

# Role of Transcranial Direct Current Stimulation in the Management of Alzheimer's Disease: A Meta-analysis of Effects, Adherence and Adverse Effects

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Transcranial direct current stimulation (tDCS) is a form of novel brain stimulating method that has attracted interest owing to its relative inexpensiveness and ease of administration. It has been evaluated in many studies for its effectiveness in improving cognitive symptoms in Alzheimer's disease (AD). However, our understanding regarding its efficacy and the most effective way of administering tDCS (in terms of lead placement to achieve response and prevent harmful consequences) is still evolving. The current meta-analysis was conducted to resolve the above issues. A search using appropriate keywords and medical subject headings was conducted on PubMed, Scopus and DOAJ database. Studies were analysed on pre-defined inclusion and exclusion criteria. Finally 11 studies were included for quantitative analysis from 1,021 obtained from initial search. All the studies included were methodologically of high quality, though an asymmetrical funnel plot raised the possibility of publication bias. tDCS was found to significantly improve the scores on cognition as compared to sham. Anodal tDCS was found to be significantly beneficial in this regards, whereas cathodal and dual stimulation were not. There were no significant difference in the number of drop-outs and adverse reaction in tDCS and sham group. The quality of evidence that we have reviewed in this study is robust. tDCS, particularly anodal tDCS is an effective treatment modality in AD. It is well tolerated in patients with AD. However, further studies are warranted to probe the role of tDCS in other domains of AD.

**KEY WORDS:** Transcranial direct current stimulation; Alzheimer's disease; Major neurocognitive disorder; Brain stimulation; Meta-analysis.

## INTRODUCTION

Dementia is a syndrome where there is decline in cognitive functions beyond what it is expected in normal aging, which ultimately hampers the day to day activity. Diagnostic and Statistical Manual of Mental Disorders (DSM 5) [1] replaced the term 'dementia' with Major and minor neurocognitive disorders. Alzheimer disease (AD) is the most common cause of dementia for patients older than 65 years of age, consisting of more than 60% of all cases of dementia worldwide. Alzheimer disease can be

divided into two groups; sporadic and familial. Sporadic form is more common and typically late onset while familial form has early onset. Memory impairment is the most common initial symptom of Alzheimer disease but symptoms can range from impaired executive function, problem solving to behavioural, psychiatric and motor symptoms. Direct and indirect cost related to Alzheimer's disease alone was more than 500 billion USD annually [2]. AD is diagnosed clinically after excluding other causes of dementia. But it can be diagnosed definitively in a living patient with analysis of Cerebrospinal fluid and Positron emission therapy (PET) scan biomarkers combined with some clinical criteria [3].

Currently, there is no cure for AD, but we can slow the disease progression by medications, lifestyle and dietary modifications. Acetylcholinesterase-inhibitors like donepezil, rivastigmine, galantamine with or without N methyl

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D aspartic acid (NMDA) receptor antagonist memantine are most widely used [4]. Brain stimulation techniques are a relatively new breakthrough in halting the progression of AD. Generally, three types of brain stimulation techniques are in use currently; Repetitive transcranial magnetic stimulation, transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS). Among them we think tDCS is particularly important in AD management because the device is portable, cheap and treatment is very convenient which doesn't hamper day-to-day activities. tDCS uses very low intensity current, so it can be done as an out-patient procedure without anaesthesia. It is particularly important for developing countries with low health-care budgets and where more percentage of patients depend on daily wages. Patients should be more compliant with the treatment because it can be done in a relatively shorter time span.

Cruz Gonzalez *et al.* [5] in their meta-analysis of 12 studies including 195 patients of dementia and 53 patients with mild cognitive impairment, found that tDCS can lead to improvement in various domains like memory and language; at least on a short term basis. Cai *et al.* [6] in their meta-analysis of 146 patients of AD also found benefit in improvement of cognitive functioning of mild and moderate AD. Their study also showed that as compared to repeated tDCS, single sessions of tDCS was significantly effective. In this context, the meta-analysis of 8 studies by Inagawa *et al.* [7] did not find anodal tDCS to have enough evidence to suggest efficacy, probably due to small number of studies and sample size. Thus, to summarize, though tDCS is deemed to have benefit in the management of AD, there are multiple questions that remain unanswered, especially regarding lead placement, treatment adherence and chances of adverse effects. The current meta-analysis was conducted to summarize the evidence of tDCS in management of AD, with focus on trying to answer the unresolved issues.

## METHODOLOGY

### Scope

The current review was conducted to study to address the following research question:

- Can tDCS be used to improve cognitive outcomes in patients with AD?
- Is there any difference in the type of tDCS stimulation

improving cognitive outcomes in patients with AD?

- Is tDCS well tolerated in patients with AD?

### Search Strategy

Two researchers individually conducted search using the same search terms in the same search engines. PubMed, Scopus and DOAJ database were searched until July, 2020. The search terms included were "tDCS"/"Transcranial direct current stimulation" AND "Alzheimer"/"Alzheimer's disease"/"Alzheimer Disease"/"Neurocognitive disorder"/"mild cognitive impairment"/"Dementia". Full text of each articles was reviewed and they were separately screened by both the researchers. Any disagreements regarding inclusion and exclusion of articles were resolved with the help of a third expert (who is not a author of this manuscript).

### Study Selection

Our study selection included randomized control trials with parallel and cross over design to ensure wide ranging coverage of studies.

### Inclusion criteria

Inclusion criteria comprised of: (a) Studies that included subjects diagnosed with AD based on a standard diagnostic criteria. (b) Cognitive impairment measured by a scale with quantifiable assessment. (c) tDCS was used as an intervention that results in outcome differences between active and control group. (d) Outcomes are measured by scales that measured various aspects of cognition and gave quantifiable assessment. (e) Studies included randomized control trials and original articles. (f) Full text of article could be accessed and was in English. (g) Studies provided original data that included mean and standard deviation (SD) or provided other variables that could be converted into mean and SD.

### Exclusion criteria

Studies with the following contents were excluded. (a) Experimental studies using animals. (b) Reviews and case reports, conference abstracts and newspaper articles were excluded. (c) repeatedly published studies. (d) Studies involving subjects with other types of dementias or other cause of neurocognitive decline and involving other modalities of brain stimulation apart from tDCS.

**Table 1.** Table showing characteristics of studies included in meta analysis

Study	Sample size	Design	Age (yr)	Sex (M/F)	Education (yr)	Duration of disease (yr)	Level of cognition (MMSE scores)	Outcome	Parameters of stimulation
Boggio <i>et al.</i> (2012) [10]	NE: 15 NC: 15	Crossover	77.5 ± 6.9 80.6 ± 9.5	4/4 4/3	13.3 ± 4.8 15.7 ± 0.8	5.0 ± 1.1 3.7 ± 2.4	Mild to moderate (≥ 15)	VRT MMSE	Anodal; 0.06 mA/cm <sup>2</sup> 30 min/d, 5 d; temporal lobes bilaterally
Gangemi <i>et al.</i> (2021) [13]									Anodal: left FT lobe, Reference: right frontal lobe.
Study 1	NE: 13 NC: 13	Parallel	67.5 ± 2.8 69.01 ± 3.1	NR	6.5 ± 2 6.1 ± 2.1	NR	15.15 ± 2.49 16 ± 1.71	MMSE MODA	2.5 mA/cm <sup>2</sup> /d for 10 d
Study 2	NE: 9 NC: 9		68.5 ± 2.8 68.7 ± 3.1		6.7 ± 2 6.2 ± 2.7		15.8 ± 1.8 15.9 ± 1.6	MMSE MODA	Anodal: left FT lobe, Reference: right frontal lobe. 2.5 mA/cm <sup>2</sup> /d for 10 d each month for 8 months
Ferrucci <i>et al.</i> (2008) [12]	NE: 10 NC: 10	Crossover	75.2 ± 7.3	3/7	10.9 ± 4.8	NR	Mild (≥ 20)	WRT MMSE	Anodal and cathodal; 0.06 mA/cm <sup>2</sup> 1 session of 15 min; 3 months; temporo-parietal areas bilaterally
Lu <i>et al.</i> (2019) [18]	NE: 69 NC: 64	RCT	74.2 ± 6.7 74.5 ± 6.6	42/21 36/17	7.3 ± 4.8 6.5 ± 4.3	NR	25.7 ± 2.6 25.6 ± 2.9	MMSE CVFT TMT	Anodal; 2 mA/cm <sup>2</sup> 20 min/d, 3 session/wk, 3 month; left lateral temporal cortex
Bystad <i>et al.</i> (2016) [9]	NE: 12 NC: 13	Parallel	70.0 ± 8.0 75.0 ± 8.7	7/5 7/6	NR	NR	Mild to moderate (≥ 18)	CVLT-II Recognition MMSE	Anodal; 0.06 mA/cm <sup>2</sup> 30 min/d, 6 d; left temporal lobe
Inagawa <i>et al.</i> (2019) [15]	NE: 7 NC: 13	Parallel, RCT	76.6 ± 5.7 76.2 ± 7.7	3/4 7/6	NR	0.9 ± 1.2 1.2 ± 1.5	Moderate MMSE < 18	MMSE FAB CDR ADAS Cog	Anodal: DLPFC Cathodal: C/L supraorbital ridge 2 mA/d, 20 min/session, 2 session/day for 5 days
Im <i>et al.</i> (2019) [14]	NE: 12 NC: 8	RCT	71.9 ± 9.2 74.9 ± 5	1/10 2/5	6.3 ± 3.8 5.4 ± 5.9	NR	20.1 ± 3.8 22.1 ± 4.6	MMSE CDR CDR-SOB	Anodal: left DLPFC Cathodal: right DLPFC 2 mA for 30 min/day for 6 months
Cotelli <i>et al.</i> (2014) [11]	NE: 12 NC: 12	Parallel	76.6 ± 4.6 74.7 ± 6.1	2/10 3/9	5.5 ± 2.4 8.9 ± 5.1	NR	Mild to moderate (above 20)	FNAT MMSE	Anodal; 0.08 mA/cm <sup>2</sup> 25 min/d, 10 d; left DLPFC
Khedr <i>et al.</i> (2014) [16]	NE: 11 NC: 11	Parallel	68.5 ± 7.2 67.3 ± 5.9	3/9 6/5	8.9 ± 5.1 NR	3.0 ± 2.6	Mild to moderate (≥ 12)	MMSE	Anodal; 0.08 mA/cm <sup>2</sup> 25 min/d, 10 d; left DLPFC
Khedr <i>et al.</i> (2019) [17]	NE: 23 NC: 23	RCT	64.22 ± 3.64 65.23 ± 4.52	13/10 13/8	4.04 ± 2.83 3.52 ± 1.96	14.08 ± 5.79 14.09 ± 4.68	14.17 ± 3.67 13.90 ± 3.46	MMSE Clock drawing test Cornell depression scale	Anodal and cathodal: 2 mA, 20 min/day, 5 session/wk for 2 wk, right /left temporal lobe

Values are presented as mean ± standard deviation.

AD, Alzheimer disease; tDCS, transcranial direct current stimulation; B/L, bilateral; C/L, contralateral; DLPFC, dorsal lateral prefrontal cortex; NC, number of subjects in control group; NE, number of subjects in experimental group; NR, not reported; CVLT-II, California verbal learning test; MODA, Milan Overall Dementia Assessment; FT, Frontotemporal; FNAT, face-name association task; M/F, male/female; MMSE, Mini-Mental State Examination; VRT, visual recognition task; ADAS Cog, Alzheimer's dementia assessment scale-cognitive subscale; CDR, clinical dementia rating scale; FAB, Frontal Assessment Battery; WRT, word recognition task.

### Data Management

For the purpose of the meta-analysis, the data from the studies were input in the Review Manager (RevMan 5.3) and emerging trends were observed. The effect size was calculated for tDCS in each arm of the studies using the standardized mean difference. For studies where data could not be obtained from tables, we used online software (<http://www.graphreader.com/>) for obtaining data from the graphs. Appropriate summary statistics were input on RevMan (mean, standard deviation and sample size for continuous variables; and number of incidents and participants for dichotomous variables). Assessment of heterogeneity of studies was done using the  $I^2$  test. If studies met statistical homogeneity ( $I^2 < 50\%$ ), we used fixed model of meta-analysis or else random effects model was used.

### Risk of bias assessment

A risk of bias assessment was carried out using guidelines of Cochrane Collaboration Network with the help of RevMan 5.3. The assessment was based on the following criteria: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of subjects and researcher (implementation bias); (4) Blindness of measurement of outcomes (measurement bias); (5) Integrity of the results (attribution bias); (6) Selective reporting of outcome (reporting bias); (7) Other bias. Following evaluation on these above stated criteria appropriate summary chart was made.

### Quality estimate of included studies

All the included studies underwent a quality estimate analyses using PEDro Scale [8]. The PEDro scale is based on the Delphi list developed in the Department of Epidemiology in the University of Maastricht. The scale is to assess the quality of randomized clinical trials in terms of sufficient statistical information that makes their results interpretable. The scale consists of 11 criteria on which the study is assessed. For each criterion, 1 point is awarded only if the criterion is clearly satisfied. A score of 0–4 is considered poor, 4–5 fair, 6–8 good and 9–10 excellent.

### Assessment of outcome

All studies included subjects that had a quantitative assessment of the outcome. All the included studies initially

had cognitive assessment based on a scale like mini mental status examination (MMSE), Apathy scale etc. or a test like trail making test, word sorting test etc. After intervention in the form of tDCS another assessment of cognitive functions was done. To assess improvement of overall cognitive function we used pre and post intervention scores of MMSE to assess the change. Adverse events reported by the studies and dropout rates between studies was also compared.

### Statistical Analyses

Meta-analysis was conducted on final MMSE scores seen after intervention using a continuous model in RevMan. We used mean, standard deviation and total sample size to derive forest plot charts in the continuous model. We also did separate assessment comparing the effect of various types of tDCS. A funnel plot was used for observing publication bias. Forest plot charts were also made after comparing dropouts and adverse effects across studies.

## RESULTS

### Literature Search

Our literature search was conducted at three data bases viz. Scopus, Pubmed and DOAJ. A total of 1,021 articles were identified out of which finally included 11 studies in our quantitative analysis (Table 1) [9-18]. All the studies included had made two groups viz. sham and active group. 9 out of 11 studies had a parallel design and 2 had cross over design. All the studies included subjects with Alzheimer's disease diagnosed according to DSM 5 and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. The characteristics of the studies included in this analysis has been depicted in Table 1 given below (Fig. 1).

### Quality Estimate Assessment

Quality estimate was carried out for all included studies and PEDro Scale [8] was used for the same. All the studies included in the meta-analysis were rated "high" quality. However, 4 studies did not mention the details of randomization and 1 study did not mention about the details of blinding procedure followed (Table 2).

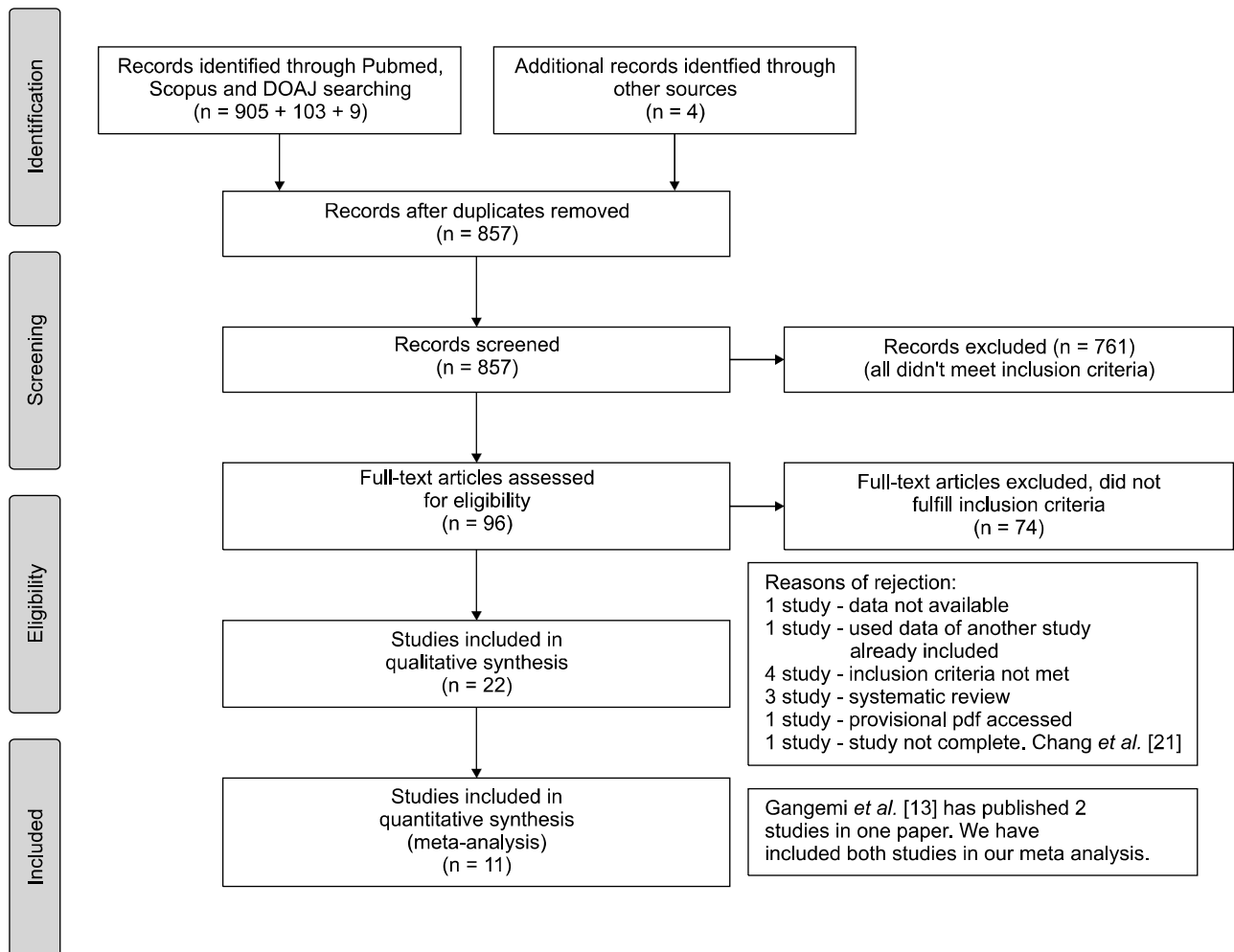


Fig. 1. Table showing the flow of studies in the course of this review.

Table 2. Table showing quality estimate of studies using PEDro scale

Studies	Criteria of PEDro											Quality	
	1	2	3	4	5	6	7	8	9	10	11		
Boggio <i>et al.</i> (2012) [10]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Bystad <i>et al.</i> (2016) [9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Cotelli <i>et al.</i> (2014) [11]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Gangemi <i>et al.</i> (2021) [13]													
Study 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Study 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Im <i>et al.</i> (2019) [14]	Yes	No	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	High
Inagawa <i>et al.</i> (2019) [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Ferrucci <i>et al.</i> (2008) [12]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Khedr <i>et al.</i> (2014) [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Khedr <i>et al.</i> (2019) [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Lu <i>et al.</i> (2019) [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

**Risk of Bias Assessment**

Risk of bias assessment was carried out using RevMan 5.3 using guidelines of Cochrane Collaboration Network.

For almost 7 studies there was low risk of selection bias. Also 1 study had unclear risk of detection bias and performance bias as the details were not mentioned. Overall

there was low risk of bias in all studies in maximum criteria (Fig. 2A).

A funnel plot was made incorporating the included studies to see for publication bias. The presence of any asymmetrical trend was noted which could be due to publication bias (Fig. 2B).

**Meta Analysis of Treatment Effect**

All the subjects in active and sham group were subjected to active and sham stimulation. All the patients were evaluated for cognitive skills using pre and posts stimulation MMSE. All the analysis of treatment effect was done using the final post stimulation MMSE scores in both groups. Forest plots were made separately showing effect of anodal tDCS vs. sham tDCS (Fig. 3A), cathodal tDCS vs. sham tDCS (Fig. 3B), dual tDCS stimulation vs. sham tDCS (Fig. 3C) and overall effect of tDCS vs. sham tDCS (Fig. 3D).

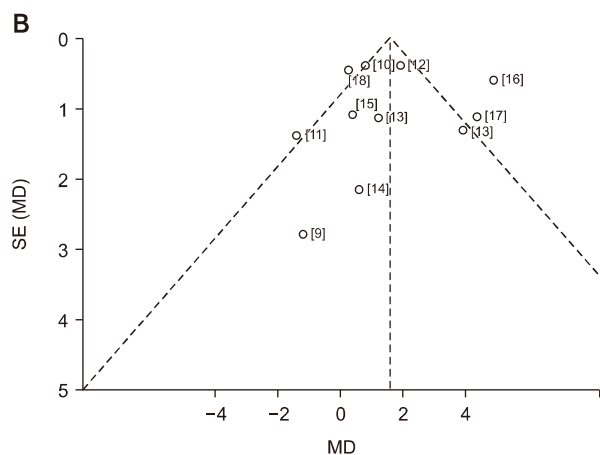
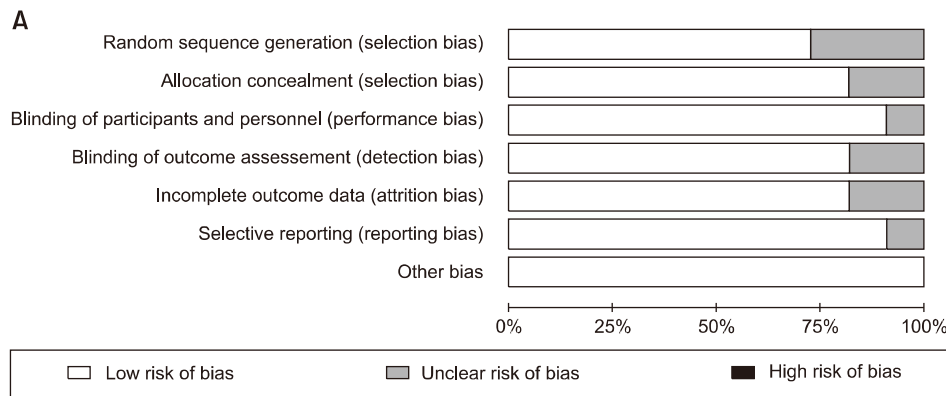
**Effect of Anodal tDCS**

Seven out of 11 studies used Anodal tDCS in the active

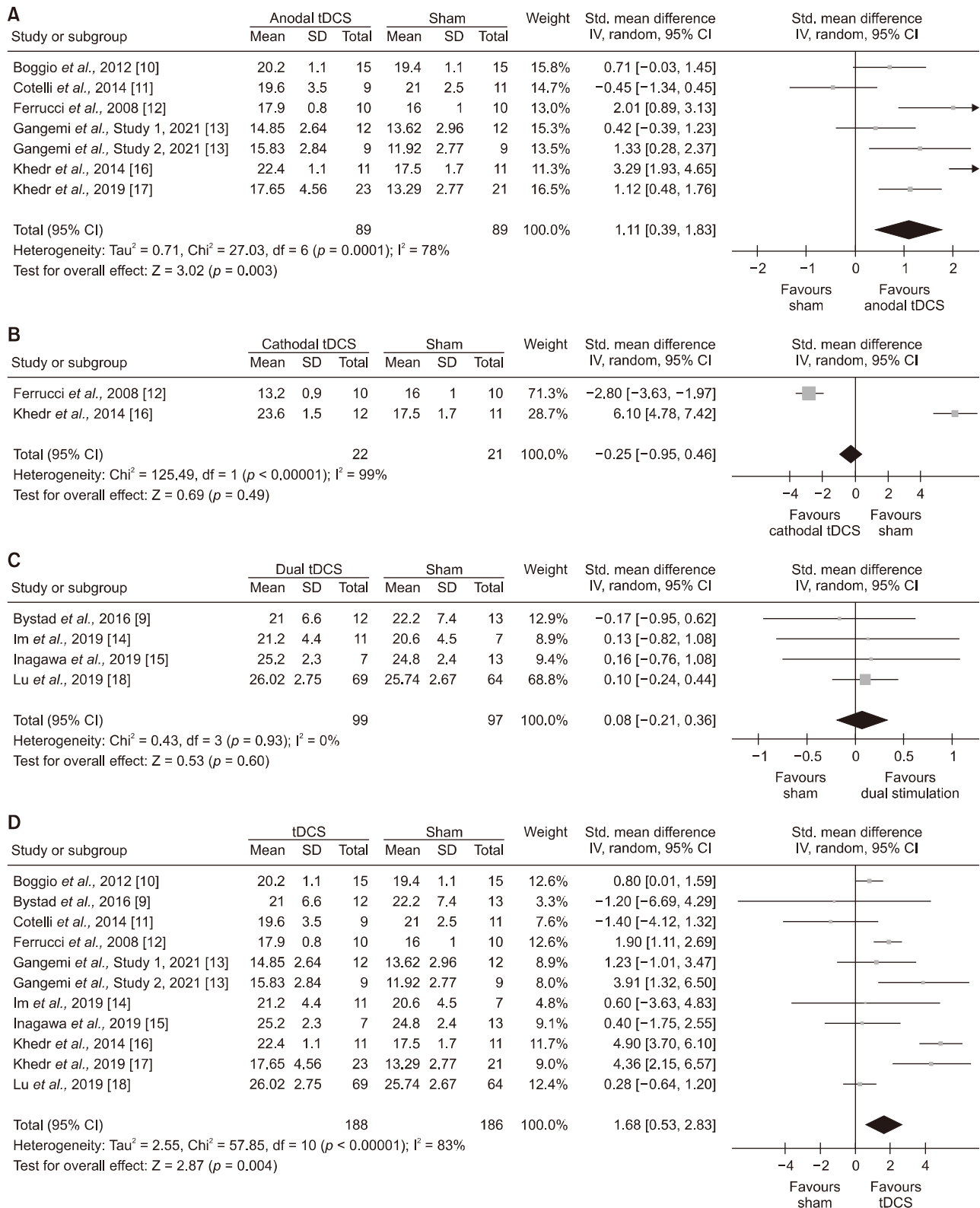
group. Stimulation was given in frontal lobe, temporal lobe, parieto temporal lobe and dorsal lateral prefrontal cortex across these 7 studies. Period of stimulation across these 7 studies ranged from 10 days to 10 days each month for 8 months. A current ranging from 0.06 mA to 2.5 mA per cm<sup>2</sup> was applied. Heterogeneity was present across studies ( $\chi^2 = 27.3, p = 0.0001, I^2 = 78\%$ ) and a random effects model was used for analysis. A total of 89 patients were given AtDCS in active group. Statistically significant improvement was found in the MMSE scores of anodal tDCS group against sham group.

**Effect of Cathodal tDCS**

Two out of 11 studies used cathodal tDCS in the active group. Stimulation was given in temporal lobe across these 2 studies. Period of stimulation across these 2 studies ranged from 2 weeks to 3 months. A current ranging from 0.06 mA to 2 mA per cm<sup>2</sup> was applied. Heterogeneity was present across studies ( $\chi^2 = 125.49, p \leq 0.0001, I^2 = 99\%$ ) and a random effects model was used for analysis. A total of 22 patients were given cathodal tDCS in active



**Fig. 2.** (A) Table showing bias assessment of studies. (B) Funnel chart showing asymmetrical distribution of the studies in Funnel plot. SE, standard error; MD, log odds ratio.



**Fig. 3.** Forest plot of studies comparing MMSE scores after (A) anodal tDCS and sham tDCS, (B) cathodal tDCS and sham tDCS, (C) dual tDCS and sham tDCS, (D) tDCS (overall) and sham tDCS. tDCS, transcranial direct current stimulation; MMSE, Mini-Mental State Examination; SD, standard deviation; CI, confidence interval.

group. No statistically significant improvement was found in the MMSE scores of cathodal tDCS group against Sham group.

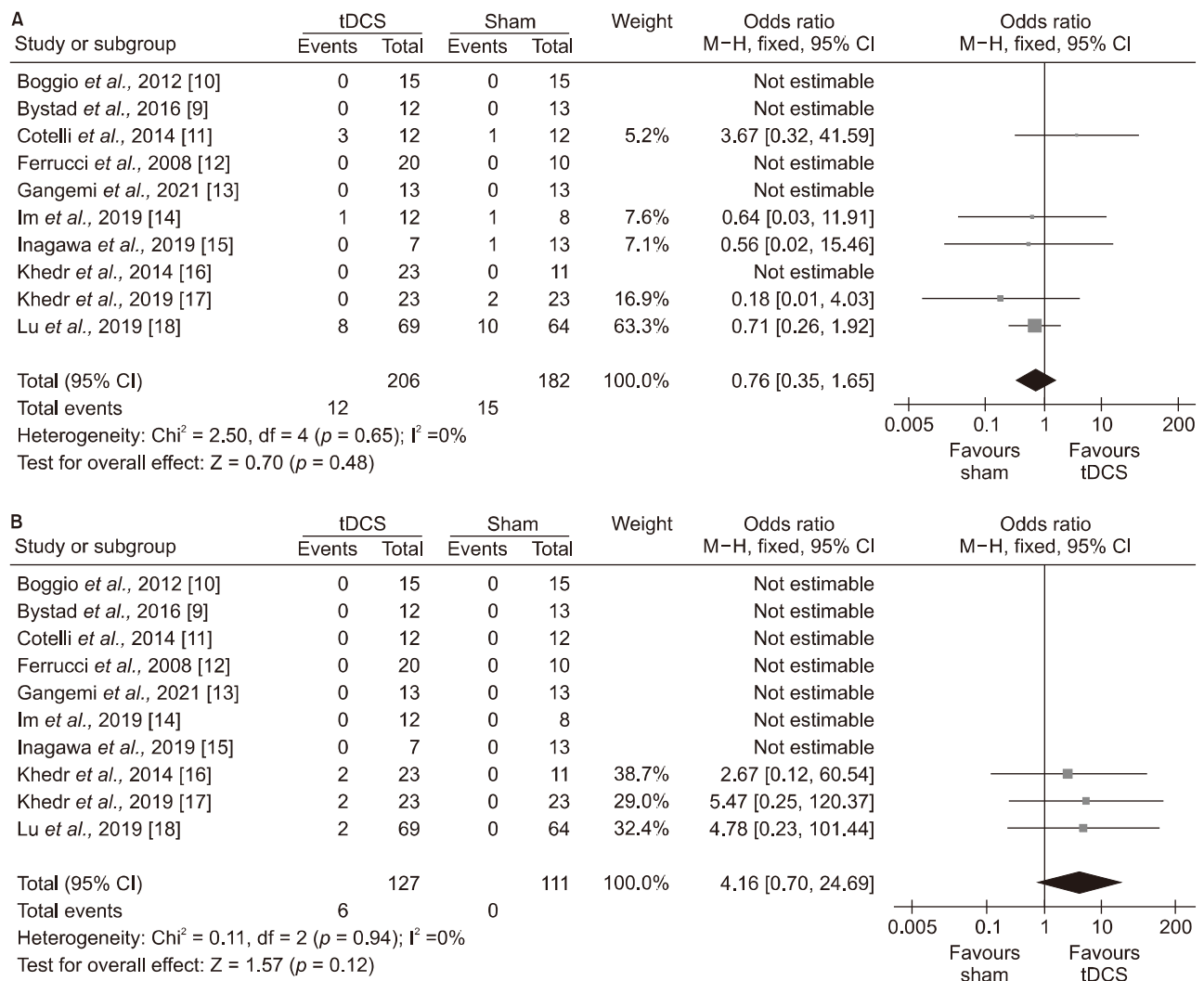
**Effect of Dual Stimulation tDCS**

Four out of 11 studies used dual stimulation tDCS in the active group. Dual stimulation has been defined as stimulation to two parallel cortices, purposefully upregulating one region of the brain, while downregulating another [19]. Stimulation was given in temporal lobe across these 4 studies. Period of stimulation across these 4 studies ranged from 2 weeks to 3 months. A current ranging from 0.06 mA to 2 mA per cm<sup>2</sup> was applied. Homogeneity was

present across studies ( $\chi^2 = 0.43, p = 0.93, I^2 = 0\%$ ) and a fixed effects model was used for analysis. A total of 99 patients were given dual stimulation tDCS in active group. No statistically significant improvement was found in the MMSE scores of dual stimulation tDCS group against sham group.

**Overall Effect of tDCS**

A total of 11 studies were analysed in this part of our analyses irrespective of the type of tDCS administered. Period of stimulation across these 11 studies ranged from 2 weeks to 8 months. A current ranging from 0.06 mA to 2 mA per cm<sup>2</sup> was applied. Heterogeneity was present



**Fig. 4.** Forest plot of studies comparing (A) drop outs in group receiving tDCS and sham tDCS. (B) Adverse effects reported in group receiving tDCS and sham tDCS.

tDCS, transcranial direct current stimulation; CI, confidence interval.



across studies ( $\chi^2 = 57.85$ ,  $p \leq 0.00001$ ,  $I^2 = 83\%$ ) and a random effects model was used for analysis. A total of 188 patients were given tDCS in active group. Statistically significant improvement was found in the MMSE scores of tDCS group against sham group.

### Meta Analysis of Drop Outs

Five studies out of 11 included studies have reported drop outs and a meta analysis for the same was performed. Homogeneity was present across studies ( $\chi^2 = 2.5$ ,  $p = 0.65$ ,  $I^2 = 0$ ) and a fixed effects model was used for analysis. A total of 15 patients dropped out in the sham group and 12 patients dropped out from tDCS group. No statistically significant difference was found in drop outs of sham and tDCS group (Fig. 4A).

### Meta Analysis of Adverse Effects

Three out of 11 studies have reported adverse effects. Mild side effects in the form of tingling, headache, heaviness in head, itching were reported by patients. A total of 6 adverse effects were reported in the tDCS group and no adverse effects were reported in sham group. Homogeneity was present across studies ( $\chi^2 = 1.1$ ,  $p = 0.94$ ,  $I^2 = 0$ ) and a fixed effects model was used for analysis. No statistically significant difference was found in adverse effects of sham and tDCS groups (Fig. 4B).

## DISCUSSION

tDCS is an upcoming modality of treatment amongst brain stimulation techniques. The ease and convenience of administering the procedure and the low cost incurred, make it a very feasible option of treatment. Owing to these factors, the effects of tDCS in improving cognitive decline in patients with AD were analysed. We analysed a total of 11 studies published between January 2000 & June 2020. All the studies had undergone randomization and blinding although one study did not give the details of blinding procedure involved.

tDCS promotes and inhibits the spontaneous activity of cerebral cortex. tDCS stimulates the brain with weak currents of around 2 mA and regulates the resting membrane potential. This induces changes at the levels of spontaneous discharges and results in activation of NMDA receptor. The effect of tDCS is dependent on the montage that is used. Anodal tDCS is known to result in cortical ex-

citability by causing depolarisation, whereas cathodal tDCS results in decrease of cortical excitability by causing hyperpolarisation [20]. In addition to that, tDCS also results regional cerebral blood flow changes and impedes the aberrant neural synchronization that is seen in AD.

Previous reviews conducted on this theme have identified that the results of tDCS in cognition of patients with AD has been conflicting [21]. The queries regarding the most effective montage and the optimal session frequency and duration has been raised in most reviews [6,7]. In our review, all studies had their follow up ranging from 2 weeks to 8 months and the sample size ranged from 20 to 210. The studies were heterogenous in the frequency and total number of sessions administered (Table 1). But overall, the results of our meta-analysis showed that tDCS was effective in improving cognition of patients with AD. Also, on evaluating for the type of stimulation that was more effective, Anodal stimulation was most effective in cognitive improvement of subjects with Alzheimer's disease. However, long term follow up studies will be required to see full effects of tDCS.

tDCS is known to have certain mild adverse effects like headache, tingling, numbness after the procedure that lasts for few hours. However our analyses should that tDCS was well tolerated in patients with AD as our analyses did not report statistically significant drop outs and adverse effects in sham or tDCS groups.

The strength of our analyses was that all the studies that have been included in the analyses have a low risk of bias and had a high score on quality estimate. Secondly, we have analysed the type of tDCS stimulation that is most effective in improving cognition of person with AD. According to our knowledge this is the first study to have analysed the type of stimulation in tDCS.

Our meta-analysis had a number of limitations. Firstly, we could only analyze literature published in English language and could not include studies published in other languages like French, German etc. Secondly, although all included studies had undergone randomization and were conducted with blinding, there was high heterogeneity amongst our studies. The high variability in sample size, duration of illness, duration of tDCS, type of stimulation, current intensity could have contributed to the same. Finally, only MMSE scores were chosen for analysis. The other aspects of cognition like visuo-spatial skills, language etc were not analyzed in our study.

We intend to extend our analysis in a few respects in near future. We would like to assess the effect of tDCS in behavioural and psychological symptoms of Dementia in subjects with AD. Also, we would like to evaluate effects of tDCS on other aspects of cognition like visual and spatial skills, language etc. It is important to see the effects of tDCS on these aspects of cognition and to assess if they also improve with tDCS or the improvement that we see in MMSE is at the expense of these functions? Also, the applicability of tDCS in improvement of other types of dementias like Lewy body dementia, Frontotemporal Dementia, Dementia secondary to traumatic brain injury, HIV, Parkinson's disease needs consideration.

To conclude, tDCS is found to be effective in improving cognition of patients with Alzheimer's disease. Anodal tDCS is more effective than dual stimulation and cathodal tDCS. tDCS is well tolerated in patients with Alzheimer's disease.

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#### ■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

#### ■ Author Contributions

Conceptualization: Vrinda Saxena, Arghya Pal. Data acquisition: Vrinda Saxena, Arghya Pal. Formal analysis: Vrinda Saxena, Arghya Pal. Funding: Nil. Supervision: Arghya Pal. Writing—original draft: Vrinda Saxena, Arghya Pal. Writing—review & editing: Vrinda Saxena, Arghya Pal.

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