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A systematic review and meta-analysis of the impact of transcranial direct current stimulation on cognitive function in older adults with cognitive impairments: the influence of dosage parameters

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Abstract

Introduction Numerous studies have demonstrated the effects of transcranial direct current stimulation (tDCS) on cognitive function in the older people. This study further explores the impact of tDCS and its dosage parameters on cognitive enhancement in older people with cognitive impairments.

Methods Randomized controlled trials (RCTs) published through November 2023 were retrieved from databases including PubMed, Scopus, EMBASE, EBSCO, and the Cochrane Library. Participants were older adults with cognitive impairments, including Alzheimer's disease (AD), mild cognitive impairment (MCI), and dementia. AD was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), or the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer' Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Dementia was diagnosed using the DSM-V or NINCDS-ADRDA criteria, while MCI was diagnosed using the DSM-V, the Petersen criteria, or assessments such as Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR). Standardized mean difference (SMD) values were analyzed to assess the effects.

Results A total of 19 RCTs were included. tDCS significantly improved the Mini-Mental State Examination score both immediately post-intervention (SMD = 0.51, $p = 0.005$) and at follow-up (SMD = 2.29, $p = 0.0003$). Significant effects were observed when tDCS was used alone (SMD = 0.39, $p = 0.04$), at current densities ≤ 0.06 mA/cm^2 (SMD = 0.25, $p = 0.04$), session durations exceeding 20 min (SMD = 0.89, $p = 0.01$), up to 15 sessions (SMD = 0.28, $p = 0.009$), and when an active electrode was placed over the temporal area (SMD = 0.33, $p = 0.02$). People with AD showed greater improvements compared to those with MCI or dementia (SMD = 0.91, $p = 0.02$). However, tDCS did not significantly improve memory or executive function.

Conclusion tDCS demonstrated efficacy in enhancing global cognition in older people with cognitive impairments, providing insight into optimal parameters for clinical application. However, no improvement were observed in memory or executive function.

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Keywords tDCS, Cognitive impairment, Cognitive function, Older people, Alzheimer's disease, Mild cognitive impairment, Dementia

Introduction

Cognitive decline is a significant public health concern among the elderly population, with a growing prevalence among individuals aged 65 and above, and it has evolved gradually over the years to decades [1]. This decline is intricately linked to age-related alterations in brain structure and function, including changes in neuronal morphology, synaptic loss, and dysfunctions in neuronal circuitry [2]. Cognitive decline results in deficits such as memory impairment, learning difficulties, and a reduced capacity to maintain focus on tasks [3]. This leads to challenges in terms of recall, the acquisition of new information, concentration, and processing speed [4]. The most common conditions that cause cognitive decline include Alzheimer's disease (AD), Lewy-Body disease, vascular dementia, mild cognitive impairment (MCI), and frontotemporal degeneration (damage and loss of nerve cells in the brain) [5].

Interventions aimed at improving cognitive decline include both pharmacological and nonpharmacological approaches. Pharmacological interventions, such as Acetylcholinesterase inhibitors (AchEIs), levetiracetam, and memantine have been used to prevent cognitive deterioration [6]. However, adverse effects such as dizziness, headache, nausea, vomiting, and diarrhea have been documented following pharmacological treatments. Long-term use of these medications can also lead to new comorbidities, requiring additional medications, which can increase the risk of progression of cognitive impairment, dependence on others, morbidity, and mortality [7]. Consequently, nonpharmacological approaches, such as non-invasive brain stimulation (NIBS), have been explored as alternative therapies. Their effectiveness could be crucial for the treatment of MCI and AD, attracting significant attention from researchers [8].

Transcranial direct current stimulation (tDCS) is a NIBS technique suggested as a promising therapeutic modality for preserving cognitive function in individuals with cognitive impairment including MCI, AD, and dementia [9, 10]. Considering the transient mild side effects of tDCS (i.e., tingling and itching), tDCS is safe and has been reported to have a tolerance profile for multiple sessions. This safety profile makes tDCS a potentially beneficial option for older adults with cognitive impairments. tDCS administers a low-level constant current, typically ranging from 0.5 to 2 milliamps, through surface electrodes on the scalp [11]. These electrodes, known as anodal and cathodal electrodes, are employed either individually or in pairs, with configurations that target specific brain regions unilaterally or bilaterally. Within dose limits, tDCS effects are associated with polarity-dependent effects on corticospinal motor excitability: anodal stimulation increases cortical excitability, whereas cathodal stimulation decreases it [12, 13]. Furthermore, tDCS can induce positive aftereffects by promoting synaptic plasticity involving glutamatergic connections, long-term potentiation and long-term depression [14]. However, despite targeting the same brain regions, the effect of tDCS depends on multiple factors, such as stimulation intensity, duration, electrode configuration, electrode size, and number of sessions. tDCS alone and in combination with other therapies has been suggested for use in the treatment of cognitive impairment [15], however, there are a variety of dosage utilizations, and which tDCS dosages should be used to improve cognitive function in older people with cognitive impairments remains a subject of investigation.

Several systematic reviews and meta-analyses have examined the effects of tDCS on cognitive function in individuals with cognitive impairment [9, 10, 16]. For example, a meta-analysis investigated the effects of tDCS combined with aerobic exercise on cognitive function in older adults with and without cognitive impairment. It has been reported that tDCS shows promise in slowing the progression of cognitive decline in older people with MCI and dementia [10]. However, the review included a limited number of studies, suggested addressing the long-term effect of intervention, and noted a lack of investigation into tDCS parameter. Another meta-analysis highlighted the positive effects of tDCS on cognitive function, particularly in enhancing overall cognitive function in individuals with MCI and mild-to-moderate AD [9]. This study reported some optimal parameters, including stimulation target, number of stimulations, and current density, for individuals with MCI and mild AD. However, it highlighted the need for a larger sample size to improve statistical power and generalizability and noted limited research on cognitive training combined with tDCS, including subgroup analyses. Moreover, a recent review [16] highlighted the need to further explore variables such as stimulation intensity, duration, electrode montage, and session frequency. Addressing these gaps, the present study updates evidence on tDCS effect in older adults with cognitive impairments, examining

stimulation parameters, and comparing tDCS alone versus tDCS combined with training. The objective is to optimize tDCS for clinical use in this population.

Methods

Registration of the systematic review protocol

This review follows the Methodological Expectations for Cochrane Intervention Reviews when conducting the review and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) specifications [17]. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration protocol number CRD42023418267, date of registration 3 September 2023.

Literature search strategy

Five electronic databases [PubMed (2003—2023), Scopus (1994—2023), EMBASE (2017—2023), the Cochrane Library (1995—2023), and EBSCO (1954—2023)] were searched for studies published in English until 7 November 2023. These five databases were chosen because they cover a wide range of peer-reviewed literature. The search strategy consisted of four key terms describing the population, impairment, intervention, and outcome by using appropriate keywords combined with a medical subject heading. The study setting and design were determined at screening. The detailed search strategy for each database is presented in Supplementary Table 1 (seeSupplementary Table 1, Additional File 1). Boolean operators (i.e., AND, OR, NOT) were adapted to individual databases. The relevant reviews and reference lists of all the articles were examined for potentially eligible studies.

Selection criteria

The inclusion criteria were determined according to the PICOS (P = population, I = intervention, C = comparator, O = outcome, S = study design) approach: 1) participants were older people with cognitive impairments or dementia, including those with AD, dementia and MCI. AD was diagnosed using the DSM-IV, or NINCDS-ADRDA criteria. Dementia was diagnosed using the DSM-V or NINCDS-ADRDA criteria, while MCI was identified based on the DSM-V, the Petersen criteria, or standardized assessments such as the MoCA and CDR; 2) participants were aged 60 years or over and/or the mean age was $\geq$ 65 years; 3) an experimental group used tDCS alone or in combination with additional intervention. tDCS configurations included unilateral tDCS (anodal or cathodal applied over the interest brain area) or bilateral/dual/bihemispheric (both electrodes applied simultaneously over both hemispheres). The control group received sham tDCS alone or in combination with additional intervention; and 4) at least one objective cognitive scale that measures the change in cognitive function. Moreover, all included studies were randomized controlled trials (RCTs) with crossover or parallel designs and were published in English. Case studies, case reports, case series, protocol papers, controlled trials, single-group pre-posttest studies, cross-sectional studies, retrospective studies, and only abstract publications, conference proceedings, theses, letters to the editor, and clinical practice guidelines were excluded. Studies that recruited participants with other clinical conditions (i.e., Parkinson's disease, stroke, multiple sclerosis, depression, etc.) were excluded.

Screening process and data extraction

Titles and abstracts were independently screened by two reviewers from a review panel (TP, TC, OV, CL) using inclusion and exclusion criteria within Covidence Systematic Review Software (Melbourne, Australia). For studies that met the inclusion criteria (or were unclear), full texts were retrieved and independently assessed for eligibility by two reviewers from a review panel (TP, TC, OV, CL). Differences of opinion between reviewers were resolved by another coauthor (WK) for clarification. The following data were extracted: 1) characteristics of the study (authors, publication year, geographical area), 2) sample size and participant characteristics (age, gender, cognitive health status, duration of education, and duration of disease), 3) intervention parameters (treatment program, electrode montage, electrode size, stimulation intensity, stimulation duration, number of sessions, stimulation area, and follow-up duration), 4) outcome measures, and 5) overall effects of the outcomes of interest. For quantitative analyses (meta-analyses), the group size and mean differences in the outcomes of interest with 95% confidence intervals (CIs) or standard deviations (SDs) for the experimental and control groups were collected. A standardized form was used to extract the data from the included studies, assess study quality, and synthesize the data. In the case of missing data, manuscript authors were contacted via e-mail and were asked to supply the data in a format that was usable for meta-analysis.

Study quality assessment

This study included RCTs, and the quality of the included studies was assessed using the Revised Cochrane Risk of Bias Tool 2 (RoB 2) [18], following Cochrane's recommendations. This tool is specifically designed to assess the risk of bias in RCTs, ensuring comprehensive evaluation of study quality.

To judge the risk of bias in each domain, we use their programmed sheet and algorithm. In the programmed sheet, each domain included signaling questions relevant to assessing the risk of bias. The response options for

each signaling question were yes, probably yes, no, probably no, or no information. After these factors were fed into the algorithm, the risk of bias in each domain was classified as low risk, some concerns, or high risk. Each study was subsequently given an overall risk score indicating a low risk of bias, some concerns, and a high risk of bias.

The quality assessment of each study was independently performed by two reviewers from a review panel (TP, IA, TC, OV, CL). A consensus was reached on discrepant scores by another co-author (WK).

Statistical analysis

Review Manager software (RevMan) version 5.4 (Cochrane Collaboration, Oxford, UK) was used for all the statistical analyses. When at least three study samples examined the same outcome measure, the data were pooled and analyzed in meta-analysis models. If multiple publications used the same sample, only one study was included in the meta-analysis. The pooled mean differences for continuous variables with the same measurement unit and standardized mean differences (SMDs) for continuous variables with different measurement units were calculated. Study weights were automatically calculated by RevMan using the standard deviation and sample size. For heterogeneity tests where $P > 0.05$ and $I^2 < 50\%$, the fixed-effects model was used; conversely, if $P \leq 0.05$ and $I^2 \geq 50\%$, the random-effects model was applied. Heterogeneity was determined via subgroup analysis. A sensitivity analysis was performed to evaluate the impact of each study. Funnel plots were used for the assessment of publication bias. The significance level for all tests was set at $\alpha < 0.05$.

Results

Selection process

A total of 3,828 studies were retrieved for this study. After removing duplicates, 562 studies were screened. Following the screening of titles and abstracts, 3,225 studies were excluded, leaving 41 for full-text screening. Finally, nineteen studies were included in the literature review. The reasons for excluding 22 studies are described in Supplementary Table 2 (see Supplementary Table 2, Additional File 1). The PRISMA flowchart depicting the selection process and the number of studies at each review stage is shown in Fig. 1.

Study characteristics

Nineteen RCTs published between 2014 and 2022 were included in the qualitative synthesis. Among the included studies, 17 [19–35] adopted parallel designs, and 2 [36, 37] adopted crossover designs. A total of 945 participants (552 women) were enrolled, with an average age of 71.66 years (SD = 5.94). These studies included individuals with cognitive impairments: AD in 8 studies [24–26, 28, 30, 31, 34, 36]; MCI in 6 studies [22, 23, 27, 29, 32, 35]; vascular dementia (VD) in one study [19]; dementia in one study [20]; executive dysfunction in one study [33]; and MCI and AD in one study [21]. One study included mixed participants and described them as having 'neurocognitive disorders', including AD or mixed AD/VD [37]. Table 1 presents the study characteristics, cognitive outcomes, and cognitive measurements of the 19 studies that used different cognitive measures to evaluate improvements in cognitive function.

Global cognition

Fifteen studies examined the effect of tDCS on global cognition [19–22, 24–28, 30–33, 35, 37], and twelve of fifteen studies evaluated global cognition by using screening tools, namely, the Mini-Mental State Examination (MMSE) [20, 21, 24, 28, 30, 31] and Montreal Cognitive Assessment (MoCA) [22, 27, 31–33, 35, 37]. Five studies assessed cognitive dysfunction by using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [19, 25, 26, 30, 37], and one study used a cognitive battery to measure global cognition as a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [28].

Learning, memory and language

Only two studies have evaluated the effect of tDCS on learning by using a word-list learning task [25, 30] and Paired Associates Learning (PAL) with the Cambridge Neuropsychological Test Automated Battery (CANTAB) [29].

Overall memory abilities were measured by the Memory Quotient (MQ) [22, 27], and one study assessed every memory skill via the Rivermead Behavioral Memory Test (RBMT) [32]. Eleven studies measured the memory domain, verbal memory measured via the Auditory Verbal Learning Test (AVLT) [27], the California Verbal Learning Test (CVLT) [29], the Chinese Version of the Verbal Learning Test (CVVLT) [35], and the Seoul Verbal Learning Test (SVLT) [24]. Three studies measured visual memory via the Rey—Osterrieth Complex Figure (ROCF) [27], Picture Naming Task (PNT) [19], Delayed Matching to Sample (DMS) and Pattern Recognition Memory (PRM) of CANTAB [23], the Logical Memory Test [21, 30], Rey's 15-word test; immediate recall and delayed recall [21], Rey Complex Figure Test (RCFT); immediate recall, delayed recall, and recognition [21, 24], Wechsler Memory Scale (WMS) [22], and recognition task [25, 36], word list learning; delayed recall [30], and non-adaptive task; and immediate recall and delayed recall [32]. Moreover, working memory was measured

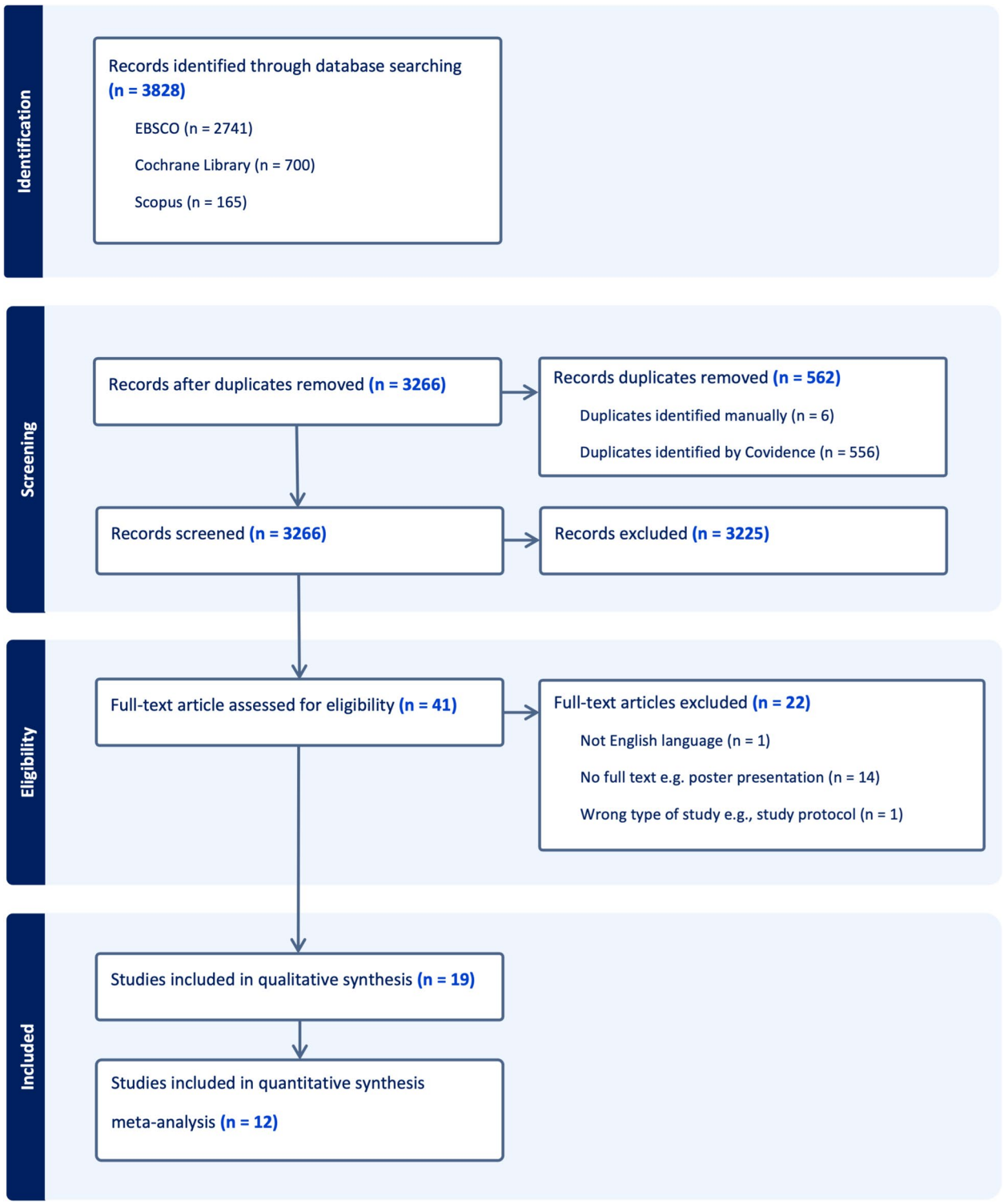

Fig. 1 PRISMA flow diagram

in nine studies via the 2-back test [19, 37], N-back task [30], Visual Working Memory (VWM) [35], verbal span and digit span [21], and Corsi's block-tapping test span [21], Spatial Working Memory (SWM) from CANTAB [23], Forward Digit Span (FDS) and Backward Digit Span (BDS) [24, 30, 32, 36].

Table 1 The characteristics of the included studies

Study (year)	Sample size	Design	Diagnosis	Gender (F / M)	Age (y)	Education (y)	Duration of disease (y)	Cognitive domain	Cognitive measures
Andrade et al. (2022) [26]	NE: 18	Parallel	AD	8 / 10	75.4 ± 4.7	4.4 ± 2.7	1.2 ± 0.4	Global cognition	ADAS-Cog
	NC: 18			9 / 9	77.1 ± 5.2	5.6 ± 3.1	1.3 ± 0.4		
André et al. (2016) [19]	NE: 13	Parallel	VD	NR	80.3 ± 5.8	NR	NR	Global cognition, Working memory, Memory, Executive function	ADAS-Cog, 2-back test, PNT, Go-no go task
	NC: 8				75.8 ± 7.4				
Boggio et al. (2009) [36]	NE: 10	Crossover	AD	6 / 4	79.1 ± 8.8	NR	NR	Working memory, Executive function, Memory	FDS, BDS, Stroop test, VRM
	NC: 10								
Gonzalez et al. (2021) [32]	NE: 21	Parallel	MCI	15 / 6	69.8 ± 5.3	9.7 ± 3.6	NR	Global cognition, Working memory, Everyday memory skill, Memory, Attention/processing speed, Executive function	MoCA, FDS, BDS, RBMT, Non-adaptive task, TMT-A, TMT-B
	NCa: 24			16 / 8	71.0 ± 6.2	9.7 ± 3.6			
	NCb: 21			17 / 4	70.6 ± 5.4	11.9 ± 4.9			
Gu et al. (2022) [22]	NE: 20	Parallel	MCI	7 / 13	63.2 ± 7.0	11.2 ± 3.0	NR	Global cognition, Overall memory, Memory	MoCA, MQ, WMS
	NC: 20			11 / 9	65.2 ± 6.2	9.9 ± 3.2			
Im et al. (2019) [24]	NE: 11	Parallel	AD	10 / 1	71.9 ± 9.2	6.3 ± 3.8	NR	Global cognition, Working memory, Memory, Executive function, Language, Visuospatial processing	MMSE, FDS, BDS, RCFT, SVLT, COWAT, Go-no go Test, Stroop Test, BNT, Clock Drawing Test
	NC: 7			5 / 2	74.9 ± 5.0	5.4 ± 5.9			
Khedr et al. (2019) [31]	NE: 23	Parallel	AD	10 / 13	64.2 ± 3.6	4.0 ± 2.8	14.1 ± 5.8	Global cogntion, Visuospatial processing	MMSE, MoCA, Clock drawing test
	NC: 21			8 / 13	65.2 ± 4.5	3.5 ± 2.0	14.1 ± 4.7		
Khedr et al. (2014) [20]	NEa: 11	Parallel	Dementia	5 / 6	68.5 ± 7.2	NR	3.0 ± 2.6	Global cognition	MMSE
	NEb:12			4 / 8	70.7 ± 5.4		2.9 ± 1.9		
	NC: 11			6 / 5	67.3 ± 5.9		3.5 ± 1.7		
Liao et al. (2021) [35]	NE: 10	Parallel	MCI	8 / 2	72.6 ± 4.1	8.5 ± 3.6	NR	Global cognition, Working memory, Executive function, Attention/precessing speed, Memory	MoCA, VWM, ToL, TMT-B, Stroop test, TMT-A, CVVLT
	NC: 10			5 / 5	73.1 ± 4.6	12.1 ± 2.9			
Liu et al. (2020) [37]	NE: 17	Crossover	AD or mixed AD/VD	7 / 10	77 ± 5	16 ± 3	NR	Global cognition, Working memory	ADAS-Cog, MoCA, 2-back test
	NC: 17								
Lu et al. (2019) [30]	NEa: 69	Parallel	AD	42 / 21	74.2 ± 6.7	7.3 ± 4.8	NR	Global cognition, Working memory, Memory, Neuropsychiatric symptoms, Attention/processing speed, Executive function, Verbal fluency	ADAS-Cog, MMSE, N-back test, FDS, BDS, word list learning task-delayed recall, NPI, TMT-A, TMT-B, CVFT,
	NEb: 68			30 / 27	73.4 ± 6.1	7.5 ± 5.3			
	NC: 64			36 / 17	74.5 ± 6.6	6.5 ± 4.3			
Manor et al. (2018) [33]	NE: 9	Parallel	Executive dysfunction	5 / 4	82 ± 4	NR	NR	Global cognition, Executive function	MoCA, TMT
	NC: 9			5 / 4	79 ± 4				

Table 1 (continued)

Study (year)	Sample size	Design	Diagnosis	Gender (F / M)	Age (y)	Education (y)	Duration of disease (y)	Cognitive domain	Cognitive measures
Martin et al. (2019) [29]	NE: 33	Parallel	MCI	20 / 13	71.8 ± 6.4	14.5 ± 3.5	NR	Memory, Learning, Attention/processing speed, Cognitive failures	CVLT, CANTAB-PAL, CANTAB-RVIP, Symbol Digit Modalities Test, Choice Reaction Time, CFQ
	NC: 35			25 / 10	71.6 ± 6.4	14.9 ± 3.2			
Rasmussen et al. (2021) [28]	NE: 10	Parallel	AD	9 / 1	69.2 ± 5.9	NR	NR	Global cognition, Visuospatial processing, Attention/processing speed	MMSE, RBANS, Clock-drawing test, TMT-A
	NC: 9			5 / 4	76.3 ± 6.8				
Rodella et al. (2022) [21]	NE: 13	Parallel	MCI/AD	5 / 8	71.6 ± 5.7	11.1 ± 5.0	NR	Global cognition, Working memory, Memory, Executive function, Attention/processing speed, Visuospatial function	MMSE, Digit Span, Verbal span, Corsi's block-tapping test span, Logical Memory Test, Rey's 15 words test, RCFT-delayed recall, Raven's Matrices 1947, FAB, Attentive Matrices, TMT-A, TMT-B, RCFT-copy
	NC: 15			6 / 9	75.1 ± 4.8	9.7 ± 5.0			
Smirni et al. (2021) [34]	NE: 20	Parallel	AD	14 / 6	73.4 ± 5.7	12.8 ± 3.4	NR	Verbal fluency	Phonemic Fluency Tasks
	NC: 20			13 / 7	73.0 ± 5.6	12.7 ± 3.7			
Stonsaovapak et al. (2020) [23]	NE: 23	Parallel	MCI	21 / 2	68.4 ± 8.4	NR	NR	Attention/ processing speed, Working meory, Memory	CANTAB; RVIP, SWM, DMS, PRM
	NC: 22			20 / 2	69.7 ± 7.6				
Suemoto et al. (2014) [25]	NE: 20	Parallel	AD	15 / 5	79.4 ± 7.1	5.0 ± 4.2	NR	Global cognition, Learning, Attention/processing speed, Memory, Neuropsychiatric symptoms	ADAS-Cog, word-list learning task, Digit cancellation task, word recognition task, NPI
	NC: 20			13 / 7	81.6 ± 8.0	4.5 ± 3.9			
Xu et al. (2023) [27]	NEa: 44	Parallel	MCI	32 / 12	59 [8.75]	9.5 [3.8]	NR	Global cognition, Overall memory, Memory, Executive function, Attention/processing speed	MoCA, MQ, AVLT, ROCF, Stroop test, TAP
	NEb: 44			23 / 21	63 [12.75]	9 [5]			
	NCa: 49			30 / 19	61 [8.5]	9 [4]			
	NCb: 43			26 / 17	58 [8]	9 [4]			

Data are expressed as mean ± SD or median [IQR]. Independent studies in the same literature are distinguished by (a) and (b)

AD Alzheimer's disease, *ADAS-Cog* Alzheimer's Disease Assessment Scale–Cognitive, *AVLT* Auditory-verbal learning test, *BDS* Backward digit span, *CANTAB* Cambridge Neuropsychological Test Automated Battery, *CFQ* Cognitive Failures Questionnaire, *COWAT* Control Oral Word Association Test, *CVFT* Category verbal fluency test, *CVLT* California Verbal Learning Task, *CVVLT* Chinese Version of the Verbal Learning Test, *FAB* Frontal Assessment Battery, *FDS* Forward digit span, *MCI* Mild Cognitive Impairment, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *MQ* Memory quotient, *NE* number of experimental group, *NC* number of control group, *NPI* Neuropsychiatric Inventory, *NR* not reported, *PAL* Paired Associates Learning, *PNT* Picture Naming Task, *RBANS* Repeatable Battery for the Assessment of Neuropsychological status, *RBMT* Rivermead Behavioral Memory Test, *RCFT* Rey Complex Figure Test, *ROCF* Rey-Osterrieth Complex Figure, *RVIP* Rapid Visual Information Processing, *SVLT* Seoul Verbal Learning Task, *SWM* Spatial Working Memory, *DMS* Delayed Matching to Sample, *PRM* Pattern Recognition Memory, *TAP* Test of Attentional Performance, *TMT* Trial Making Test, *ToL* Tower of London task, *VD* Vascular Dementia, *VRM* Visual Recognition Memory task, *VWM* Visual working memory, *WMS* Wechsler Memory Scale-Revised of China, *y* number of year, *F / M* Female / Male

Only one study, which used the Boston Naming Test (BNT), measured the language domain [24].

Executive function

Nine studies evaluated executive function via the Stroop test [24, 27, 35, 36], the Trial Making Test part B (TMT-B) [30, 32, 35] or part B minus part A (B-A) [33], the Go/no-Go task [19, 24], the Controlled Oral Word Association Test (COWAT) [24], Raven's Matrices 1947, the Frontal Assessment Battery, semantic and phonological fluencies (FAB) [21], and the Tower of London task (ToL) [35].

Visuospatial processing

Visuospatial processing was measured in four studies via RCFT, copy [21, 24] and clock drawing tests [24, 28, 31].

Attention and processing speed

Attention and processing speed were measured in nine studies via auditory reaction time, visual reaction time, sustained attention time, Digital-Symbol Coding (DSC) reaction time [27], Rapid Visual Information Processing (RVIP) from CANTAB [23, 29], a digit cancellation task [25], a symbol digit modality test, a choice reaction time [29], attentive matrices [21], and the Trail Making Test part A (TMT-A) [21, 28, 30, 32, 35].

Verbal fluency

Verbal fluency was measured in two studies via the Category Verbal Fluency Test (CVFT) [30] and phonemic fluency performance [34].

Neuropsychiatric symptoms and cognitive failure

Two studies measured neuropsychiatric symptoms by using the Neuropsychiatric Inventory (NPI) [25, 30]. Only one study measured cognitive failure via the Cognitive Failure Questionnaire (CFQ) [29].

Quality assessment

The risk of bias summary, which is based on the RoB 2 tool, for the included studies is shown in Supplementary Fig. 1 (see Supplementary Fig. 1, Additional File 1). The overall ratings indicated a low risk of bias in nine studies, a high risk in six studies, and some concerns of bias in four studies.

tDCS parameters

Table 2 provides a summary of the tDCS protocols used across the 19 studies. Overall, eight studies [21, 26, 27, 29, 30, 32, 34, 35] used a combination of tDCS and training; of these, seven studies [21, 26, 27, 29, 30, 32, 35] used anodal tDCS, and one study [34] used cathodal tDCS. The other 11 studies [19, 20, 22–25, 28, 31, 33, 36, 37] used tDCS alone: anodal tDCS in seven studies [19, 22, 23, 25, 28, 33, 36], cathodal tDCS in one study [20], bilateral tDCS (anodal tDCS in one hemisphere and cathodal tDCS in another hemisphere) in one study [24], and bilateral anodal tDCS in two studies [31, 37]. Most of the studies used rectangular electrodes [19–23, 25–27, 29–37], with the exceptions of two studies that used round electrodes [24] and one study that used high-definition tDCS [28]. The electrode size ranged from 2.5–35 cm^2, the current intensity ranged from 1—2 mA with a duration ranging from 20–40 min, the current density ranged from 0.03—2.22 mA/cm^2, and the total charge density ranged from 0.01—26.67 mAh/cm^2. Only three studies [34, 36, 37] performed a single session, whereas 16 studies [19–33, 35] performed multiple sessions. Most studies applied electrodes over the dorsolateral prefrontal cortex (DLPFC) [19–21, 23–25, 27–29, 32–37], three studies focused on the temporal area, and only one study focused on multiple areas, including the frontal, parietal, and centroparietal areas [26]. For the reference electrode, 14 studies used the intracephalic region as a reference area, such as the contralateral supraorbital area, inion, and contralateral side of the active electrode. Five studies [21, 22, 30–32] used extracephalic areas such as the upper limb, including the deltoid and brachioradialis muscles. Nine studies [19–23, 25, 29, 30, 32] evaluated long-term effects, which ranged from 1—24 weeks. Six studies [21, 24, 26, 27, 32, 34] did not report adverse events, whereas 13 studies [19, 20, 22, 23, 25, 28–31, 33, 35–37] reported minor adverse events, including tingling, scalp burning, skin redness, sleepiness, headache, and scalp pain. Moreover, other studies reported that the transient skin sensation of tingling was the most common side effect [23, 30].

Meta-analyses

Seven out of 19 studies [21, 23, 28, 29, 34, 36, 37] were excluded from the meta-analysis because of insufficient information on outcomes.

Effects of tDCS on participant characteristics

Considering the observed improvement in overall global cognition, meta-analyses were conducted to assess the effect of tDCS on global cognition on the basis of participants' diagnoses: 1) AD, 2) MCI, and 3) dementia. One study [33] was excluded from this subgroup analysis because of its inclusion of individuals with executive dysfunction. If a study used more than one outcome measure for evaluating overall global cognition, only MMSE results were selected. Figure 2 illustrates a significant improvement in global cognition in older people with cognitive impairments (SMD = 0.35; 95% CI 0.01, 0.69; Z = 2.03; $p = 0.04$; $I^2 = 75\%$). Subgroup analysis revealed a significant improvement in global cognition among older

Table 2 Summary of tDCS protocol of included studies

Study (year)	Type of intervention	Electrode size (cm^2)	Intensity (mA)	Duration (minutes)	Number of session	Current density (mA/cm^2) / Total charge density (mAh/cm^2)	Anode	Cathode	Follow up duration (weeks)	Adverse effects
Andrade et al. (2022) [26]	Anodal + CS Sham + CS	25	2	30 (10 min for each area)	24 (3 sessions/ week, 2 months)	0.08 / 0.96	F5, CP5, F4 and F3, P4, P5	Contralateral supraorbital area	No	NR
André et al. (2016) [19]	Anodal Sham	35	2	20	4 consecutive day	0.06 / 0.08	Left-DLPFC (F3)	Right supraorbital area	2	No serious adverse events reported
Boggio (a) et al. (2009) [36]	Anodal Sham	35	2	30	1	0.06 / 0.03	Left-DLPFC (F3)	Right supraorbital area	No	No serious adverse events reported
Boggio (b) et al. (2009) [36]	Anodal Sham	35	2	30	1	0.06 / 0.03	Left temporal cortex (T7)	Right supraorbital area	No	No serious adverse events reported
Gonzalez et al. (2021) [32]	Anodal + CT Sham + CT	15	1.5	30	9 (3 sessions/ week, 3 weeks)	0.1 / 0.45	Left-DLPFC (F3)	Contralateral brachioradialis muscle	6	NR
Gu et al. (2022) [22]	Anodal Sham	35	2	20	5 consecutive days	0.06 / 0.10	Left temporal area (T3)	Right deltoid	4	No serious adverse events reported
Im et al. (2019) [24]	Bilateral Sham	28.26	2	30	Every day for 6 months	0.07 / 6.37	Left-DLPFC (F3)	Right-DLPFC (F4)	No	NR
Khedr et al. (2019) [31]	Bilateral-anodal Sham	35	2	40 (20 min for each side)	10 (5 sessions/ week, 2 weeks)	0.06 / 0.38	T3-P3 and T4-P4	Left deltoid	No	No serious adverse events reported
Khedr (a) et al. (2014) [20]	Anodal Sham	24	2	25	10 consecutive days	0.08 / 0.35	Left-DLPFC (F3)	Right supraorbital area	4 and 8	No serious adverse events reported
Khedr (b) et al. (2014) [20]	Cathodal Sham	24	2	25	10 consecutive days	0.08 / 0.35	Right supraorbital area	Left-DLPFC (F3)	4 and 8	No serious adverse events reported
Liao et al. (2021) [35]	Anodal + Tai Chi Sham + Tai Chi	35	2	20	36 (3 sessions/ week, 12 weeks)	0.06 / 0.69	Left-DLPFC (F3)	Right supraorbital area	No	No serious adverse events reported
Liu (a) et al. (2020) [37]	Bilateral-anodal Sham	35	2	20	1	0.06 / 0.02	Left DLPFC (F3) and right DLPFC (F4)	Inion (Iz)	No	No a serious dverse events reported

Table 2 (continued)

Study (year)	Type of intervention	Electrode size (cm^2)	Intensity (mA)	Duration (minutes)	Number of session	Current density (mA/cm^2) / Total charge density (mAh/cm^2)	Anode	Cathode	Follow up duration (weeks)	Adverse effects
Liu (b) et al. (2020) [37]	Bilateral-anodal Sham	35	2	20	1	0.06 / 0.02	Left temporal cortex (T3) and right temporal cortex (T4)	Inion (Iz)	No	No serious adverse events reported
Lu et al. (2019) [30]	Anodal + WMT Sham + WMT Anodal + CCT	35	2	20	12 (3 sessions/ week, 4 weeks)	0.06 / 0.23	Left lateral temporal cortex (LTC)	Contralateral upper limb	4 and 8	3 cases had transient skin sensation of tingling and burning induced by tDCS without producing any sustainabel effects
Manor et al. (2018) [33]	Anodal Sham	35	2	20	10 (5 sessions/ week, 2 weeks)	0.06 / 0.19	Left-DLPFC (F3)	Right supraorbital area (Fp2)	No	No serious adverse events reported
Martin et al. (2019) [29]	Anodal + CT Sham + CT	35	2	30	15 (3 sessions/ week, 5 weeks)	0.06 / 0.43	Left-DLPFC (F3)	F8	12	No serious adverse events reported
Rasmussen et al. (2021) [28]	Anodal Sham	12 mm in diameter (HD-tDCS)	2	20	6 (3 sessions/ day, 2 days)	1.80 / 3.33	Left-DLPFC (F3)	Surrounded anodal electrode	No	No serious adverse events reported
Rodella et al. (2022) [21]	Anodal + CT Sham + CT	16	2	30	12 (3 sessions/ week, 4 weeks)	0.125 / 0.75	Left-DLPFC (F3)	Right deltoid	24	NR
Smirni (a) et al. (2021) [34]	Cathodal + Phonemic fluency task Sham + Phonemic fluency task	35	1	20	1	0.03 / 0.01	Contralateral shoulder	Left-DLPFC (F3)	No	NR
Smirni (b) et al. (2021) [34]	Cathodal + Phonemic fluency task Sham + Phonemic fluency task	35	1	20	1	0.03 / 0.01	Contralateral shoulder	Right-DLPFC (F4)	No	NR
Stonsaovapak et al. (2020) [23]	Anodal Sham	25	2	20	12 (3 sessions/ week, 4 weeks)	0.08 / 0.32	Right-DLPFC (F4)	Left supraorbital area	4	The most common side effect is a tingling sensation

Table 2 (continued)

Study (year)	Type of intervention	Electrode size (cm^2)	Intensity (mA)	Duration (minutes)	Number of session	Current density (mA/cm^2) / Total charge density (mAh/cm^2)	Anode	Cathode	Follow up duration (weeks)	Adverse effects
Suemoto et al. (2014) [25]	Anodal Sham	35	2	20	6 (3 sessions/ week, 2 weeks)	0.06 / 0.11	Left-DLPFC (F3)	Right orbit	1	The minor side effects; tingling, scalp burning, skin redness, somnolence, headache, and scalp pain were more common in the anodal compared to sham group
Xu (a) et al. (2023) [27]	Anodal + Tai Chi Sham + Tai Chi	0.9	2	20	36 (3 sessions/ week, 12 weeks)	2.22 / 26.67	Right-DLPFC (F4)	Supraorbital (Fp1)	No	NR
Xu (b) et al. (2023) [27]	Anodal + walking Sham + walking	0.9	2	20	36 (3 sessions/ week, 12 weeks)	2.22 / 26.67	Right-DLPFC (F4)	Supraorbital (Fp1)	No	NR

The current density and total charge density were computed by using the following calculations [38];

Current density (mA/cm^2) = Current (mA) ÷ electrode size (cm^2)

Charge (mAh) = Current (mA) × tDCS duration (minutes) ÷ 60

Charge Density (mAh/cm^2) = Charge (mAh) ÷ electrode size (cm^2)

Total Charge Density (mAh/cm^2) = Charge Density (mAh/cm^2) × tDCS sessions

CCT Control cognitive training, *CS* Cognitive stimulation, *CT* Cognitive training, *DLPFC* Dorsolateral prefrontal cortex, *NR* not reported, *WMT* Working memory training

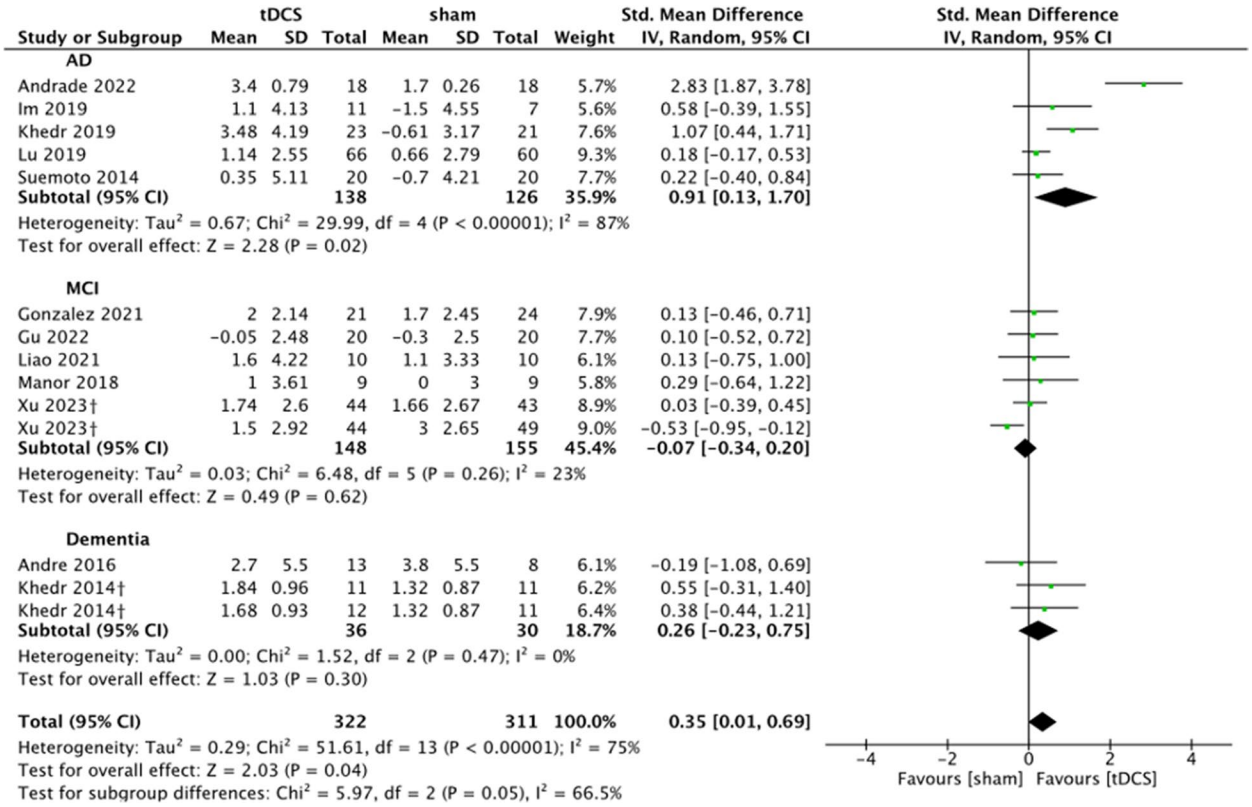

Fig. 2 Forest plot of studies evaluating global cognition in older people with cognitive impairments. The study with 2 tDCS groups vs sham is represented by †

people with AD (SMD = 0.91; 95% CI 0.13, 1.70; Z = 2.28; $p = 0.02$; $I^2 = 87\%$) but not among older people with MCI (SMD = —0.07; 95% CI -0.34, 0.20; Z = 0.49; $p = 0.62$; $I^2 = 23\%$) or dementia (SMD = 0.26; 95% CI -0.23, 0.75; Z = 1.03; $p = 0.30$; $I^2 = 0\%$). However, due to the the lack of subtype specification in the included studies, we were unable to perform a subgroup analysis based on MCI types.

Effects of tDCS on cognitive function

Twelve studies were included in the meta-analysis of global cognition, and the ADAS-Cog, MoCA, and MMSE were used to evaluate global cognition at immediately post-intervention. Overall analysis revealed significant improvement in global cognition in the tDCS group compared with the sham group (SMD = 0.45; 95% CI 0.10, 0.80; Z = 2.54; $p = 0.01$; $I^2 = 80\%$). Subgroup analysis revealed non-significant improvements in the ADAS-Cog (SMD = 0.70; 95% CI -0.31, 1.71; Z = 1.36; $p = 0.17$; $I^2 = 90\%$) and MoCA scores (SMD = 0.28; 95% CI -0.28, 0.84; Z = 0.99; $p = 0.32$; $I^2 = 83\%$), whereas the MMSE score had a positive effect (SMD = 0.51; 95% CI 0.15, 0.86; Z = 2.81; $p = 0.005$; $I^2 = 24\%$). Six studies measured long-term effects at 1–8 weeks post-intervention and reported significant improvement in global cognition at follow-up (SMD = 0.91; 95% CI 0.35, 1.38; Z = 3.29; $p = 0.001$; $I^2 = 90\%$). Subgroup analyses revealed non-significant improvements in the ADAS-Cog (SMD = -0.06; 95% CI -0.30, 0.17; Z = 0.53; $p = 0.60$; $I^2 = 0\%$) and MoCA scores (SMD = 0.04; 95% CI -0.29, 0.49; Z = 0.17; $p = 0.61$; $I^2 = 0\%$), whereas the MMSE score had a positive long-term effect (SMD = 2.29; 95% CI 1.04, 3.55; Z = 3.58; $p = 0.0003$; $I^2 = 94\%$).

For memory function, six studies focusing on immediate effects reported non-significant improvement (SMD = 0.01; 95% CI -0.17, 0.20; Z = 0.14; $p = 0.89$; $I^2 = 30\%$). Subgroup analysis revealed non-significant improvements in verbal (SMD = 0.14; 95% CI -0.10, 0.38; Z = 1.14; $p = 0.25$; $I^2 = 0\%$) and working memory (SMD = -0.17; 95% CI -0.46, 0.12; Z = 1.18; $p = 0.24$; $I^2 = 50\%$). Two studies measured working memory at follow-up periods from 6–8 weeks and reported non-significant improvement (SMD = -0.01; 95% CI -0.25, 0.22; Z = 0.10; $p = 0.92$; $I^2 = 0\%$).

For executive function, three studies assessed immediate effects by the Stroop test, revealing non-significant improvements in Stroop test color (SMD = 0.44; 95% CI -1.71, 2.58; Z = 0.40; $p = 0.69$; $I^2 = 0\%$), Stroop test

word (SMD = 0.03; 95% CI -5.44, 5.50; Z = 0.01; $p = 0.99$; $I^2 = 69\%$), and Stroop test color-word (SMD = 3.07; 95% CI -0.35, 6.49; Z = 1.75; $p = 0.08$; $I^2 = 0\%$) scores. Only one study measured long-term effects. Table 3 summarizes the subgroup analysis results, and Supplementary Figs. 2 to 4 (see Supplementary Figs. 2–4, Additional File 1) present the forest plots of the effects of tDCS on cognitive function.

tDCS configuration

The effect of tDCS on global cognition was observed immediately post-intervention. A meta-analysis of the tDCS configuration was conducted on the basis of the MMSE results. The interventions were categorized into tDCS combined with training and tDCS alone. The current density, which was calculated by dividing the intensity (mA) by the electrode size (cm^2), was classified as $\leq$ 0.06 mA/cm^2 or > 0.06 mA/cm^2. The stimulation duration was divided into 20 min and > 20 min, and the number of sessions was categorized as $\leq$ 15 sessions or > 15 sessions. The total charge density, which was calculated by multiplying the charge density (mAh/cm^2) by the number of tDCS sessions, was separated into < 0.50 mAh/cm^2 and > 0.50 mAh/cm^2. To categorize the targeted brain stimulation, the areas where the active electrode was applied were divided into the left DLPFC and other areas, such as the temporal areas. Moreover, the tDCS montage was classified as extracephalic or intracephalic on the basis of the reference electrode location.

Subgroup analysis (Table 4) revealed that tDCS alone improved global cognition (SMD = 0.39; 95% CI 0.11, 0.67; Z = 2.74; $p = 0.006$; $I^2 = 7\%$), whereas tDCS combined with training did not (SMD = 0.36; 95% CI -0.25, 0.97; Z = 1.16; $p = 0.25$; $I^2 = 88\%$). Significant effects were found for current density $\leq$ 0.06 mA/cm^2 (SMD = 0.25; 95% CI 0.02, 0.49; Z = 2.10; $p = 0.04$; $I^2 = 13\%$) and stimulation duration > 20 min (SMD = 0.89; 95% CI 0.18, 1.60; Z = 2.47; $p = 0.01$; $I^2 = 80\%$). Improvements were noted for $\leq$ 15 sessions (SMD = 0.28; 95% CI 0.07 0.50; Z = 2.60; $p = 0.009$; $I^2 = 5\%$) and total charge density < 0.50 mAh/cm^2 (SMD = 0.28; 95% CI 0.07, 0.50; Z = 2.60; $p = 0.009$; $I^2 = 5\%$). Targeted stimulation of temporal areas improved cognition (SMD = 0.33; 95% CI 0.06, 0.61; Z = 2.35; $p = 0.02$; $I^2 = 69\%$), but stimulation of the left DLPFC did not (SMD = 0.24; 95% CI -0.04, 0.51; Z = 1.68; $p = 0.09$; $I^2 = 0\%$). No significant improvement was found for either the intracephalic (SMD = 0.36; 95% CI -0.17, 0.89; Z = 1.32; $p = 0.19$; $I^2 = 81\%$) or extracephalic reference electrodes (SMD = 0.34; 95% CI -0.06, 0.74; Z = 1.65; $p = 0.10$; $I^2 = 56\%$). Supplementary Figs. 5 to 11 (see Supplementary Figs. 5–11, Additional File 1) show the forest plots of the subgroup analysis regarding tDCS configurations. Moreover, Table 4 reports tDCS parameters for different patient diagnosis.

Publication bias

A funnel plot illustrating the analyses of publication bias is shown in Supplementary Fig. 12 (see Supplementary

Table 3 Subgroup analyses of the effects of tDCS on cognitive function

Variables	Number of studies / subjects	SMD (95%CI)	I^2 (%)	*p*-value
Global cognition at immediate effects				
- ADAS-Cog	4 / 223	0.70 (-0.31, 1.71)	90	0.17
- MMSE	5 / 203	0.51 (0.15, 0.86)	24	**0.005**
- MoCA	7 / 347	0.28 (-0.28, 0.84)	83	0.32
Global cognition at long-term effects				
- ADAS-Cog	3 / 272	-0.06 (-0.30, 0.17)	0	0.60
- MMSE	6 / 322	2.29 (1.04, 3.55)	94	**0.0003**
- MoCA	3 / 103	0.10 (-0.29, 0.49)	0	0.61
Memory function at immediate effects				
- Verbal	5 / 277	0.14 (-0.10, 0.38)	0	0.25
- Working	3 / 189	-0.17 (-0.46, 0.12)	50	0.24
Memory function at long-term effects				
- Working	3 / 277	-0.01 (-0.25, 0.22)	0	0.92
Executive function at immediate effects				
- Stroop test color	3 / 198	0.44 (-1.71, 2.58)	0	0.69
- Stroop test word	3 / 198	0.03 (-5.44, 5.50)	69	0.99
- Stroop test color-word	3 / 200	3.07 (-0.35, 6.49)	0	0.08

ADAS-Cog Alzheimer's Disease Assessment Cognitive Scale- Cognitive Subscale, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *SMD* standardized mean differences

Table 4 Summarized the results of tDCS parameter subgroup analysis based on the participants characteristics

tDCS parameter / Diagnosis	AD	MCI	Dementia	Summary of all analyses	*p*-value
Type of intervention					
- tDCS + training	●1 ⊘9	⊘3 ⊘8 ⊘12† ○12†		●1 ⊘9 ⊘3 ⊘8 ⊘12† ○12†	0.25
- tDCS alone	⊘5 ●6 ⊘11	⊘4 ⊘10	⊘2 ⊘7† ⊘7†	⊘5 ●6 ⊘11 ⊘4 ⊘10 ⊘2 ⊘7† ⊘7†	**0.0006**
Current density					
- ≤ 0.06 mA/cm^2	●6 ⊘9 ⊘11	⊘3 ⊘4 ⊘8 ⊘10	⊘2	●6 ⊘9 ⊘11 ⊘3 ⊘4 ⊘8 ⊘10 ⊘2	**0.04**
- > 0.06 mA/cm^2	●1 ⊘5	⊘12† ○12†	⊘7† ⊘7†	●1 ⊘5 ⊘12† ○12† ⊘7† ⊘7†	0.15
Duration					
- 20 minutes	⊘9 ⊘11	⊘4 ⊘8 ⊘10 ⊘12† ○12†	⊘2	⊘9 ⊘11 ⊘4 ⊘8 ⊘10 ⊘12† ○12† ⊘2	0.92
- > 20 minutes	●1 ⊘5 ●6	⊘3	⊘7† ⊘7†	●1 ⊘5 ●6 ⊘3 ⊘7† ⊘7†	**0.01**
Number of sessions					
- ≤ 15 session	●6 ⊘9 ⊘11	⊘3 ⊘4 ⊘10	⊘2 ⊘7† ⊘7†	●6 ⊘9 ⊘11 ⊘3 ⊘4 ⊘10 ⊘2 ⊘7† ⊘7†	**0.009**
- > 15 sessions	●1 ⊘5	⊘8 ⊘12† ○12†		●1 ⊘5 ⊘8 ⊘12† ○12†	0.25
Total charge density					
- < 0.50 mAh/cm^2	●6 ⊘9 ⊘11	⊘3 ⊘4 ⊘10	⊘2 ⊘7† ⊘7†	●6 ⊘9 ⊘11 ⊘3 ⊘4 ⊘10 ⊘2 ⊘7† ⊘7†	**0.009**
- > 0.50 mAh/cm^2	●1 ⊘5	⊘8 ⊘12† ○12†		●1 ⊘5 ⊘8 ⊘12† ○12†	0.25
Targeted brain stimulation					
- Left DLPFC	⊘5 ⊘11	⊘3 ⊘8 ⊘10	⊘2 ⊘7† ⊘7†	⊘5 ⊘11 ⊘3 ⊘8 ⊘10 ⊘2 ⊘7† ⊘7†	0.09
- Temporal areas	●6 ⊘9	⊘4		●6 ⊘9 ⊘4	**0.02**
Montage					
- Intracephalic	●1 ⊘11	⊘8 ⊘10 ⊘12† ○12†	⊘2 ⊘7† ⊘7†	●1 ⊘11 ⊘8 ⊘10 ⊘12† ○12† ⊘2 ⊘7† ⊘7†	0.19
- Extracephalic	●6 ⊘9	⊘3 ⊘4		●6 ⊘9 ⊘3 ⊘4	0.10

Study (1) Andrade et al., [26]; (2) André et al., [19]; (3) Gonzalez et al., [32]; (4) Gu et al., [22]; (5) Im et al., [24]; (6) Khedr et al., [31]; (7) Khedr et al., [20]; (8) Liao et al., [35]; (9) Lu et al., [30]; (10) Manor et al., 2018; [33] (11) Suemoto et al., [25]; (12) Xu et al., [27]. The black symbol (●) indicates a positive effect on MMSE score, the white symbol (○) indicates a negative effect, and the grey striped symbol (⊘) indicates an unclear effect

AD Alzheimer's disease, *MCI* mild cognitive impairment

The studies with 2 tDCS groups vs sham are represented by †

Fig. 12, Additional File 1). Egger's test for asymmetry, which evaluates publication bias, revealed significant results ($p=0.026$), indicating potential publication bias in our sample. The trim-and-fill analysis [38] imputed five studies, increasing the effect size to 0.703 (95% CI: 0.306, 1.100), suggesting that the observed effect size may underestimate the true effect. The revised funnel plot is shown in Supplementary Fig. 13 (see Supplementary Fig. 13, Additional File 1).

Sensitivity analysis

A high risk of bias due to selective outcomes reporting was identified. A sensitivity analysis was conducted after removing 4 studies [19, 22, 26, 33], showing that the pooled estimate remained robust despite the risk of bias.

Discussion

Summary of results

This study aimed to systematically and meta-analytically review existing data to evaluate the effects of tDCS on cognitive function and to assess the impact of tDCS parameters in older people with cognitive impairments. The results indicated tDCS significantly improved overall global cognition only immediately post-intervention, with no significant changes at follow-up. However, according to the subgroup analysis of global cognition, improvement was found immediately post-intervention and at follow-ups up to 8 weeks (when the MMSE was used as an outcome measure), whereas there was no significant improvement when global cognition was assessed by the ADAS-Cog and MoCA scores. Moreover,

tDCS did not lead to significant improvements in memory function or executive function among older people with cognitive impairments. Additionally, this systematic review revealed that tDCS significantly enhanced the global cognition of older individuals with AD but not of those with MCI or dementia.

The subgroup analysis of the tDCS parameters revealed that, compared with tDCS combined with training, tDCS alone was more effective at improving global cognition. A current density of ≤ 0.06 mA/cm^2, a duration of > 20 min, ≤ 15 sessions, or a total charge density of < 0.50 mAh/cm^2 resulted in greater results. For the stimulation target, the temporal areas showed greater improvement in global cognition than did the left DLPFC. There were no statistically significant differences based on the type of montage or the location of the reference electrode.

Overall tDCS effects

tDCS in older people with cognitive impairments

Our analysis revealed that multiple sessions of tDCS significantly improved the global cognition of older people with AD but not of those with MCI or dementia. These findings align with previous meta-analysis results, which reported a significant cognitive benefit of tDCS in individuals with AD but not in individuals with MCI [9]. Moreover, individuals with AD may have a better response to NIBS, including repetitive transcranial magnetic stimulation (rTMS) and tDCS, than those with MCI [39]. AD and MCI represent different clinical stages of cognitive disorders. AD is characterized by significant neuronal loss, which leads to severe cognitive deficits [40], whereas MCI involves mild neurodegeneration with relatively preserved neural networks and subtle cognitive impairments [41] and generally represents the early stage of AD [42]. These conditions might respond differently to NIBS. More severe cognitive impairment (i.e., AD) may result in noticeable improvement because of the greater deficit at baseline.

Moreover, it should be noted that only MMSE data were used for analysis among population groups in this study, and only one study of individuals with MCI was included in our systematic review. Xu et al. [27] reported non-significant improvement in the MMSE scores following 12 weeks of tDCS combined with walking training. However, a different arm of the same study demonstrated a significant improvement in MMSE score when Tai Chi was combined with tDCS, indicating that the type of adjunct training may play a crucial role. Nevertheless, we did not perform a subgroup analysis on the basis of the type of training due to the insufficient number of available studies. For dementia, no significant differences were observed in improving global cognition in these populations. This may be due to the limited sample size, as only 36 participants with dementia were included, compared with 138 with AD and 148 with MCI. Further studies with larger sample sizes and diverse types of adjunct training are needed to draw definitive conclusions on the effect of tDCS on global cognition in individuals with dementia and MCI.

Cognitive measurement to evaluate tDCS effects

Our meta-analysis revealed significant improvements in overall global cognition immediately post-intervention when the data from the ADAS-Cog, MMSE, and MoCA were pooled. However, such improvement was not sustained until the follow-up period. For subgroup analysis, only the MMSE score significantly improved both immediately post-intervention and at the 8-week follow-up. This finding aligns with previous meta-analyses that reported significant improvements in global cognition assessed by the MMSE immediately post-intervention, with no significant changes when assessed by the ADAS-Cog [9]. Despite the MMSE having lower sensitivity than the ADAS-Cog and MoCA do [43], it remains the most commonly used screening tool for assessing cognitive impairment in clinical practice, particularly in cognitively healthy older people [44]. On the basis of our analysis, the MMSE appears to evaluate global cognition changes after tDCS. Nonetheless, limitations such as sensitivity and ceiling and floor effects should be considered. Our results suggest that tDCS may enhance overall cognitive function, as captured by the MMSE's broad assessment. The MMSE's sensitivity to general cognitive changes could explain this finding, whereas the MoCA and ADAS-Cog, which are more specific to particular cognitive domains, such as executive functions, visuospatial abilities, and memory [45], might not detect the same improvement. This discrepancy highlights the importance of selecting appropriate cognitive assessment tools in tDCS studies and considering their domain-specific sensitivities. Additionally, the non-significant results of the MoCA and ADAS-Cog might also reflect the need for specific interventions to observe significant changes in specific cognitive functions.

Executive and memory functions did not change significantly after tDCS, as assessed by the Stroop test and the forward digit span task, respectively. Our findings align with those of a recent systematic review and meta-analysis, which reported that the immediate effect of tDCS did not significantly affect executive functions in older people [46]. Although that recent systematic review and meta-analysis included studies with different outcome measures (i.e., backward digit span task, category verbal fluency test, and virtual reality task) than our study did, we still found similar results. In addition, most original studies included in our review did not have a follow-up

period. Therefore, it is still inconclusive whether tDCS can induce long-term effects on executive function. With respect to memory function, Cruz et al. [47] reported a significant immediate improvement in individuals with MCI and dementia that was not maintained for the long term. However, our study revealed no significant effects of tDCS on memory function in either the immediate or long-term assessments. While the previous meta-analysis included a small number of studies ($n=4$ studies), our meta-analysis included 6 studies. The limited number of studies may have contributed to the lack of significant findings in both analyses.

tDCS parameters

The tDCS protocols included in this review are varied. On the basis of our results, improvements in global cognition were associated with the effects of tDCS. Subgroup analysis was performed only for global cognitive outcomes, which revealed that tDCS alone was more effective than tDCS combined with cognitive training. The enhanced cognition induced by tDCS alone may be caused by the modulation of the resting membrane potential of neurons [48]. Moreover, it presumably improves cognition by modifying the levels of acetylcholine, dopamine, gamma-aminobutyric acid (GABA), and cortical activation [49]. However, a recent systematic review and meta-analysis reported more significant improvements in cognitive functions, particularly working memory, executive function, and global cognition, when tDCS was combined with aerobic exercise in older people with cognitive impairments [10]. Our included studies used tDCS combined with various types of training [26, 27, 30, 32, 35], such as working memory training, cognitive training, Tai Chi, and walking training. Only two included studies [27, 35] combined tDCS with aerobic exercises, i.e., Tai Chi, and walking. However, the results seem to be controversial, as tDCS combined with Tai Chi significantly improved global cognition [27, 35], whereas no significant improvement was found when tDCS was combined with walking training [27]. These findings suggest that the type of training combined with tDCS may influence the effectiveness of tDCS intervention. However, variation in tDCS parameters were observed across the included studies on "tDCS alone" and "tDCS with taining". These findings should be interpreted with caution, as multiple confounding factor, not just training, were present.

Current density (the ratio of current intensity to electrode size) is a crucial factor in determining tDCS effects. Our results indicated that a current density of less than or equal to 0.06 mA/cm^2 was more effective than a current density greater than 0.06 mA/cm^2. A current density of 0.06 mA/cm^2 (i.e., 2 mA intensity with a 35 cm^2 electrode size) is a commonly used parameter in clinical studies; seven out of the eight studies included in our meta-analysis employed this current density. A recent systematic review suggested that current densities of approximately 0.05 mA/cm^2 were associated with cognitive improvement in older people with MCI [50]. Our findings, however, disagree with those of a meta-analysis by Chen et al. [9], which reported that a high current density of 2.5 mA/cm^2 significantly improved global cognition, whereas a low current density of 0.06 mA/cm^2 did not result in significant improvement. However, only one study in the meta-analysis by Gangemi et al. [51] used a high current density of 2.5 mA/cm^2, which may have limited the power of their analysis. Additionally, an original study suggested that a higher current density was not always associated with greater changes in cortical excitability [52].

With respect to stimulation duration, our results indicated that stimulation durations longer than 20 min were more effective at improving global cognition in people with cognitive impairments than a session of 20 min. This partly agrees with a previous systematic review, which reported that 2 mA stimulation of the left DLPFC or frontotemporal areas for 25—30 min yielded beneficial effects on global cognition in individuals with AD [53]. On the basis of our analysis, it appears that a stimulation duration longer than 20 min but not exceeding 40 min may be useful for improving global cognition. However, despite longer durations of stimulation, a recent meta-analysis in healthy and clinical populations revealed that tDCS durations of less than 15 min induced significantly greater effects than those exceeding 15 min on working memory, whereas durations of more than 15 min induced greater effects on theory of mind accuracy [54]. Notably, varying stimulation durations can impact cognitive performance.

In terms of the number of stimulation sessions, our subgroup analysis revealed that the number of tDCS sessions significantly impacted the improvement in global cognition. Specifically, no significant improvement was observed when the total number of sessions exceeded 15, whereas significant improvements were noted when the number of sessions was 15 or fewer. In partial alignment with our findings, a previous systematic review and meta-analysis indicated that global cognition improved significantly following 10—15 sessions of stimulation [9]. In addition, we found that a total charge density of less than 0.50 mAh/cm^2 significantly improved global cognition compared with a total charge density of over 0.50 mAh/cm^2. As the total charge density refers to the total electrical charge delivered per unit area of the electrode multiplied by the number of sessions [55], a low total charge density was associated with a low number of sessions, given similar intensities and durations. This suggests that

a high number of sessions may not always be required to achieve improvements in global cognition for individuals with cognitive impairments. Thus, stimulation for 15 sessions or fewer, together with a total charge density of less than 0.50 mAh/cm^2 may be enough to improve global cognitive function.

Stimulation target

The effects of tDCS can vary depending on the brain region stimulated. Our results revealed that stimulation of the temporal areas led to greater improvement in cognitive function than stimulation of the left DLPFC. Our findings are consistent with those of a previous systematic review and meta-analysis, which reported that tDCS over temporal areas significantly improved global cognition in individuals with MCI and mild-to-moderate AD but not when tDCS over the left DLPFC was stimulated [9]. The greater effect following temporal area stimulation than following DLPFC stimulation could be due to differences in the neurophysiological mechanism of both areas. The temporal lobe shows significant neurodegeneration in AD, making it a target for enhancing neural plasticity and connectivity [56]. Moreover, the temporal lobe's role in integrating sensory information and memory makes its stimulation beneficial for global cognition, whereas the DLPFC mainly plays a significant role in executive function; therefore, changes in DLPFC activity may not broadly affect global cognition [57]. This suggests that for interventions aimed at enhancing overall cognitive performance in individuals with MCI and AD, targeting temporal regions may be more beneficial.

Moreover, our study revealed that applying a reference electrode extracephalically (outside the skull) had a more positive effect than did an intracephalic montage (within the skull). A previous study demonstrated that, compared with an intracephalic montage, an extracephalic montage might create greater total current density in deeper brain regions, specifically in white matter [58]. This suggests that the placement of the reference electrode influences the electrical current distribution delivered during tDCS. An increased current density in a deeper brain region when an extracephalic montage is used may potentially lead to more effective modulation of neural activity [59]. These findings highlight the importance of optimizing electrode placement to maximize the therapeutic benefits of tDCS.

Tolerability

Despite fifteen studies reporting minor side effects, which were mostly cutaneous sensations, all participants tolerated tDCS well, and the sensations experienced were mild. This suggests that tDCS employed at 2 mA for up to 30 min of stimulation and stimulation for up to 36 sessions (3 sessions per week for 12 weeks) is safe.

Study limitations and recommendations for future research

This systematic review and meta-analysis was performed by independent selection of research, data extraction, and risk of bias assessment, which helped to avoid selective reporting of specific results. By examining the possible influencing factors of tDCS effects, this study provides valuable guidelines for optimizing tDCS configurations to improve global cognition in older people with cognitive impairments. However, our study has notable limitations. First, we analyzed different severities of cognitive impairments together without performing subgroup analyses for each severity level. Cognitive impairment can be classified into mild, moderate, or severe dementia as well as different types of MCI and AD. However, the number of included studies was insufficient to perform subgroup analyses for each level or type of cognitive impairment. This limits conclusions regarding the different severities of disease. Second, we included only studies published in English, leading to potential language bias. Third, the constraints of the inclusion criteria resulted in a relatively small final sample size, which potentially limited the statistical power. Future research should include more studies to separate analyses involving various severities of disease (i.e., mild, moderate, and severe AD) and studies published in multiple languages. This would help ensure a more comprehensive understanding and prevent the absence of critical findings. Additionally, the studies investigating global cognitive function during follow-up periods were limited to six studies [20, 22, 25, 30, 32, 33], with only two studies examining memory function [30, 32] and one study evaluating executive function [30]. More studies determining the long-term effects of tDCS on cognitive function are needed. Additionally, high heterogeneity was observed in this meta-analysis due to differences in study design and population. However, subgroup and sensitivity analyses confirmed consistent results despite variability. The random-effects model accounted for heterogeneity, but future studies should standardize methodologies to improve precision.

Implications for tDCS in older people with cognitive impairments

The findings from this systematic review and meta-analysis highlight the potential of tDCS to improve cognitive function in older people with cognitive impairments. Older people with AD seem to benefit more from tDCS than those with MCI and other forms of dementia. However, the efficacy of tDCS may vary depending on the specific protocol used. Different configurations of tDCS,

such as current intensity and electrode size, were found to influence the effects of tDCS. Moreover, tDCS alone was effective in improving global cognition, but it should be applied with caution. The studies on 'tDCS + training' and 'tDCS alone' showed heterogeneity in tDCS parameters, and as we found that tDCS parameters also influenced outcomes, training was not the sole influencing factor. For safety concerns, transient minor side effects were reported, suggesting that tDCS is a safe intervention and that participants were generally well tolerated.

Conclusions

In summary, this systematic review and meta-analysis revealed that tDCS can significantly improve the overall global cognition of older people with cognitive impairments. This improvement was more evident immediately post-intervention. However, the effect was more pronounced when the MMSE was used as an outcome measure. Notably, the most effective results were observed with a current density of less than or equal to 0.06 mA/cm^2, a duration of greater than 20 min, a number of stimulations less than or equal to 15, or a total charge density lower than 0.50 mAh/cm^2. Additionally, tDCS over temporal areas with an extracephalic montage proved to be beneficial in improving global cognition. The effect of tDCS alone was greater than that of tDCS combined with training, however, this point should be applied with caution. Moreover, older people with AD might benefit more from tDCS than those with MCI and other forms of dementia. However, tDCS did not significantly improve memory or executive function. Further research should focus on exploring an optimal tDCS configuration to maximize cognitive benefits across different types and severities of cognitive impairment.

Abbreviations

AchEIs	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AVLT	Auditory Verbal Learning Test
BDS	Backward Digit Span
BNT	Boston Naming Test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDR	Clinical Dementia Rating
CFQ	Cognitive Failure Questionnaire
CIs	Confidence intervals
COWAT	Controlled Oral Word Association Test
CVFT	Category Verbal Fluency Test
CVLT	California Verbal Learning Test
CVVLT	Chinese Version of the Verbal Learning Test
DMS	Delayed Matching to Sample
DLPFC	Dorsolateral prefrontal cortex
DSC	Digital-Symbol Coding
DSM	Diagnostic and Statistical Manual of Mental Disorder
FAB	Frontal Assessment Battery
FDS	Forward Digit Span
GABA	Gamma-aminobutyric acid
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MQ	Memory Quotient
NIBS	Non-invasive brain stimulation
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
PAL	Paired Associates Learning
PNT	Picture Naming Task
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRM	Pattern Recognition Memory
PROSPERO	International Prospective Register of Systematic Reviews
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBMT	Rivermead Behavioral Memory Test
RCFT	Rey Complex Figure Test
RCTs	Randomized controlled trials
RevMan	Review Manager
RoB 2	Risk of Bias Tool 2
ROCF	Rey—Osterrieth Complex Figure
rTMS	Repetitive transcranial magnetic stimulation
RVIP	Rapid Visual Information Processing
SDs	Standard deviations
SMD	Standardized mean difference
SVLT	Seoul Verbal Learning Test
SWM	Spatial Working Memory
tDCS	Transcranial direct current stimulation
TMT	Trial Making Test
ToL	Tower of London task
VD	Vascular dementia
VWM	Visual Working Memory
WMS	Wechsler Memory Scale

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

WK supervised the study. TP and TC contributed to the study conception, design of the review, and literature search. TP, TC, OV, and CL assisted in screening the literature and data extraction. TP, IA, TC, OV, and CL contributed to the quality assessment. TP and WK contributed to the data analysis and drafted the manuscript. BA, CY and KL provided critical feedback and helped shape the analysis. All the authors have read and agreed to the published version of the manuscript.

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Data availability

Data will be made available on request. The request for analyses of data from this review should be directed to the corresponding author (wanalee.klo@mahidol.edu).

Declarations

Ethics approval and consent to participate
Ethical approval was noted for all published papers included in the review. No further ethics approval was sought for this review of existing literature.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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