Twice daily for 5 days, for a total of 10 sessions.	Identical to the active arm, but the current was gradually decreased to zero.	NA
Bersani et al (2017), Italy	NR	BrainSTIM EMS Srl, Bologna, Italy	Anode: Left DLPFC Cathode: Right cerebellar cortex	2	20	Once daily, 5 days a week, for 3 weeks. A total of 15 sessions.	Identical to the active arm, but the stimulator was turned off after 30 seconds.	NA
Brunoni et al (2016), Brazil	University Hospital, University of São Paulo, Brazil	Chattanoogalont Dual Channel Devices, Chattanooga Group, Hixson, TN, USA	Anode: Left DLPFC Cathode: Right DLPFC	2	30	Once daily, 5 days a week, for 2 weeks. Then 1 session after 2 weeks and 1 session after 4 weeks. A total of 12 sessions.	Identical to the active arm, but the stimulator was turned off after 1 minute.	Same stimulation frequency as active arm with (a) Sertraline Group (50 mg/day) and (b) Placebo Group
Kumar et al (2020), Canada	Centre for Addiction and Mental Health in Toronto, Canada	Magstim device, model: HDCstim	Anode: Left and Right DLPFC Cathode: Iz position	1 (anode) 2 (cathode)	30	Once daily, 5 days a week, for 2 weeks. A total of 10 sessions.	Identical to the active arm, but the stimulator was turned off after 30 seconds with a gradual ramp up and ramp down.	NA
Loo et al (2012), Australia	Black Dog Research Institute in Sydney	Eldith DC-stimulator, NeuroConn GmbH, Germany	Anode: Left DLPFC Cathode: Right DLPFC	2	20	Once daily, 5 days a week, for 3 weeks. A total of 15 sessions.	Identical to the active arm, but 1 mA current was applied for 30 seconds with a 10 second ramp up and down.	NA
Loo et al (2010), Australia	NR	DC stimulator, J. Lagopoulos and the Eldith DC-stimulator, NeuroConn GmbH, Germany	Anode: Left DLPFC Cathode: Lateral aspect of the contralateral orbit.	1	20	Three active or sham sessions per week for 5 sessions, followed by 5 active sessions for a total of 10 sessions.	Identical to the active arm, but the stimulator was tramped down to zero after 30 seconds.	NA

(*Continued*)

Table 2. Study Interventions (*Continued*)

Study	Intervention							
				Active tDCS Protocol				
Author and Country	Treatment Setting	tDCS Manufacturer	Electrode Placement	Stimulation Amplitude (mA)	Stimulation Duration (min)	Stimulation Frequency	Sham tDCS Protocol	Other Comparators
McClintock et al (2020), USA & Australia	University of New South Wales, Duke University School of Medicine, Emory University School of Medicine, Rowan University, Sheppard Pratt Health System, and UT Southwestern Medical Center	Soterix Medical, Inc., New York, NY	Anode: Left DLPFC Cathode: Right DLPFC	2.5 (high dose) 0.034 (low dose)	30	Once daily, 5 days a week for a total of 20 sessions.	Identical to the active arm, but the current was rapidly ramped up to 1 mA over 10 second and then ramped down over a minute to a constant current of 0.034	NA
Moreno et al (2020), Brazil	Hospital Universitário and Institute of Psychiatry, at the University of São Paulo.	SoterixMedical, New York, NY	Anode: Left DLPFC Cathode: Right DLPFC	2	30	Once daily, 5 days a week for 3 weeks. Then once a week for 7 weeks. A total of 22 sessions.	Identical to the active arm, but the stimulator was turned off after 30 seconds.	Same stimulation frequency as active arm with (a) Escitalopram (10 mg/day for 3 weeks, then 20 mg/day for 7 weeks. (b) placebo group
Oh et al (2022), Korea	At home and Seoul St. Mary's Hospital	YDS-301N; Ybrain Inc., Seongnam, Korea	Anode: Left DLPFC Cathode: Right DLPFC	2	30	Once daily, 5 days a week for 6 weeks. A total of 30 sessions.	Identical to the active arm, but the current was slowly ramped up for the first 30 seconds and then ramped down for the next 30 seconds.	Same stimulation frequency as active arm with Escitalopram (5-20 mg/day as required by participant)
Palm et al (2012), Germany	NR	Eldith DC-stimulator, NeuroConn GmbH, Germany	Anode: Left DLPFC Cathode: Right supraorbital region.	1 (first 10 patients) 2 (remaining 12 patients)	20	Once daily, 5 days a week, for 4 weeks. A total of 20 sessions.	Identical to the active arm, but the current was ramped up and down to zero within the first 15 seconds.	NA
Salehinejad et al (2017), Iran	NR	ActivaDose Iontophoresis, by Activa Tek	Anode: Left DLPFC Cathode: Right DLPFC	2	20	Once daily for a total of 10 sessions.	Identical to the active arm, but the current was slowly ramped up for the first 30 seconds and then turned off.	NA
Salehinejad et al (2015), Iran	NR	tDCS Stimulator Model 101, TCT Research Limited, Hong Kong, China	Anode: Left DLPFC Cathode: Right DLPFC	2	20	Once per day for a total of 10 sessions.	Identical to the active arm, but the stimulator was turned off after 30 seconds.	NA

(*Continued*)

Table 2. Study Interventions (*Continued*)

Study	Intervention							
				Active tDCS Protocol				
Author and Country	Treatment Setting	tDCS Manufacturer	Electrode Placement	Stimulation Amplitude (mA)	Stimulation Duration (min)	Stimulation Frequency	Sham tDCS Protocol	Other Comparators
Tortella et al (2020), Brazil	University Hospital of the University of São Paulo, in São Paulo, Brazil	Soterix Medical, New York, NY, USA, Model 1 × 1 tDCS-CT	Anode: Left DLPFC Cathode: Right DLPFC	2	30	Once daily, 5 days a week, for 2 weeks. Then 1 session after 4 weeks and 1 session after 6 weeks. A total of 12 sessions.	Identical to the active arm, but the stimulator was turned off after 30 seconds.	NA
Zanardi et al (2020), Italy	NR	M.S. BrainSTIM© stimulator	Anode: Left DLPFC Cathode: contralateral supraorbital area.	2	30	Once or twice daily, 5 days a week, for 2 weeks. A total of 10-20 sessions depending on the group.	Identical to the active arm, but the stimulator was gradually ramped down to zero after 30 seconds.	NA

DLPFC, dorsolateral prefrontal cortex; min, minutes; NA, not applicable; NR, not reported; tDCS, transcranial Direct Current Stimulation.

mania in their participants with MDD, and 1 study reported 9 cases of treatment-emergent affective switches in participants with BD. Ten of the participants who experienced an episode of hypomania/mania or affective switches were receiving active tDCS treatment, 5 received combined tDCS and sertraline treatment, 5 received sham treatment, and 1 received sertraline treatment. Dropout rates varied from 0% to 22%. A comprehensive list of all reported side effects and a number of dropouts can be found in (Table 3).

Risk of Bias

The overall risk of bias was assessed for all included studies. Six of the articles had a high risk of bias due to problems in the randomization process or missing outcome data. Six articles demonstrated some risk of bias, and the remaining two articles were a low risk of bias. The complete risk of bias assessment is found in Figure 2.

DISCUSSION

This systematic review provides an update on the most recent evidence for effectiveness of tDCS in improving cognitive symptoms in patients diagnosed with MDD or BD. Our analysis of the 14 available randomized controlled trials found limited support that tDCS treatment improves cognition. Of the 49 cognitive measures used across the included studies, only 13 measures demonstrated significant improvement in the active tDCS group compared to the sham group in at least 1 study. However, this significance did not always translate across different studies that used the same cognitive measure. This inconsistency in significance was observed in 5 of the cognitive measures: Trail Making Test Part A (TMT A), Trail Making Test Part B (TMT B), Rey Auditory Verbal Learning Test (RAVLT), Choice reaction-time test (CRT), and the Verbal Fluency Test (FAS).

Trail Making Test Part A (measure of rote memory) and TMT B (measure of executive functioning) were used by 7 of the studies[25,28,31,33-36] and significant score improvement following tDCS treatment was noted in 1 study for TMT A and 2 studies for TMT B.[31,34] The 2 studies that found significant improvement in the TMT measures provided the participants with the most treatment sessions across the 7 studies with 22 sessions[34] and 15 sessions.[31] Similarly, FAS (measure of verbal fluency) was used by 2 studies[31,33] and the 1 with the most treatment sessions (22 sessions) noted significant improvement.[31] This may suggest that more treatment sessions are required to see improvements in the TMT and FAS measures of cognition.

Conversely, significant improvement in the RAVLT test (measures of short-term, working, and long-term memory) was only observed in 1 out of 3 studies[29,33,36] with the lowest number of treatment sessions (10 sessions) and stimulation amplitude (1 mA).[36] Choice reaction-time test

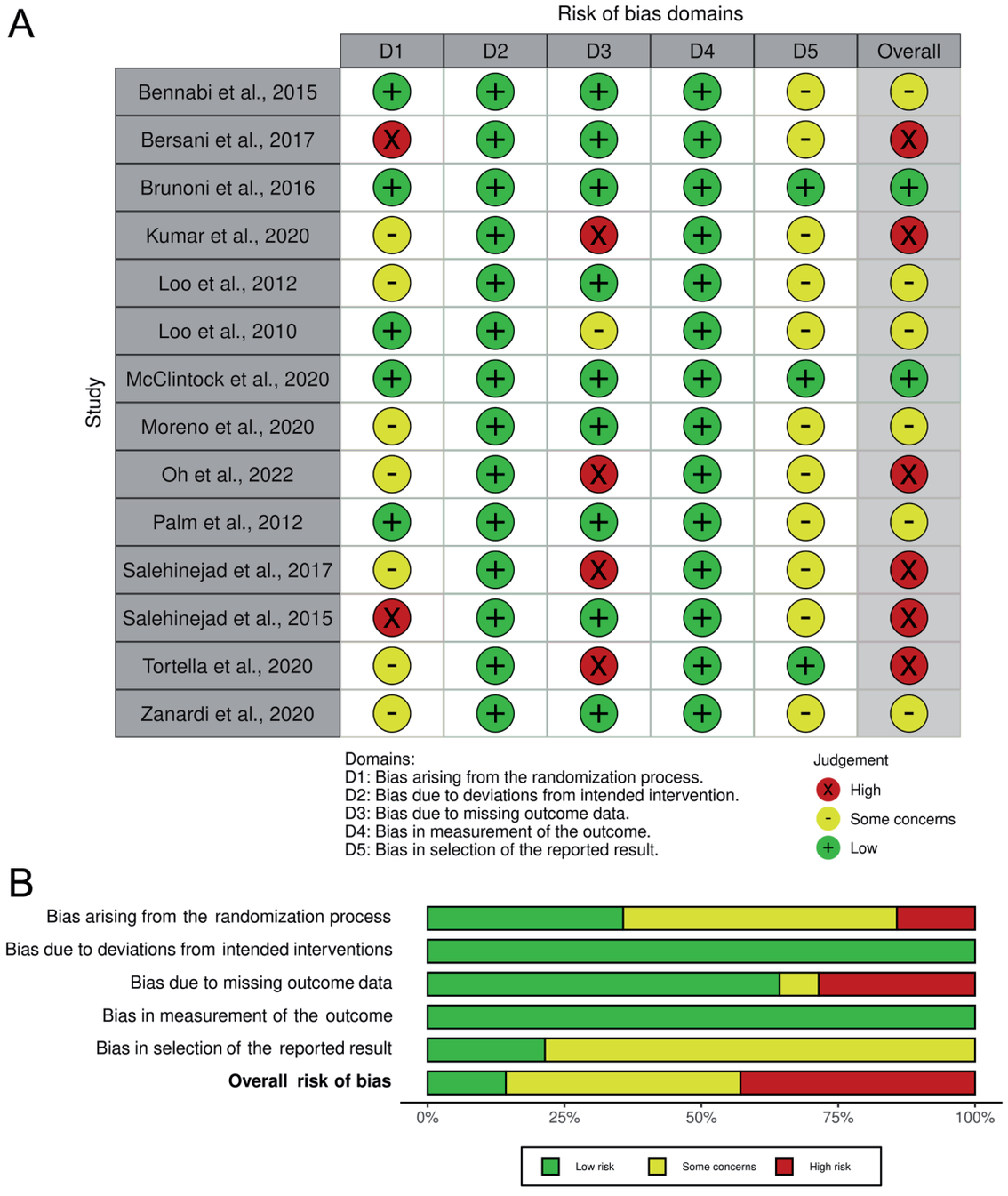

Figure 2. Article assessment using Revised Cochrane Collaboration's Tool for Assessing Risk of Bias in randomized control trials

(measure of attention and motor speed) showed significant improvement in 1[27] out of 3 studies.[27,29,36] The one study[27] that saw significant improvement in CRT did not differ greatly in intervention or participant characteristics when compared to the other 2 studies.[29,36]

Due to the high degree of heterogeneity among the included studies, our ability to draw confident conclusions on the efficacy of tDCS in improving cognition is limited. Heterogeneity is presented as a varying number in the frequency of treatment sessions, a large array of cognitive measures used, and the different patient populations included. Moreover, the effectiveness of tDCS may be underestimated due to the allowance of continued benzodiazepine use during at least 8 of the studies. A 2013 naturalistic study found that patients treated for MDD using tDCS performed worse with concurrent benzodiazepines when compared to participants who were not on benzodiazepines.[37]

Transcranial Direct Current Stimulation treatment appears to be safe with moderate-to-mild transient symptoms. The most severe risk associated with tDCS treatment is the onset of treatment-emergent episodes

Table 3. Study Outcome and Main Results

Study	Outcome			
Author and Country	Primary	Drop Out	Side Effects	Main Conclusion
Bennabi et al (2015), France	MMSE, TMT A, TMT B, COT, IST, MIS, DO 30 = no significant improvements.	One participant dropped out of the active tDCS group because they experienced mania.	Skin redness and burning/heating sensation around the electrode site. One case of mania.	No clinically significant effects were observed in the active tDCS group compared to the sham tDCS group based on the HDRS-21, MADRS, and all cognitive measures. Limitations include small sample size and the fact that all patients were taking psychotropic medications.
Bersani et al (2017), Italy	TMT B, RCFT-DR = significant improvements. TMT A, WCST, RCFT = no significant improvements.	No dropouts	Transient migraine and burning sensation around electrode site.	Clinically significant improvements in executive functioning and visuospatial memory were observed in the active tDCS group compared to the sham group using the TMT-B and RCFT-DR cognitive tests, respectively. Limitations include the fact that all patients had to be on a stable psychopharmacological treatment and the presence of practice effects with repeated neuropsychological assessments.
Brunoni et al (2016), Brazil	MOCA, DSF, DSB, StW, StIC, TMT-A, MMSE, StC, TMT-B = no significant improvements.	Active + Sertraline = 3 dropouts. Active + Placebo = 4 dropouts. Sham + Sertraline = 6 dropouts. Sham + Placebo= 4 dropouts.	Skin redness, hypomania (5 episodes), and clinical mania (2 episodes).	Cognitive improvement was observed in all the tests, except the StC and the MMSE, regardless of the intervention and depression improvement. Limitations include the poor sensitivity of neuropsychological tests used, possible ceiling effects observed in the sample, confined time point assessments, and differences in electrode placement.
Kumar et al, 2020, Canada	1-back = significant improvement 2-back, 3-back, BNT, BVMT, CDT, COWAT-FAS, CPT, CVLT, DSF, DSB, StC, StCW, TMT-A, TMT B = no significant improvements.	Three participants dropped out from the sham tDCS group (travel difficulties (n = 1) and depression relapse (n = 2)).	Headache, nausea, dizziness, fatigue, disrupted sleep, mood symptoms, and treatment site discomfort, redness, burning sensation, tingling, and itching.	The active tDCS group performed better on the 1-back test compared to the sham group during the 90-day follow up. No other differences on cognitive scales were observed between the intervention groups. Limitations include small sample size, having no immediate assessments of the intervention, the use of composite scores for global cognition, heterogeneous sample, and the lack of control for antidepressants.
Loo et al (2012), Australia	RAVLT, DSF, DSB, StIC, COWAT, LNSWAIS, SRT, CRT, SDMT = no significant improvements.	Seven participants dropped out of the active tDCS group (too unwell, no improvement, travel difficulties, busy, switched to a different trial, travel difficulties, side effects). Five participants dropped out of the sham tDCS group (busy, headaches, personal reasons, surgery, became hypermanic).	Transient and mild-to-moderate skin redness, tingling, itching, burning/heating sensation, pain, and pulsing at electrode site, as well as headaches, dizziness/light-headedness, fatigue, nausea, blurred vision, neck soreness, visual effects when close eyes, seeing dots in the periphery, giddiness, flaky skin, watery eyes, a feeling of being "spaced out," shakiness, right ear ache, ringing in ears, twitching of right arm, stiffness in neck and shoulders, tingling on neck, tingling on tongue, a "funny feeling" in head, facial numbness, reflux, and one case of hypomania.	After a single session of active, but not sham, tDCS significant improvement on the SDMT was observed (measure of attention and working memory). By the end of treatment, there was no decline in neuropsychological functioning across the measures for either intervention. A limitation of this study is the concurrent use of antidepressants.

(*Continued*)

Table 3. Study Outcome and Main Results (*Continued*)

Study Author and Country	Outcome			
	Primary	Drop Out	Side Effects	Main Conclusion
Loo et al (2010), Australia	RAVLT=significant improvements. TMT A, DSF, COWAT, SDMT, SRT, CRT=no significant improvements.	One participant withdrew from the active group due to feeling unwell. Four participants withdrew from sham group due to feeling unwell, and 1 patient died by suicide.	Mild-to-moderate skin redness, itchiness, pulsing, and tingling at electrode site, as well as mild nausea, headache, light-headedness, ringing in the ears, blurred vision, clearer vision, brighter/illuminated vision, tingling in face/body, alleviation of neuropathic pain, reduced concentration, slight eyelid jolt, nausea, euphoria, disorientation, tiredness, constriction when swallowing, insomnia, anxiety, and transient hypomania in one participant.	The active tDCS group showed significant improvement on the RAVLT compared to the sham group after 5 sessions. A limitation of the study is the short duration of the sham treatment.
McClintock et al (2020), USA & Australia	Unipolar group: CVLT-II, SDMT, Ruff 2&7 Total speed t score, Ruff 2&7 Total accuracy t score, D-KEFS, CFQ, DS=no significant improvements. Bipolar group: CVLT-II, SDMT, Ruff 2&7 Total speed t score, Ruff 2&7 Total accuracy t score, D-KEFS, CFQ, DS=no significant improvements.	Active=14 dropouts. Sham=12 dropouts.	Blurred vision, burning, fatigue, headache, itching, light-headedness/dizziness, nausea, pain, redness, and tingling.	Improvements in verbal learning and recall, selective attention, information processing speed, and working memory were observed in both high- and low-dose tDCS conditions. Limitations include the absence of a true sham group, small sample size, and the limited neurocognitive battery assessment.
Moreno et al (2020), Brazil	DSC, DSF, DSB=no significant improvements. TMT-A, TMT-B, MOCA, FAS, Processing Speed (z-score), Verbal Fluency (z-score), Working Memory (z-score)=significant improvements.	42 dropouts.	Skin redness, tinnitus, nervousness, and new-onset mania developed in 2 patients in the active tDCS group.	Patients who were treated with tDCS demonstrated increased performance in verbal fluency and reduced practice gains when compared to the placebo group. No group presented with cognitive worsening. Limitations include low sensitivity in the neurocognitive assessments, lack of healthy control group, and confined electrode placement configurations.
Oh et al (2022), Korea	CERQ=not reported. MMSE=no significant improvement.	Nine dropouts from the active tDCS group (poor compliance, electric-burn) and 4 dropouts from the sham group (poor compliance).	Mild headache and a mild electrical burn were reported in the active tDCS group.	No clinically significant effects on cognitive functioning were observed in the active tDCS group compared to the sham tDCS. Limitations include concomitant use of medications with treatment, risk of type II error in depression symptom assessments, difference in sex ratio between groups, and potential bias relating to enrollment and drop out.
Palm et al (2012), Germany	VLMT, LNSWAIS, RWT=no significant improvement.	Two dropped out because of personal reasons.	Slight headaches, itching skin sensations, skin lesions under the cathode when tap water was used. No more skin lesions were observed when physiologic saline solution was used instead.	No clinically significant effects were observed in the active tDCS group compared to the sham tDCS in measures of verbal learning, verbal fluency, and working memory. Limitations include small sample size, lack of randomization for current strengths, and potential carry over effects from the cross-over design.

(*Continued*)

Table 3. Study Outcome and Main Results (*Continued*)

Study Author and Country	Outcome			
	Primary	Drop Out	Side Effects	Main Conclusion
Salehinejad et al (2017), Iran	PAL (memory scores/ error), SRM (% correct/ latency), RVP (latency), CRT (latency/% correct/ error)=significant improvements.	NR	NR	Active tDCS treatment improved executive dysfunction in patients. Limitations include the lack of long-term follow up and low-focality of tDCS which may have stimulated other unintended areas.
Salehinejad et al (2015), Iran	DMS (correct/latency), PRM immediate phase (corrects/latency), PRM delay phase (corrects)=significant improvements. PRM delay phase (latency)=no significant improvement.	NR	NR	Clinically significant improvements were observed in measures of visuospatial memory following 10 active tDCS treatment sessions. Limitations include lack of long-term follow up and small sample size.
Tortella et al (2020), Brazil	RAVLT, LMT, FAS, BDT, StC, StW, StIC, DSF, DSB, TMT-A, TMT-B, DSC=no significant improvements.	Four participants dropped out of the active tDCS group (3 due to excessive visits missed and 1 due to personal reasons). Three participants dropped out of the sham tDCS group due to excessive visits missed.	Skin redness, 9 cases of treatment-emergent affective switches episodes throughout the trial (5 in the sham and 4 in the active group).	No clinically significant effects were observed in the active tDCS group compared to the sham tDCS in any of the cognitive measures. A limitation of the study is the use of a small sample.
Zanardi et al (2020), Italy	MODA=significant improvement in active arms (groups I and II).	Zero dropouts.	Redness, burning sensation, itching, tingling, headache, and pain.	The active treatment arms showed significant improvement on the MODA compared to the sham group. Limitations include the use of a non-specific cognitive measure, non-homogeneous previous psychopharmacological treatments among participants, and the use of a sham protocol which only included one daily session.

BDT, block design test; BNT, Boston naming test; BVMT, brief visuospatial memory test; CDT, clock drawing test; CERQ, cognitive emotion regulation questionnaire; CFQ, cognitive failures questionnaire; COT, crossing off test; COWAT, controlled oral word association test; COWAT-FAS, controlled oral word association test-letters verbal fluency test; CPT, continuous performance test; CRT, choice reaction-time test; CVLT-II, California verbal learning test-II; CVLT, California verbal learning test; D-KEFS, Delis-Kaplan executive function system; DMS, delayed matching to sample; Do 30, picture naming test; DS, digit span test (Wechsler Adult Intelligence Scale-IV); DSB, digit span backward (Wechsler Adult Intelligence Scale-III); DSC, digit-symbol coding test (Wechsler Adult Intelligence Scale-III); DSF, digit span forward (Wechsler Adult Intelligence Scale-III); FAS, verbal fluency test; HDRS-21, Hamilton Depression Rating Scale 21 item version; IST, Isaacs set test; LMT, logic memory test; LNSWAIS, letter number sequencing task of the Wechsler adult intelligence scale; MADRS, Montgomery–Åsberg depression rating scale; MIS, memory impairment screen; MMSE, mini-mental state examination; MOCA, Montreal cognitive assessment; MODA, Milan overall dementia assessment; NR, not reported; PAL, paired associates learning; PRM, pattern recognition memory; RAVLT, Rey auditory verbal learning test; RCFT-DR, Rey complex figure test delay recall; RCFT, Rey complex figure test; RVP, rapid visual information processing; RWT, Regensburg word fluency test; SDMT, symbol digit modalities test; SRM, spatial recognition memory; SRT, simple reaction-time test; StC, Stroop color test; StCW, Stroop color-word test; StIC, Stroop interference test; StW, Stroop word test; tDCS, transcranial Direct Current Stimulation; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VLMT, verbal learning memory test; WCST, Wisconsin card sorting test.

of hypomania/mania. A 2018 review found that tDCS-induced hypomania is a rare occurrence and is associated with high stimulation amplitude (2 mA or higher), 20-30-minute treatment sessions, and a diagnosis of BD.[38] All the studies included in our review administered 20-30-minute treatment sessions, and all but one study used a stimulation amplitude of 2 mA or more, yet the occurrence of treatment-emergent episodes of hypomania/mania and affective switching did not exceed 2% suggesting that even with high-intensity tDCS treatment, the risk of mania remains low.

More research and analysis of individual patient data across a large data set is needed to improve our understanding of the effectiveness of tDCS in improving cognitive outcomes.

Such methods will also help to define optimal stimulation parameters for individual patients. In recent years, there has been a shift toward alternative techniques when analyzing clinical trial data such as machine learning (ML) approaches. Machine learning, whether supervised or unsupervised, is a powerful approach that is more sensitive to real-world data because it focuses on individual cases as opposed to group-level analyses.[39] Meta-analyses, on the other hand, take advantage of forest plots which are useful for summarizing data in aggregate, but they still use measures of central tendency so trends at the individual level will not be optimally captured. Due to the high heterogeneity in the literature when assessing the effectiveness of tDCS in improving cognition in MDD and BD patients, the feasibility of ML approaches to data analysis needs to be considered as a next step.

A study by Al-Kaysi et al used an ML algorithm to predict improvement in mood and cognition following tDCS, based on the spectral power of baseline electroencephalography (EEG) in a sample diagnosed with MDD.[40] The study successfully classified responders and non-responders in cognitive improvement with 92% accuracy based on pre-intervention EEG measurements. This evidence demonstrates the unique advantage of using EEG and ML technology for the early identification of participant responders to tDCS treatment, which will help avoid treatment delays and save time for staff and resources going forward. If patients are stratified based on pre-intervention EEG information prior to the start of treatment, this will potentially have positive implications for future tDCS cost-benefit analyses. Although previous tDCS-related meta-analyses show mixed results for improving cognition,[18] this study suggests that groups can be heterogeneous and that a further individual-level analysis is required. Future studies need to increase the sample size to at least 50 for follow-up replication studies.[40]

Future Directions

Previous meta-analyses do not strongly support the effectiveness of tDCS for improving cognition,[18] but the majority of studies published so far lack a thorough exploration of nonlinear effects and individual differences in modeling and ML. Petrovskaya and colleagues[41] conducted a tDCS study with a healthy sample and noted several important observations. The results from the study[41] indicate that individual differences are an essential parameter to include in the current study and also future tDCS replication studies. Study authors note that more sensitive measures of tDCS cognition and neural effects can be implemented, such as resting state connectivity,[42] GABA and glutamate concentrations,[43] and cerebral blood flow.[44] Performing within-subject analyses is a crucial step toward the personalization of treatment. By only relying on group-level analysis, we may be limiting the true effectiveness of tDCS by not considering which sample characteristics tend toward more favorable treatment outcomes at varying intervention intensities.

Applying ML approaches to tDCS clinical trial data is highly novel and emerging at this point. The studies, discussed above, indicate potential benefits in cost-effectiveness, and the overall move toward precision health.[45] There is also a need for more specific training in terms of best practices surrounding the parameters and protocols of tDCS as an intervention. This will help to ensure that future replication trials using ML techniques have a lower rating of bias, which will then set up future meta-analyses with more adequately powered studies.

Limitations

This review considered a range of evidence that affect treatment outcomes in tDCS. There are several variables that will impact adult outcomes for psychiatric interventions. One notable variable is large-scale events such as pandemic illnesses (i.e., SARS-CoV-2-pandemic), which have been linked to increases in depressive symptoms for all sexes and genders.[46] Given the evidence collected in this review, it was not possible to assess the impact of events such as COVID-19, since most of the studies were done pre-pandemic and no specific analysis across included studies accounted for this. Also, the degree of heterogeneity in methodology across studies was high and with the given data available, a meta-analysis was not possible for the study to quantitatively assess the effectiveness of tDCS for improving adult cognitive outcomes.

CONCLUSION

Our review provides the most recent evidence reporting on the efficacy of tDCS for improving cognitive outcomes in MDD and BD. Seven out of the 14 studies showed significant improvements in at least 1 cognitive outcome measure in the active tDCS group compared to the sham group. The evidence for cognitive changes overall, however, is mixed and so further work is needed to assess efficacy on an individual level. Generally speaking, tDCS is safe as a technique with mild transient side effects, but issues around accessibility and standards around parameters for the intervention need further work. Recent technological advancements have shown promise for ML techniques, which take advantage of individual-level real-world data analyses. Machine learning applications have the potential to improve the cost-benefit ratio in identifying responders and non-responders as well as helping us further understand the mechanism of tDCS as a brain stimulation technique.

Data Access Statement: Data from this manuscript can be found in the tables, figures, and supplementary materials.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G., B.C., Y.Z., M.D., S.D., R.S.; Design – J.J., H.A., R.M., J.S., R.S., T.M., A.G., B.C., Y.Z., M.D., S.D., L.D., R.S.; Supervision – A.G., B.C.,

Y.Z., M.D., S.D., R.S.; Materials – R.S.; Data Collection and/or Processing – J.J., H.A., R.M., J.S., R.S., T.M., M.D., L.D., R.S.; Analysis and/or Interpretation – J.J., H.A., A.G., B.C., S.D.; Literature Search – J.J., H.A., R.M., J.S., R.S., T.M., M.D., L.D., R.S.; Writing – J.J., H.A.; Critical Review – J.J., H.A., A.G., B.C., Y.Z., M.D., S.D.

Acknowledgments: We acknowledge the support of Jessica Li, at the University of Alberta, for assistance and consultation regarding the synthesis of results.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This work was supported by funding from the Canadian Institutes of Health Research (CG Scholarship to JJ) and the Alberta Innovates Graduate Student Scholarship (AI-GSS).

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Supplementary Table 1. Sample Characteristics

Author and Country	Disorder	Method of Diagnosis	Depression/Mania Severity (mean (SD))	Cognitive Assessments	Sample size	Mean age (SD)	% Female	Education (years)	Remained on Psychiatric Medications During the Study	Continued Psychotherapy During the Study
Bennabi et al., 2015, France	TR MDD, Current	DSM-IV	MADRS: Active= 29.2(4.0) Sham= 33.5(7.5) HDRS-21: Active= 22.7(5.3) Sham= 24.2(5.6) BDI: Active= 18.7(6.1) Sham= 19.5(7.3)	MMSE, TMT A, TMT B, COT, IST, MIS, DO 30.	24	Active= 60.4(12.0) Sham= 59.9(15.4)	Active= 83.3% Sham= 45.5%	Active= 10.2(2.4) Sham= 11.9(3.1)	Yes	NR
Bersani et al., 2017, Italy	BD, Euthymic	DSM-IV, SCID	HDRS: Active= 4.7(1.8) Sham= 4.7(1.7) YMRS: Active= 3.9(1.2) Sham= 4.4(1.4)	TMT A, TMT B, WCST, RCFT, RCFT-DR.	Active= 21 Sham= 21	Active= 48.1(10.7) Sham= 49.2(10.2)	Active= 71.4% Sham= 38.1%	Active= 13.3(3.8) Sham= 13.1(3.1)	Yes	NR
Brunoni et al., 2016, Brazil	MDD, Current	DSM-IV, M.I.N.I.	MADRS: Active+Placebo= 31.0(5.8) Active+Sertraline= 30.7(7.0) Sham+Placebo= 31.0(5.3) Sham+Sertraline= 30.5(6.0)	MOCA, MMSE, DSF, DSB, StC, StW, StIC, TMT-A, TMT-B.	Active+Placebo= 30 Active+Sertraline= 30 Sham+Placebo= 30 Sham+Sertraline= 30	Active+Placebo= 41.0(12.0) Active+Sertraline= 41.0(13.0) Sham+Placebo= 46.4(14.0) Sham+Sertraline= 41.0(12.0)	Active+Placebo= 70.0% Active+Sertraline= 80.0% Sham+Placebo= 67.0% Sham+Sertraline= 56.0%	Active+Placebo= 13.5(3.0) Active+Sertraline= 14.0(4.0) Sham+Placebo= 13.0(4.0) Sham+Sertraline= 14.6(4.0)	Yes	NR
Kumar et al., 2020, Canada	MDD, Euthymic	DSM-IV, SCID	MADRS: Active= 2.8 (2.5) Sham= 4.3 (3.1)	N-back, BNT, BVMT, CDT, COWAT-FAS, CPT, CVLT, DSF, DSB, StC, StCW, TMT A, TMT B.	Active= 18 Sham= 15	Active= 66.3(5.8) Sham= 66.7(5.8)	Active= 72.0% Sham= 60.0%	Active= 15.2(2.8) Sham= 16.1(2.1)	Yes	NR
Loo et al., 2012, Australia	MDD, Current	DSM-IV, M.I.N.I.	MADRS: Active= 30.4(6.0) Sham= 29.5(5.0) IDS: Active= 36.6(9.6) Sham= 35.7(7.4) QIDS-C: Active= 15.3(3.5) Sham= 14.9(2.5) QIDS-SR: Active= 14.6(4.7) Sham= 16.0(3.3)	RAVLT, DSF, DSB, StIC, COWAT, LNSWAIS, SDMT, SRT, CRT.	Active= 33 Sham= 31	Active= 47.8(12.5) Sham= 48.6(12.6)	Active= 45.0% Sham= 48.0%	NR	Yes	NR

(*Continued*)

Supplementary Table 1. Sample Characteristics (*Continued*)

Author and Country	Disorder	Method of Diagnosis	Depression/Mania Severity (mean (SD))	Cognitive Assessments	Sample size	Mean age (SD)	% Female	Education (years)	Remained on Psychiatric Medications During the Study	Continued Psychotherapy During the Study
Loo et al., 2010, Australia	MDD, Current	DSM-IV, M.I.N.I.	HDRS-17: Active= 18.3(5.8) Sham= 17.3(4.7) MADRS: Active= 29.2(4.9) Sham= 28.4(4.4) BDI: Active= 27.8(8.0) Sham= 27.5 (9.9)	RAVLT, TMT A, TMT B, DSB, DSF, COWAT, SDMT, SRT, CRT.	Active= 20 Sham= 20	Active= 49.0(10.0) Sham= 45.6(12.5)	Active= 55.0% Sham= 55.0%	NR	Yes	NR
McClintock et al., 2020, USA & Australia	MDD and BD, Current	DSM-IV, M.I.N.I.	MADRS: Active= 29.7(5.2) Sham= 28.6(5.4)	CVLT-II, D-KEFS, SDMT, Ruff 2&7, CFQ, DS.	Active= 61 Sham= 59	Active= 49.0(13.7) Sham= 47.0(15.7)	Active= 54.1% Sham= 50.8%	Active= 16.1(3.0) Sham= 16.7(2.9)	Yes	NR
Moreno et al., 2020, Brazil	MDD, Current	DSM-5, M.I.N.I.	HDRS-17: Active+Placebo= 21.8(3.9) Escitalopram+Sham= 21.7(3.5) Placebo+Sham= 22.7(4.3)	MOCA, TMT-A, TMT-B, DSF, DSB, FAS, DSC.	Active+Placebo= 93 Escitalopram+Sham= 91 Placebo+Sham= 59	Active+Placebo= 44.6(11.8) Escitalopram+Sham= 41.8 (12.5) Placebo+Sham= 40.9(12.9)	Active+Placebo= 94.0% Escitalopram+Sham= 91.0% Placebo+Sham= 60.0%	Active+Placebo= 15.3(4.9) Escitalopram+Sham= 14.8(4.1) Placebo+sham= 15.8(3.8)	Yes	NR
Oh et al., 2022, Korea	MDD, Current	DSM-5	MADRS: Active+Escitalopram= 29.5(8.5) Sham+Escitalopram= 26.6(8.6) HDRS: Active+Escitalopram= 18.8(5.8) Sham+Escitalopram= 18.1(6.2) BDI: Active+Escitalopram= 27.0(12.0) Sham+Escitalopram= 21.6(10.0) PDQ-D: Active+Escitalopram= 31.4(16.5) Sham+Escitalopram= 28.7(18.9)	CERQ, MMSE.	Active+Escitalopram= 29 Sham+Escitalopram= 29	Active+Escitalopram= 29.7(11.6) Sham+Escitalopram= 28.5(11.0)	Active+Escitalopram= 50.0% Sham+Escitalopram= 40.0%	Received a bachelor's degree: Active+Escitalopram =75.0% Sham+Escitalopram= 80.0%	Yes	NR
Palm et al., 2012, Germany	TR MDD and BD, Current	DSM-IV, Psychiatrist	HDRS: Active= 33.0(7.3) Sham= 34.6(5.4) BDI: Active= 27.9(7.2) Sham= 31.3(12.1) PANAS: Active= 17.5(2.3) Sham= 17.3(2.6)	VLMT, LNSWAIS, RWT, MMST.	Active= 11 Sham= 11	Active= 56.0(12.0) Sham= 58.0(12.0)	Active= 45.0% Sham= 27.0%	NR	Yes	NR
Salehinejad et al., 2017, Iran	MDD, Current	DSM-IV, Psychiatrist	HDRS: Active= 24.6 (2.6) Sham =22.6 (1.9) BDI: Active= 33.7(6.5) Sham= 28.6(2.6)	PAL, SRM, RVP, CRT.	Active= 12 Sham= 12	Active= 26.8(7.1) Sham= 25.5(4.6)	Active= 58.3% Sham= 66.7%	Active: Diploma=7 BA=3 MA+= 2 Sham: Diploma= 6 BA=3 MA+= 3	No	NR

(*Continued*)

Supplementary Table 1. Sample Characteristics (*Continued*)

Author and Country	Disorder	Method of Diagnosis	Depression/Mania Severity (mean (SD))	Cognitive Assessments	Sample size	Mean age (SD)	% Female	Education (years)	Remained on Psychiatric Medications During the Study	Continued Psychotherapy During the Study
Salehinejad et al., 2015, Iran	TR MDD, Current	DSM-IV, Psychiatrist	BDI: Active= 34.2 (6.1) Sham= 28.3(2.5) HDRS: Active= 24.7(3.1) Sham= 22.8 (2.1)	DMS, PRM.	Active= 15 Sham= 15	Active= 28.7 (28.7) Sham=27.9 (27.9)	57.0%	NR	No	NR
Tortella et al., 2020, Brazil	BD, Current	DSM-5	HDRS-17: Active= 23.1 (3.9) Sham= 23.5(4.7) YMRS: Active= 2.4(2.1) Sham= 2 (1.9)	TMT-A, TMT-B, BDT, DSB, DSF, StC, StW, StIC, DSC, RAVLT, LMT, FAS.	Active= 30 Sham= 29	Active= 46.2 (11.8) Sham= 45.7 (10.3)	Active= 53.0% Sham= 83.0%	Active= 15.7(4.0) Sham= 17.4(6.6)	Yes	NR
Zanardi et al., 2020, Italy	TR MDD or BD, Current	DSM-5	HDRS-21: Group I= 25.5(4.0) Group II= 24.6(5.3) Sham= 24.8(2.7)	MODA.	Group 1= 31 Group 2= 31 Sham= 31	Group I= 70.8(5.9) Group II= 73.6(4.9) Sham= 70.5(5.9)	78.5%	NR	Yes	NR

Abbreviations: BD, bipolar disorder; BDI, Becks Depression Inventory; BDT, Block design test; BNT, Boston Naming Test; BVMT, Brief Visuospatial Memory Test; CDT, Clock Drawing Test; CERQ, Cognitive Emotion Regulation Questionnaire; CFQ, Cognitive Faliures Questionnaire; COT, Crossing Off Test; COWAT-FAS, Controlled Oral Word Association Test- letters verbal fluency test; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CRT, Choice reaction-time test; CVLT-II, California Verbal Learning Test-II; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; DMS, Delayed Matching to Sample; Do 30, Picture naming test; DS, Digit Span test (Wechsler Adult Intelligence Scale -IV); DSB, Digit Span Backward (Wechsler Adult Intelligence Scale -III); DSC, Digit-symbol coding test (Wechsler Adult Intelligence Scale -III); DSF, Digit Span Forward (Wechsler Adult Intelligence Scale -III); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders fourth edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders fifth edition; FAS, Verbal Fluency Test; HDRS-17, Hamilton Depression Rating Scale 17 item version; HDRS-21, Hamilton Depression Rating Scale 21 item version; HDRS, Hamilton Depression Rating Scale; IDS, Inventory of Depressive Symptomatology; IST, Isaacs Set Test; LMT, Logic Memory Test; LNSWAIS, Letter Number Sequencing Task of the Wechsler Adult Intelligence Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; M.I.N.I, mini International Neuropsychiatric Interview; MIS, Memory Impairment Screen; MMSE, Mini-Mental State Examination; MMST, Mini-Mental Status Test; MOCA, Montreal Cognitive Assessment; MODA, Milan Overall Dementia Assessment; NR, not reported; PAL, Paired Associates Learning; PANAS, positive and negative affect scale; PDQ-D, Perceived Deficits Questionnaire – Depression; PRM, Pattern Recognition Memory; QIDS-C, Quick Inventory of Depressive Symptomatology- Clinician rated; QIDS-SR, Quick Inventory of Depressive Symptomatology- Self Reported; RAVLT, Rey Auditory Verbal Learning Test; RCFT-DR, Rey Complex Figure Test delay recall; RCFT, Rey Complex Figure Test; RVP, Rapid Visual Information Processing; RWT, Regensburg Word Fluency Test; SCID, Structured Clinical Interview for DSM; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SRM, Spatial Recognition Memory; SRT, Simple reaction-time test; StC, Stroop color test; StCW, Stroop color-word test; StIC, Stroop interference test; StW, Stroop word test; TMT A, Trail Making Test-Part A; TMT B, Trail Making Test-Part B; TR, treatment-resistant; VLMT, Verbal Learning Memory Test; WCST, Wisconsin Card Sorting Test; YMRS, Young Mania Rating Scale.