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PREDICTORS OF EFFICACY, TOLERABILITY AND DISCONTINUATION OF TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) FOR MILD COGNITIVE IMPAIRMENT (MCI) AND ALZHEIMER'S DISEASE (AD): A META-ANALYSIS AND META-REGRESSION

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Abstract

Numerous patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD) are refractory to pharmacological treatment, and non-invasive brain neurostimulation has been investigated as another possibility for improving cognition. The performed meta-analysis and meta-regression verified predictors of efficacy, tolerability, and discontinuation of transcranial direct current stimulation (tDCS) for treating MCI or AD. The analyzed studies used the Mini-Mental State Exam, Montreal Cognitive Assessment, or Alzheimer's Disease Assessment Scale - Cognitive Subscale scores as outcome measures. Databases (PubMed, Embase, and Web of Science - primary collection) were searched, resulting in 12 published randomized and controlled trials. The risk of bias assessment was based on Cochrane Review recommendations, considering study characteristics. Other evaluated outcomes were the number of adverse effects (tolerability) and dropouts. Overall and anodal tDCS improved cognition compared to the sham protocol. Group comparisons did not show statistically significant differences for adverse effects and dropouts. Session duration was a response predictor, as stimulations of up to 20 minutes for ten days or more improved the outcome achievement. The AD diagnosis covariate also affected efficacy. The findings should be interpreted carefully in clinical practice because the stimulation effect may vary among subjects.

Keywords: Alzheimer's disease. Mild cognitive impairment. Transcranial direct current stimulation.

1. Introduction

Mild cognitive impairment (MCI) is an objective decline in one or more cognitive domains without significantly impairing daily activities. Its occurrence is associated with several underlying causes, including the pathophysiology of Alzheimer's Disease (AD) (Petersen et al. 2014; Jack et al. 2018). MCI prevalence increases with age and has an incidence between 21.5 and 71.3 per 1,000 population/year. The annual rate of progression to dementia ranges from 8% to 15% (Ward et al. 2012; Petersen 2016). AD is the most common cause of dementia, affecting up to 20% of individuals over 80 years old, representing a cognitive decline that influences daily activities or social functioning (Schneider et al. 2007; Vidoni et al. 2012).

Despite intensified efforts and numerous attempts at pharmaceutical trials, optimal MCI and AD treatments remain inconsistent, and it is imperative to validate interventions to delay cognitive decline

before irreversible dementia symptoms appear (Boyle et al. 2006; Cummings et al. 2014). Systematic reviews and meta-analyses have evaluated the effectiveness of cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) for treating MCI and AD, showing no convincing evidence that these drugs benefit cognitive test scores or combat the progression of cognitive impairment from MCI to AD (Russ and Morling 2012; Tricco et al. 2013).

Alternative non-pharmacological treatments for MCI and AD, such as exercise and training, have been explored for their potential to improve cognition and quality of life, reduce disruptive behaviors, and delay MCI progression to dementia and institutionalization (Horr et al. 2015). More recently, transcranial direct current stimulation (tDCS) has stood out as a non-pharmacological intervention for treating MCI and AD symptoms. However, divergent findings caused uncertainties about using this non-invasive brain stimulation as a clinical therapy (Liu et al. 2017). tDCS induces neuroplasticity in the human brain, has a low cost and compact design, and is easy to handle (Goldsworthy and Hordacre 2017).

Aspects such as electrical current intensity, electrode position and size, stimulation time, current polarization (anode or cathode), and the number of sessions are related to the tDCS effectiveness rate (Nitsche et al. 2009; Clark et al. 2011). However, studies have shown highly variable responses to tDCS among individuals, and the underlying reasons remain poorly explained (López-Alonso et al. 2014; Wiethoff et al. 2014; Chew et al. 2015; Strube et al. 2016; Ammann et al. 2017). The lack of consensus about parameters and individual differences may contribute to such divergences (Datta et al. 2012; Laakso et al. 2015; Opitz et al. 2015).

Regarding the safety and tolerability of non-invasive neurostimulation, highly relevant analyses have been performed in the last 14 years involving tDCS application in adults (Poreisz et al. 2007; Brunoni et al. 2011; Aparício et al. 2016; Bikson et al. 2016). The first safety study, published by Poreisz et al. (2007), reported the frequency of side effects during and after tDCS in 102 participants in 567 sessions, demonstrating a relationship with adverse effects such as scalp tingling (70.6%), itching (30.4%), and fatigue (35.3%). In contrast, Bikson et al. (2016) reviewed nearly 7,000 subjects (with over 1,000 exposed to five or more sessions) and over 33,000 sessions, revealing zero serious adverse events. Furthermore, a recent systematic review showed that many studies have not addressed sufficient data to generate relevant indicators for tDCS safety in clinical settings of cognitive dysfunction (Yan et al. 2020).

Clinical applicability must identify the patients most likely to respond to therapy based on initial assessments and knowledge of factors that influence tDCS discontinuation, preventing an ineffective prolongation of therapy (Dagnino et al. 2022). Previous studies have analyzed tDCS efficacy and safety, but none have investigated all discontinuation causes to assess the risk-benefit ratio of this treatment (Brunoni et al. 2011; Iannone et al. 2019; Yoosefee et al. 2020). These investigations have also not extensively examined the variability sources across studies regarding different discontinuation, efficacy, and safety outcomes. This study presents a meta-analysis and a meta-regression investigating predictors of efficacy, safety, and tolerability of tDCS in MCI and AD patients.

2. Material and Methods

Data sources

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022303544).

Two investigators (KG and AA) independently searched for articles published up to 2023, using the terms “tDCS,” “Transcranial direct current stimulation” AND “Alzheimer,” “Alzheimer’s disease,” “Alzheimer Disease,” “Neurocognitive disorder,” “Mild cognitive impairment,” “Dementia” at PubMed, Embase, and ISI (Web of Science – primary collection). Three authors (MECO, CCOM, and SMMSA) re-evaluated potentially eligible articles to determine whether they met the selection criteria. The other authors (SA and CO) discussed and reached a consensus on disagreements. The research question followed the PICO strategy (P = population, I = intervention, C = comparator, O = outcome). The search had no

restrictions on study location to capture all possible relevant titles. Figure 1 details the flowchart of our search process.

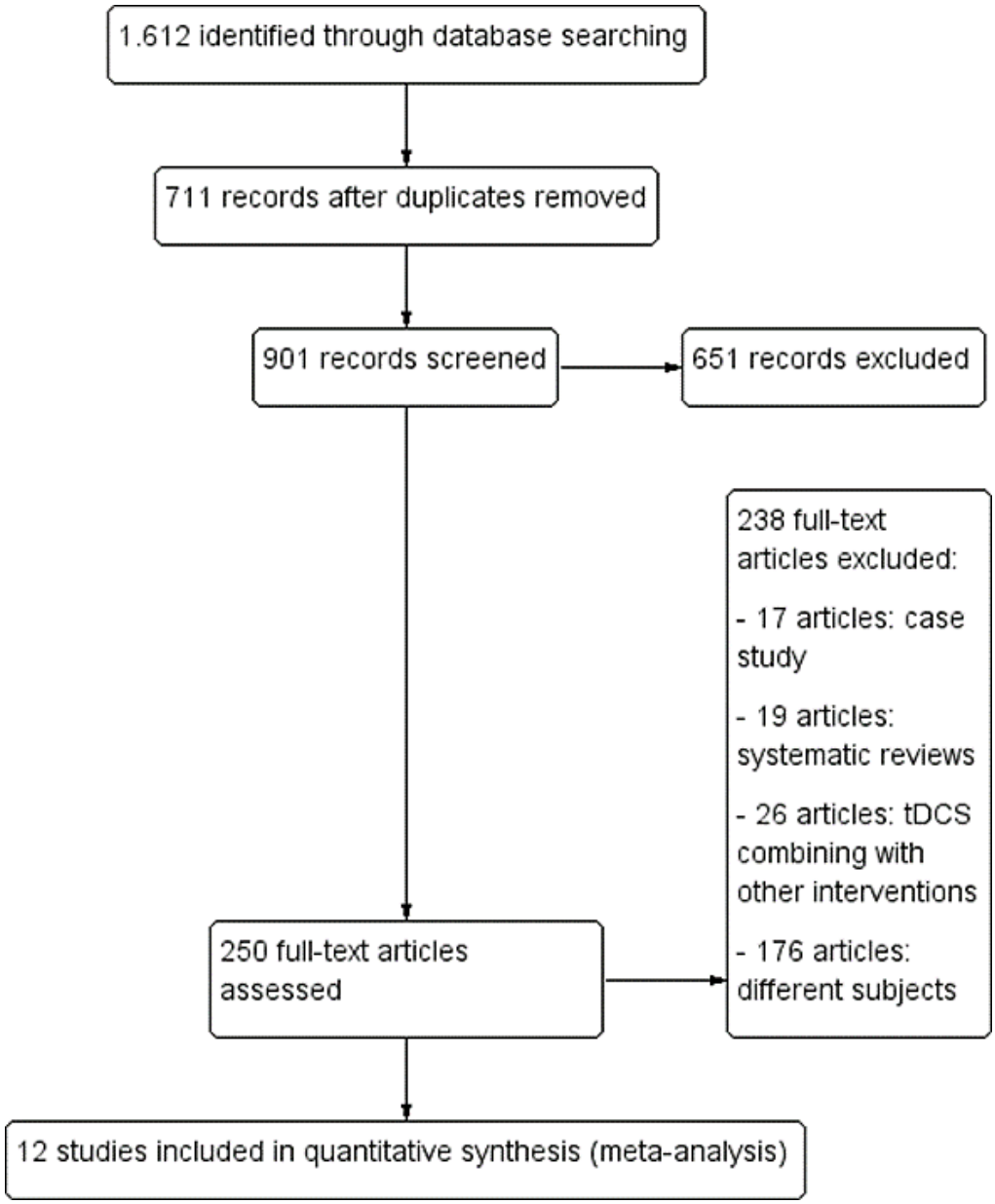


Figure 1. Flowchart of search and selection procedures.

Inclusion criteria for the meta-analysis

The primary inclusion criteria were all randomized, double-blinded, placebo-controlled clinical trials (RCTs) investigating the efficacy, safety, and tolerability of tDCS for treating MCI and/or AD. The studies had to 1) be double-blinded and randomized; 2) use a placebo as a comparator, regardless of having an active comparator; 3) clearly describe all inclusion and exclusion criteria; 4) compare the outcomes from using placebo and tDCS in MCI and/or AD patients. There were no restrictions for cognition status severity, treatment basis (i.e., inpatient or outpatient), or study location.

Data extraction, quality assessment, and risk of bias

A data-collection form extracted information, including study authors, publication year, sample size, patient characteristics (mean age, sex), treatment duration, dosage, baseline findings, and study design. RCT quality assessments were based on Cochrane Review recommendations. Two authors (KG and AA) independently assessed the risk of bias in individual studies, including sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessments, incomplete

outcome data, selective outcome reporting, and other sources. An evaluator (KG) also analyzed the quality of evidence, suggesting a moderate certainty level for the findings (Brożek et al. 2009). The SPSS 21.0 analyzed the data from the included studies by authors, and Cohen's Kappa (K) statistic assessed inter-examiner reliability for each item, providing a substantial reliability value (K=0.625; p<0.002) (Landis and Koch 1977). The authors were contacted via e-mail in case of relevant data missing from the articles.

Study outcomes

The primary outcome measures were study baseline to endpoint changes in the total score of objective cognitive scales (Mini-Mental State Examination – MMSE, Montreal Cognitive Assessment – MoCa, and Alzheimer's Disease Assessment Scale – Cognitive Subscale – Adas-Cog). Safety and tolerability outcomes included the number of adverse events (Aes) and dropouts due to Aes. The meta-analysis included common Aes, such as itching, headache, and others.

Statistical analysis

RevMan – Review Manager Version 5.4 software (Cochrane Collaboration, Oxford, UK) provided the statistical analysis. Binary measures used an odds ratio (OR) at 95% confidence intervals (95% CIs) with the Mantel-Haenszel method to show differences from study baseline to endpoint between active tDCS and control groups. Additionally, continuous measures used standardized mean differences (SMD) with the method by Hedges (Hedges g) at 95% CIs. I^2 statistics measured heterogeneity, evaluating the degree of variance among studies that may be attributed to their actual differences rather than to chance. Studies suggested that an I^2 value of 75−100% indicates considerable heterogeneity. The random-effects model extracted the pooled estimates. Comprehensive Meta-Analysis (CMA) software provided the meta-regression. The findings were presented as an odds ratio (OR) at a 95% CI. The p-value was considered <0.05.

3. Results

Study characteristics

The electronic searches in all mentioned databases found 1,612 potentially relevant articles, of which 711 were duplicates and removed. The remaining 901 studies underwent screening for titles and abstracts in the first stage and for the full texts of 250 articles in the second stage. Finally, the analysis included 12 articles (Figure 1). It is worth noting that Gangemi's publication reported two studies with different samples, and they were considered separately for analysis purposes (part 1 and part 2) (Gangemi et al. 2021).

The included articles covered a sample of 401 elderly with MCI or AD who underwent tDCS treatment. Two studies did not specify the male-to-female ratio, and the other articles showed 137 male and 234 female participants. All included studies had two groups, comparing sham and active groups. The designs of ten of 12 studies were parallel, and two were cross-over. Diagnoses were based on criteria from the DSM-V and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Table 1 summarizes the most relevant information about study characteristics, including protocols. All studies applied anodal tDCS, and only two used both anodal and cathodal tDCS (Ferrucci et al. 2008; Khedar et al. 2014).

Based on Cochrane Review recommendations to determine an outcome risk of bias compared to all investigations analyzing such outcome, this study considered the risk of bias low when most information came from studies classified as a low risk of bias, uncertain when most information came from low-risk and uncertain-risk analyses, or high when the rate of high-risk information was sufficient to affect the interpretation of findings. This assessment showed that all included studies had good quality regarding methodologies (Figure 2).

Table 1. Characteristics of the included studies.

	Diagnosis	Diagnosis criteria	Number of participants in each group	Mean age in each group (years)	Sex (M/F)	Disease's duration (years)	Education	Cognition level in each group (MMSE scores)	Anodal stimulation	Cathodal stimulation	Stimulation site	Reference electrode	Stimulation protocol	Sham	Cognition assessment	Adverse effects	Reasons for drop-outs (n)
Boggio *et al.* (2012)	AD	NINCDS-ADRDA, DSMV-IV	EG: 15 SG: 15	EG:77.5± 6.9 SG: 80.6 ± 9.5	EG: 4/4 SG: 4/3	4.5±2.2	EG: 13.3 ± 4.8 SG:15.7 ± 0.8	EG: 20.3 ± 1.0 SG: 19.2 ± 1.1	Yes	No	L-DLPFC LTC	Right frontal Lobe	2 mA, 30 min/d, 1 d	First 30s current	MMSE; MoCA	No	
Bystad *et al.* (2016)	AD	NINCDS-ADRDA	EG: 12 SG: 13	EG: 70.0 ± 8.0 SG: 75.0 ± 8.7	EG: 7/5 SG: 7/6	NS	NS	EG: 20.0 ± 2.8 SG: 21.2 ± 3.9	Yes	No	Left temporal lobe	Right temporal lobe	2 mA, 30 min/d, 6 d	First 30s current	MMSE	No	
Cotelli *et al.* (2014)	AD	NINCDS-ADRDA	EG: 12 SG: 12	EG: 76.6± 4.6 SG: 74.7± 6.1	EG: 2/10 SG: 3/9	NS	EG: 5.5 ± 2.4 SG: 8.9 ± 5.1	EG: 20.1 ± 2.4 SG: 20.8 ± 2.1	Yes	No	L-DLPFC	Deltoid	2 mA, 25 min/d, 5 d	First 10s current	MMSE	No	NS (n=3)
Ferrucci *et al.* (2008)	AD	NINCDS-ADRDA	EG: 10 SG: 10	75.2 ± 7.3	3/7	NS	10.9 ± 4.8	22.7 ± 1.8	Yes	Yes	L, R-Temporoparietal areas	Middle temporal and posterior temporal	0.06 mA, 15 min/d for each stimulation 3 months	First 10s current	MMSE	No	
Fileccia *et al.* (2019)	MCI	NS	EG:17 SG: 17	EG: 71.6± 1.4 SG: 69.7± 1.6	EG: 13/4 SG: 11/6	M_d and SE	M_d and SE	EG: 25.9 ±0.5 SG: 26.1 ±0.6	Yes	No	L-DLPFC	Deltoid	2 mA, 20 min/d, 20 d	First 20s current	MMSE	No	
Gangemi *et al.* (2020) – *Part 1*	AD	NINCDS-ADRDA, DSMV-IV	EG: 13 SG: 13	EG: 67.5±2.8 SG: 69.01 ± 3.1	NS	NS	EG: 6.5 ± 2.0 SG: 6.1 ± 2.1	EG: 14.9 ± 1.8 SG: 15.3 ± 1.8	Yes	No	Left frontotemporal lobe	Right frontal lobe	2.5 mA, 20 min/d, 10 d	First 10s current	MMSE	No	
Gangemi *et al.* (2020) – *Part 2*	AD	NINCDS-ADRDA, DSMV-IV	EG: 09 SG: 09	EG: 68.5 ± 2.8 SG: 68.7 ± 3.1	NS	NS	EG: 6.7 ± 2 SG: 6.2 ± 2.7	EG: 15.8 ± 1.8 SG: 15.9 ± 1.6	Yes	No	Left frontotemporal lobe	Right frontal lobe	2.5 mA, 20 min/d, 10 d	First 10s current	MMSE	No	
Gomes *et al.* (2019)	MCI	NS	EG: 29 SG: 29	EG: 73.0 ± 9.2 SG: 71.6 ± 7.9	EG: 9/ 20 SG: 7/ 22	NS	NS	EG: 26.93 ± 0.5 SG: 27.14 ± 0.48	Yes	No	L-DLPFC	Right supraorbital area	2 mA, 30 min/d, 10 d	First 30s current	MMSE	No	Cancer (n=1) and dengue (n=1)
Im *et al.* (2019)	AD	NINCDS-ADRDA, DSMV-IV	EG: 12 SG: 08	EG: 71.9 ± 9.2 SG: 74.9 ± 5	EG: 1/10 SG: 2/5	NS	EG: 6.3 ± 3.8 SG: 5.4 ± 5.9	EG: 20.1 ± 3.8 SG: 22.1 ± 4.6	Yes	No	R, L-DLPFC	R, L-DLPFC	2 mA, 29 min/d, 3 d	First 60s current	MMSE	No	Refusal or time conflict of a caregiver (n=2)

Table 1. Continued.

Khedar *et al.* (2014)	AD	NINCDS-ADRDA	EG: 11 SG: 11	EG: 68.5 ± 7.2 SG: 67.3 ± 5.9	EG: 3/9 SG: 6/5	3.1±2.1	EG: 8.9 ± 5.1 SG: NS	EG: 18.4 ± 3.9 SG: 16.9 ± 2.9	Yes	Yes	L-DLPFC	Supraorbital region	2 mA, 25 min/d, 10 d	First 30s current	MMSE	Yes	
Khedar et al. (2019)	AD	NINCDS-ADRDA	EG: 23 SG: 23	EG: 64.22 ± 3.64 SG: 65.23 ± 4.52	EG: 13/10 SG: 13/08	1.17±0.48	EG: 4.04 ± 2.83 SG: 3.52 ± 1.96	EG: 14.17 ± 3.67 SG: 13.90 ± 3.46	Yes	No	R, L-TP	Deltoid	2 mA, 20 min/d, 10 d	First 30s current	MMSE	Yes	
Satorres *et al.* (2023)	AD	DSM-V	EG:17 SG:16	EG:76.6 ± 5.7 EG:73.4 ± 6.2	EG: 9/8 EG: 8/8	NS	EG:10.35 ± 3.9 EG:10.8 ± 4.6	EG:23.88 ± 3.2 EG:22.94 ± 3.9	Yes	No	L-DLPFC	Right frontal lobe	2 mA, 20 min/d, 10 d	First 30s current	MMSE		
Suemoto *et al.* (2014)	AD	NINCDS-ADRDA	EG: 20 SG: 20	EG: 79.4 ± 7.1 SG: 81.6 ± 8.0	EG: 5/15 SG: 7/13	NS	EG: 5.0 ± 4.2 SG: 4.5 ± 3.9	EG: 15.0 ± 3.1 SG: 15.4 ± 2.6	Yes	No	L-DLPFC	Supraorbital region	2 mA, 20 min/d, 6 d	First 20s current	Adas-Cog	Yes	Pneumonia (n=1) and diarrhea (n=1)

Values are presented as mean ± standard deviation; AD: Alzheimer's Disease; DSM-IV: Diagnostic and Statistical Manual-IV; EG: Experimental Group; M/F: Male/Female; MCI: Mild Cognitive Impairment; M_d: Median; MMSE: Mini-Mental Status Evaluation; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NS: Not Specified; SG: Sham Group; SE: Standard Error.

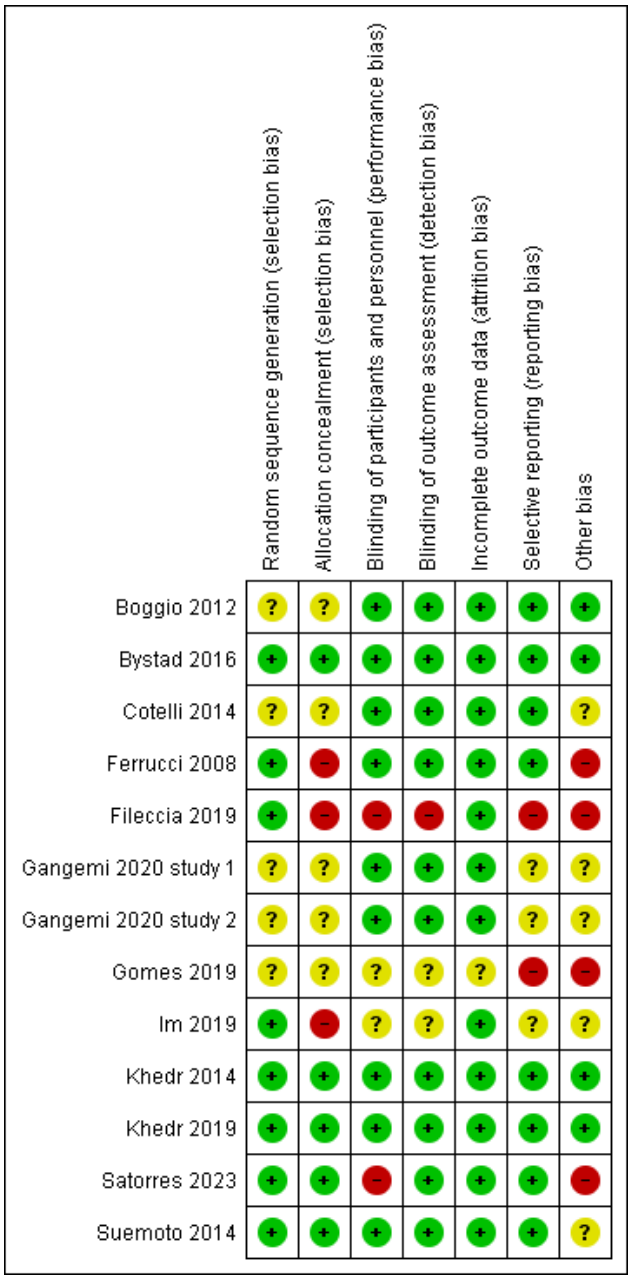


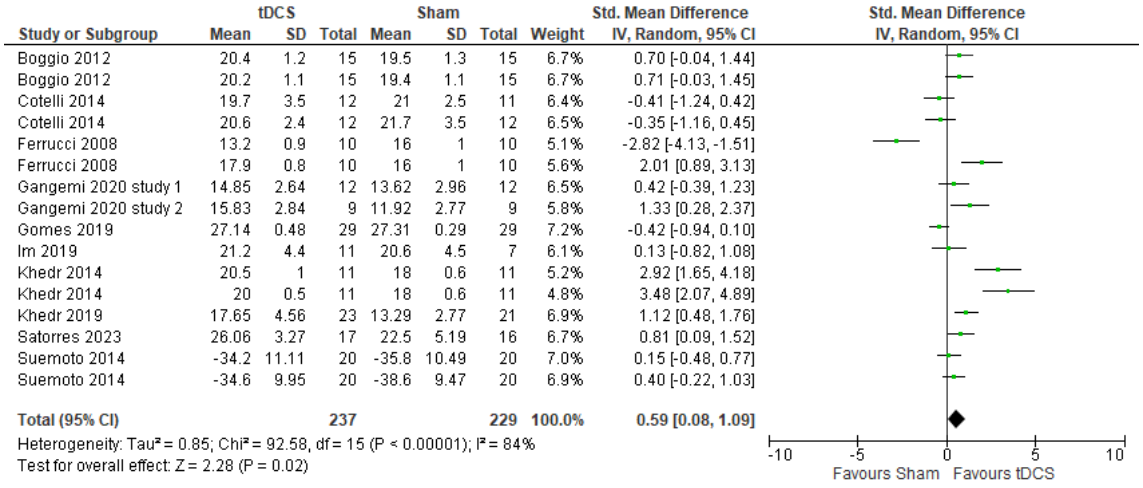
Figure 2. Risk of bias in individual studies included in the meta-analysis, considering the performance and description of randomization, allocation, blinding, outcome data, selection bias, and other biases.

Efficacy

Forest plots present meta-analysis outcomes regarding primary endpoints and mean total cognitive score changes from study baseline to endpoint (Figure 3). The meta-analysis showed that overall tDCS improved cognition compared to the sham protocol ($\chi2$= 92.58; p<0.00001; I^2: 84%), with very high heterogeneity (Figure 3A). The subgroup analysis showed the superiority of anodal tDCS (Figure 3B) compared to sham stimulation ($\chi2$= 48.48; p=0.00001; I^2: 79%). The opposite occurred with cathodal tDCS, not showing statistically significant differences between this tDCS and patients in the sham group (p=0.71). Individuals stimulated with an intensity current of 2 mA (Figure 3C) obtained better overall cognition outcomes than sham groups ($\chi2$= 101.54; p<0.00001; I^2: 92%). tDCS stimulation for ten days or more also seemed to improve overall cognition in the experimental group ($\chi2$= 97.11; p<0.00001; I^2: 95%) (Figure 3D). The meta-regression in the latter subgroup showed that the session duration influenced the efficacy outcome. Thus, stimulations of up to 20 minutes seemed more effective than prolonged tDCS applications, and this covariate explained 97% of the identified variance (R^2= 0.97; p=0.00). Figure 4 shows analysis findings in a bubble plot.

No other covariate modified the tDCS effect on the efficacy outcome. We tested the diagnosis as a moderating variable for the subgroup using anodic stimulation and the other applying the 2mA intensity, not finding a statistical significance (p=0.14; p=0.17). Our study also used this variable for the subgroup using the protocol for ten days or more, showing a statistically significant influence on efficacy (p=0.04). Age (p=0.25), education (p=0.17), and baseline scores of instruments assessing cognition (p=0.70), such as moderating variables, did not explain the heterogeneity. Age also could not explain the heterogeneity of subgroups applying the 2mA current (p=0.13) and using the protocol of ten days or more (p=0.9).

A



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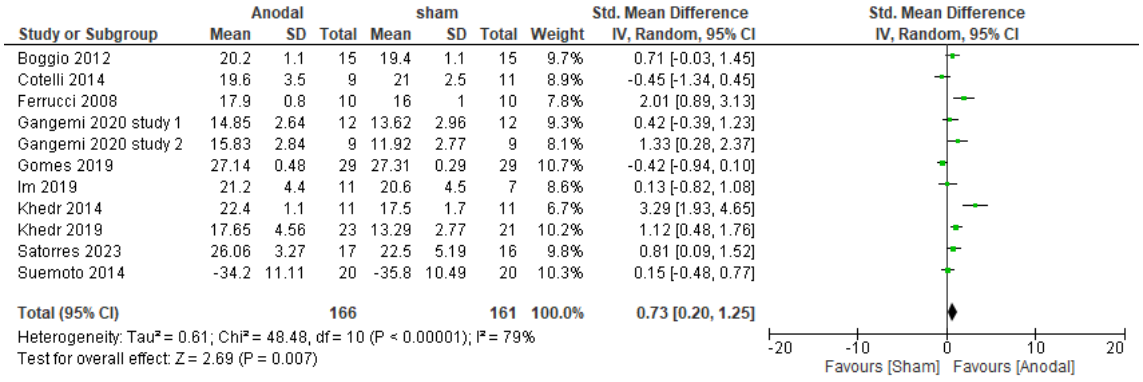

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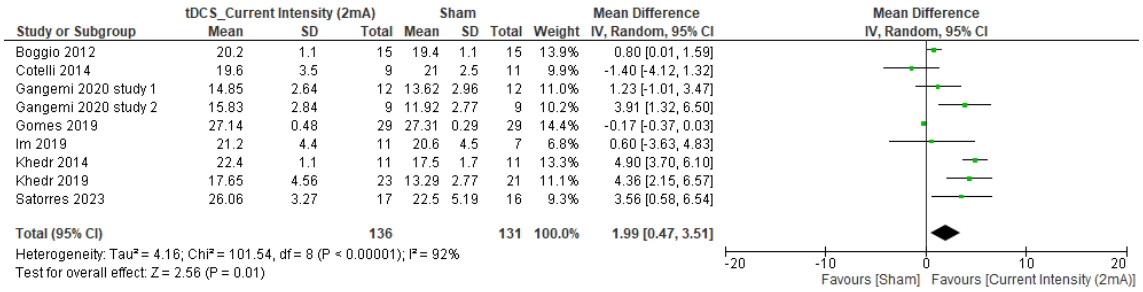

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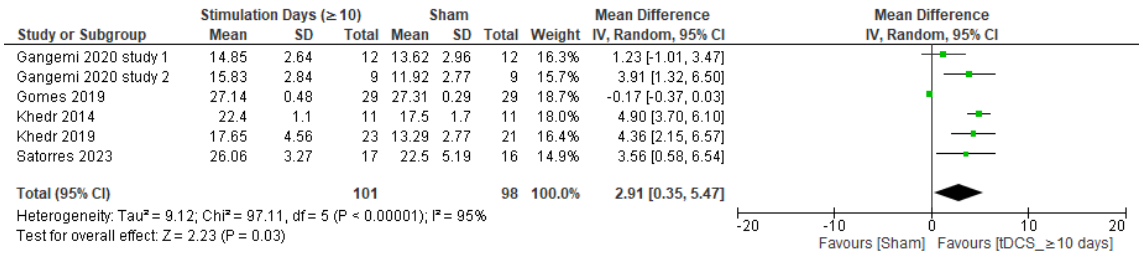

Figure 3. Forest plot on the efficacy in A - all studies with tDCS, B - anodal tDCS and sham tDCS, C - tDCS with a 2mA intensity, and D - tDCS for ≥10 days.

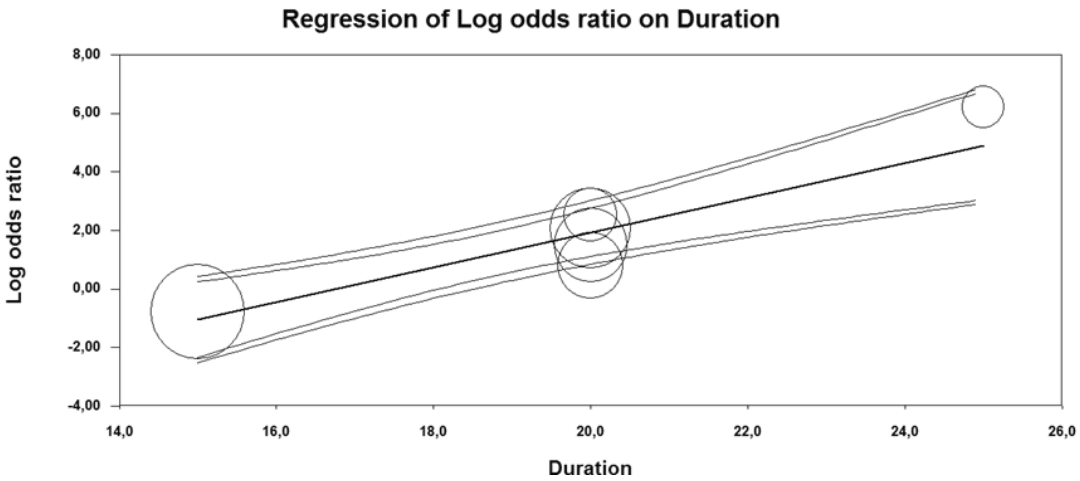

Figure 4. Bubble plot of session duration.

Safety and discontinuation

Three of 12 studies reported adverse effects in active groups: tingling, headache, heaviness in the head, and itching (Khedar et al. 2014; Suemoto et al. 2014; Khedar et al. 2019). Similarly, three studies identified adverse effects in the sham group (Cotelli et al. 2014; Suemoto et al. 2014; Khedar et al. 2019). Homogeneity occurred across studies ($\chi 2 = 0.88$, $p = 0.65$, $I^2 = 0$) without statistically significant differences for adverse effects in sham and tDCS groups (Figure 5). Five of 12 studies reported dropouts, with six patients dropping out from the sham group and six others from the tDCS group. Homogeneity occurred across studies ($\chi 2 = 2.49$, $p = 0.65$, $I^2 = 0$) without statistically significant differences for dropouts in sham and tDCS groups. Thus, a meta-regression could not be performed because of the lack of heterogeneity.

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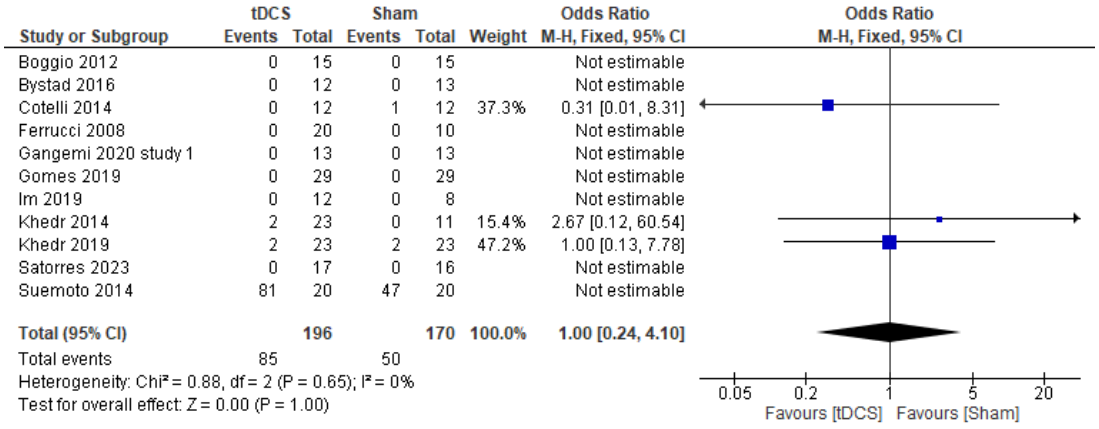

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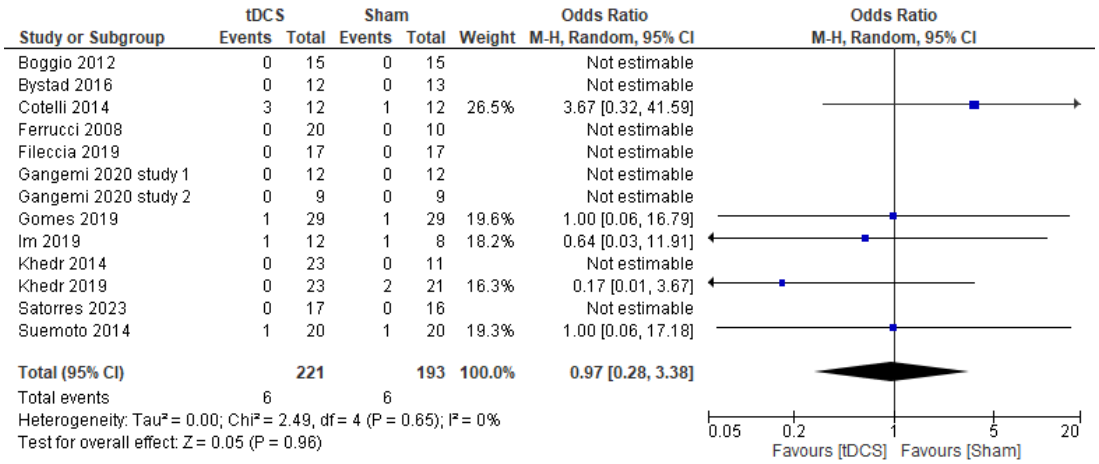

Figure 5. Forest plot of studies comparing A) adverse effects reported in groups receiving tDCS and sham tDCS (tolerability) and B) dropouts in groups receiving tDCS and sham tDCS.

4. Discussion

The present study shows transcranial direct current stimulation (tDCS) as an effective alternative for managing cognition in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD). However, it was impossible to identify many efficacy predictors, even when including those well established in the literature as influencers, such as age, education, and cognitive scores before intervention and diagnosis. The "session duration" moderator variable influenced efficacy in the subgroup of patients receiving tDCS for ten days or more. The diagnosis also affected this subgroup, such that AD patients seemed to respond more consistently to tDCS than those with MCI.

Habich et al. (2020) affirm that tDCS may be promising to neutralize or compensate for neurophysiological changes. However, the non-invasive neurostimulation parameters from studies in young adults must be adapted appropriately for the elderly population. Additionally, computational models based on individual anatomical images can help choose suitable electrode positions to ensure the applied current reaches the defined target location, considering anatomical and neurophysiological variations.

Regarding session duration, Hassanzahraee et al. (2020) studied 15 healthy participants, reporting an increase in corticospinal excitability with increasing stimulation of up to 24 minutes for anodal tDCS (a-tDCS) over the motor cortex and a decrease in or even reversed excitability for stimulations of 26, 28, and 30 minutes. Changes in short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval facilitation (LIF) indicated the involvement of glutamatergic and GABAergic systems in these effects. Prolonged stimulations may activate neuronal counterregulatory mechanisms, reversing corticospinal excitability (CSE). Monte-Silva et al. (2013), Misonou et al. (2004), and Yasuda et al. (2003) stated that the existing Ca^{2+} induced by prolonged stimulation activates potentially excessive channels, limiting the extended Ca^{2+} influx and converting the effects. High levels of synaptic activity yielded by prolonged a-tDCS enhance the intracortical inhibitory interneuron activation on excitatory interneurons and decrease the N-methyl-d-aspartate receptor (NMDA).

A pioneer recent double-blinded, sham-controlled, and between-subject study with 28 participants (12 AD/16 MCI) showed that education moderates tDCS effects on memory performance, using the anode over the left dorsolateral prefrontal cortex (F3) and the cathode on the contralateral supraorbital region at 1mA for 20 minutes. The authors found a significant three-way interaction such that patients with MCI and higher education benefited significantly from stimulation, and those with AD only improved when they were less educated [$F_{(1, 20)} = 4.55$, $p < .05$, $R^2_{change} = 0.09$, $p < 0.05$]. However, the effect direction was not consistent in all patients, indicating additional influencing factors (Krebs et al. 2020).

A randomized controlled trial with 47 AD patients showed that the active group displayed higher associative memory (AM) improvements than the sham group at week two ($p = 0.003$) and sustained at week ten (Wu et al. 2022). Authors associated higher Mini-Mental State Examination (MMSE) scores at baseline with higher AM improvements at weeks two and ten. Most neuropsychological tests markedly improved in the active group, demonstrating that the ameliorating effects were more effective and robust among patients with high MMSE scores at baseline. However, further studies need to elucidate the neural mechanisms that influence efficacy.

Despite these promising findings, the studies indicate highly relevant issues related to individual characteristics that require further investigations and consideration for clinical practice. Although scientific rigor is essential to control variables during clinical trials, a critical reflection is needed to determine potential interferences of subjects' particularities with neurostimulation effectiveness and whether they remain neglected in daily clinical activities and investigations. For instance, the articles in the present study did not detail aspects of depressive disorders or comorbidities, especially those related to chronic diseases.

Previous studies have suggested that tDCS preferentially affects synapses undergoing plasticity, and research has increasingly supported the efficacy of applying anodal tDCS on the dorsolateral prefrontal cortex (DLPFC) to enhance cognitive performance in MCI patients and improve memory in those with AD (Ferrucci et al. 2008; Boggio et al. 2009; Boggio et al. 2012; Meinzer et al. 2015; Gomes et al. 2019).

The present meta-analysis and meta-regression attempted to investigate efficacy, safety, and discontinuation predictors. Session duration appears to interfere with efficacy, mainly in groups stimulated

for ten days or more, and an a-tDCS application of up to 20 minutes promoted higher benefits. This moderator variable behaves as a response predictor for non-invasive neurostimulation, and it should be considered for clinical practice to optimize the duration of the treatment proposed for AD and MCI patients. An AD diagnosis also potentiated the perception of tDCS efficacy. Besides the high number of studies addressing dementia, the ceiling effect related to cognitive test scores may be among the factors that make the findings more limited and controversial for the population with MCI.

Moreover, tDCS was safe considering the insignificant number of adverse events, and did not cause patient dropout. These safety and tolerability outcomes are supported by an Indian study with 171 patients [156 adults (Age=35.9 ± 13.5 years) and 15 adolescents (Age=15.4 ± 1.2 years)] who sought the clinical services of the National Institute of Mental Health & Neurosciences, showing that tDCS is safe for therapeutic non-invasive neuromodulation in psychiatric disorders in adults and adolescents (Chhabra et al. 2020).

The limitation of this study was the inclusion of articles with small samples and few data about relevant topics that might help identify predictors for the analyzed outcomes. Depression, anxiety, physical activity level, comorbidities, genetic factors, and other issues might elucidate the controversial findings of studies and better guide clinical practice. Conversely, this study verified that tDCS benefits the cognition of MCI and AD patients, guiding health professionals to apply tDCS in sessions with an adequate duration.

5. Conclusions

Additional biomarkers for predicting the therapeutic success of tDCS must be investigated, such as relevant genes, inflammatory markers, neurotransmitter concentrations, markers of cortical excitability and neurodegeneration, and neuronal activation patterns (i.e., neural activation during task execution and resting-state functional connectivity). Individual parameters and characteristics must be studied in an intertwined way to clarify the remaining questions.

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