Review Article

Effects of Transcranial Direct-Current Stimulation and Cognitive Training on Individuals with Mild Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

Chu Ka Yin[1*], Cheng King Hei[2]

1- Department of Occupational Therapy, Wong Tai Sin Hospital, Hong Kong, China
2- Department of Occupational Therapy, Ruttonjee Hospital, Hong Kong, China

***Corresponding Author**: Chu Ka Yin, MSc
Department of Occupational Therapy, Wong Tai Sin Hospital, Hong Kong, China
E-mail: ckyinchu@gmail.com

ORCID ID:
Chu Ka Yin: 0009-0009-5799-4185
Cheng King Hei: 0009-0004-2084-7521

Article info:
Received: 10 Mar 2024
Accepted: 25 Jul 2024

Citation: Ka Yin Ch, King Hei Ch,. Effects of Transcranial Direct-Current Stimulation and Cognitive Training on Individuals with Mild Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis. Journal of Modern Rehabilitation. 2024; 19(1):?-?

Running Title: Effects of tDCS & CT on memory of MCI and Dementia

Abstract

Objectives: To systematically evaluate the most recent evidence regarding the potential short-term and long-term synergistic effects of transcranial direct current stimulation (tDCS) and cognitive training (CT) on memory in individuals with mild cognitive impairment (MCI) or dementia and to explore the optimal treatment protocol.

Methods: In accordance with the PRISMA guidelines, a comprehensive literature search on PubMed, Medline, CINAHL, and EMBASE was conducted to identify eligible randomized controlled trials (RCTs) published up to December 2022. The identified studies were summarized and analyzed to examine the efficacy of the combined intervention.

Results: Ten studies involving participants with MCI or dementia were included. Four RCTs with memory-related outcomes were analyzed. A small-to-medium effect size of 0.28 was found for the short-term effect (95% confidence interval [CI], 0.02 to 0.55). However, the long-term effect was non-significant, with an effect size of 0.17 (95% CI, -0.09 to 0.44).

Conclusion: The combined intervention appears to effectively mitigate cognitive decline in the short term only. Optimal treatment protocol remains inconclusive due to heterogeneity among studies. More robust evidence is required to determine whether the combined approach can serve as an effective intervention in clinical practice.

Keywords: Rehabilitation, Cognitive dysfunction, Transcranial direct current stimulation, Cognitive training, Neurosciences

Introduction

Mild Cognitive Impairment (MCI) is characterized by a cognitive function decline that falls below average yet allows individuals to maintain functional independence in daily activities [1]. Viewed as a transitional phase between normal cognitive decline and dementia-related deterioration, MCI elevates the risk of dementia development [2]. Epidemiological data indicate that the global prevalence of dementia, estimated at 55.5 million, is projected to rise to 75.62 million by 2030. This increment will impose an estimated two trillion dollars burden on our healthcare system [3]. Over the last decade, drug trials aimed at curbing cognitive decline, particularly in Alzheimer's Disease (AD), have yielded insignificant results. One plausible explanation is that pathophysiological alterations commence years before the manifestation of overt cognitive deficits, rendering cognitive function irreparable at the diagnosis stage [4]. Given the scarcity of pharmaceutical solutions, researchers have shifted their focus towards delaying the progression from MCI to dementia. Cognitive Training (CT), involving tasks designed to stimulate basic cognitive domains like memory, attention, and processing speed, has emerged as an effective strategy. A recent review proposed CT as a potential means to decelerate cognitive decline in MCI patients, citing a moderate to large effect size for this intervention [5].

Beyond CT, novel neuromodulation techniques, such as Transcranial Direct Current Stimulation (tDCS), have attracted researchers' attention. tDCS is a safe, economical, and non-invasive brain stimulation method that delivers an unidirectional flow of weak current through electrodes placed on the scalp [6]. Stimulation-induced electric fields can alter the membrane potential threshold, causing cortical excitation or inhibition, contingent upon the electrode montage [7]. These alterations manifest during the stimulation period potentially induce changes in local neurotransmitter concentrations like glutamate and GABA [8]. Accumulation of these transient effects may further induce long-term potentiation (LTP) or depression (LTD), which are the crucial components of neuroplasticity underpinning memory and learning processes [9]. Animal models have robustly established these long-standing effects [10], and clinical trials have demonstrated tDCS's efficacy in eliciting neuronal changes across various neurodegenerative disorders, including AD, with encouraging results [11,12].

Given its modulatory capabilities, tDCS has the potential to modify the cerebral physiology underlying cognition, thereby enhancing cognitive performance in individuals with MCI or dementia [13]. Specific neural circuits are activated with increased neuronal firing when they are engaged by cognitive stimuli, and these active circuits can be targeted and reinforced further by tDCS [14]. Therefore, a combined approach of tDCS and CT might yield enhanced effects. Previous research assessing therapeutic modalities for MCI or dementia generally support the role of CT in combating cognitive decline [15,16], as well as tDCS [17]. However, evidence summarizing the combined effect of both therapies remains insufficient. This study seeks to explore the synergistic effect of tDCS and CT on MCI or dementia patients' cognition especially on memory, in both short-term and long-term, by reviewing the most recent evidence. Additionally, this research aims to identify the optimal treatment protocol considering different stimulation parameters and CT patterns.

Methods

This research adhered to the PRISMA guidelines [18]. The methodological steps include a systematic literature search, study selection, data extraction, methodological quality assessment, and data analysis.

Literature Search

A comprehensive search of the literature was conducted across the databases of PubMed, Medline, CINAHL, and EMBASE. The search criteria encompassed articles published from the inception of these databases until December 2, 2022. The search strategy involved using a

combination of the following keywords: (1) tDCS OR transcranial direct current stimulation; AND (2) cognitive rehabilitation OR cognitive enhancement OR cognitive training OR cognitive therapy; AND (3) MCI OR mild cognitive impairment OR Dementia OR Alzheimer's disease. No restrictions were applied in the search strategy. A manual hand search was also performed to identify additional relevant studies from the reference lists of selected articles.

Study Selection

The study selection process involved an initial screening of articles based on their titles, keywords, and abstracts. After the removal of duplicate studies, the remaining articles were further scrutinized by two independent investigators under the following inclusion criteria: (1) subjects had a confirmed diagnosis of MCI or dementia, (2) the study was a RCT, (3) the treatment group underwent both tDCS and cognitive training, and (4) the control group received sham tDCS or no brain stimulation. Exclusion criteria were: (1) unavailability in full text, (2) non-English publications, (3) studies involving alternative brain stimulation techniques, (4) animal or computational studies.

Data Collection and Risk of Bias in Individual Studies

The full text of the selected articles was thoroughly reviewed. Key study data were meticulously extracted and summarized, including study design, participant characteristics, tDCS parameters, detail of cognitive training, mode of intervention, timepoints of assessments, outcome measures and effect on cognition. The Physiotherapy Evidence Database (PEDro) scale was applied to assess the methodological quality of each selected study [19]. Two independent investigators were involved in the selection and assessment process.

Data Analysis

The clinical heterogeneity among the studies was carefully examined. Available quantitative data for the outcome measures regarding the memory domain were targeted for further analysis, as impaired memory is one of the most prominent symptoms in MCI and patients with dementia [20]. In instances of multiple memory-related outcomes across studies, the most conservative outcome was selected [21]. Numerical data, including the mean, standard deviation, and sample size, were treated as continuous variables and processed in RevMan5.4.1 to calculate the effect size. A random-effect model was applied since assuming a fixed common true effect across studies is implausible given the variabilities in the study designs and outcome measures [22]. Effect size calculation was expressed as the standardized mean difference with a 95% confidence interval, differentiated into small, medium, and large effects according to Cohen's Convention (d=0.2; d=0.5; d=0.8) [23]. The I2 statistic was used to measure heterogeneity, with a value of ≥40% indicating statistical heterogeneity. The statistical significance threshold was set at p=0.05. The short-term synergistic effect of tDCS with CT was evaluated by calculating the difference between the experimental and control groups at post-treatment evaluation relative to baseline. For the long-term effect, the difference between the two groups at follow-up evaluation relative to baseline was calculated. Data from the most distant follow-up session were used for this calculation.

Results

Study Selection

We identified 542 articles from databases comprised of PubMed (n=365), EMBASE (n=133), Medline (n=28), and CINAHL Ultimate (n=16). After removing duplicates, 455 articles remained. Upon further screening, 28 articles appeared potentially eligible. Eventually 10 were

selected for review, with 4 showing memory-related outcomes further selected for meta-analysis. The selection process is detailed in Figure 1.

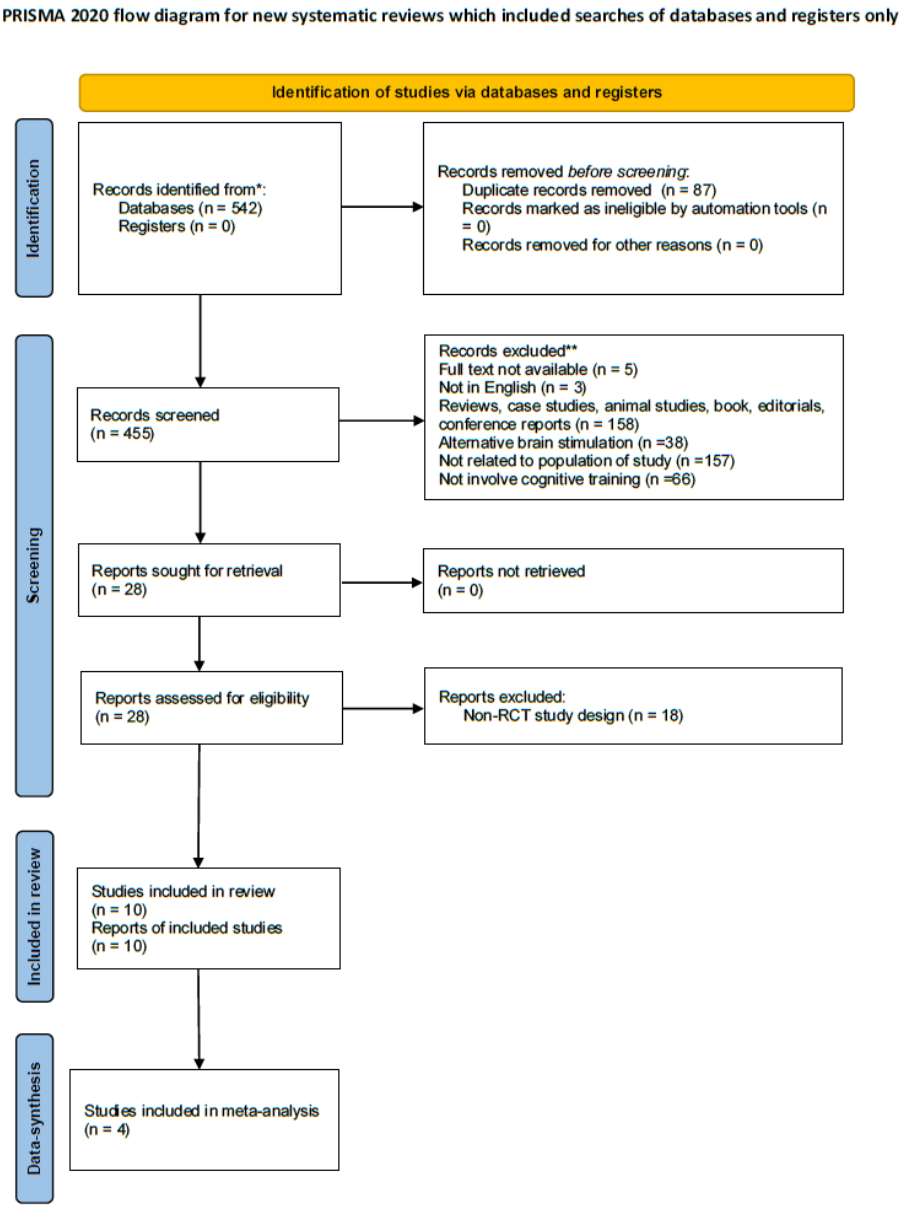

Fig. 1. Flowchart of study selection process. n , number; RCT, randomized controlled trial.

Characteristics of the Studies

Table 1 enumerates the primary findings of the 10 studies included, which involved a total of 503 participants. This included 229 individuals with MCI and 274 with dementia. Four studies focused on MCI [24,25,26,27], four on dementia [28,29,30,31], while the remaining two studies recruited a mixed group of participants [32,33].

The study designs varied, with three of the four studies examining MCI using a parallel design [24,25,26], and one employing a crossover design [27]. Of the studies investigating dementia, two used a parallel-group design [30,31], while the remaining two employed a crossover design

[28,29]. The two studies examining a mixed group of participants implemented a parallel-group design [32,33].
All studies conducted post-intervention assessments within one week after the last treatment to ascertain short-term effects of transcranial direct current stimulation (tDCS). Except for one study [28], all studies incorporated follow-up assessments, ranging from two weeks to six months after the last treatment, to evaluate long-term effects. Cognitive domains assessed varied across studies and the study characteristics were outlined in Table 1.

Stimulation Parameters
All studies employed anodal stimulation for cortical excitability induction, with electrode montages varying based on cognitive domains of interest. Most of the studies focused on the dorsolateral prefrontal cortex (DLPFC) to modulate memory, either in isolation [31], or in conjunction with other cognitive functions [25,26,32,33]. Another five studies explored alternative brain regions for stimulation. For instance, one study utilized left lateral temporal cortex stimulation to enhance memory [30], while another targeted the left inferior frontal gyrus to improve executive function and memory [24]. Another three studies applied anodal stimulation to the left inferior parieto-temporal region [29], medial frontal cortex [28], and right temporoparietal cortex [27], respectively, with the aim of enhancing multiple cognitive domains. Current intensity ranged from 1mA to 2mA, with 2 mA most frequently used. Stimulation duration varied from 10 to 30 minutes, with 20 minutes most common. Only two studies implemented a single stimulation session [25,28], while the others delivered multiple stimulation ranging from two to twenty.

Mode of Cognitive Training
The majority of studies implemented individualized CT, utilizing various types of cognitive exercises that targeted specific cognitive domains of interest. However, one study provided the participants with group-based cognitive training [24], adopting the "Strategic Memory Advanced Reasoning Training" (SMART) protocol, which consisted of eight hourly group sessions. As previously illustrated in studies that have adopted the same protocol [34,35], the cognitive strategies featured in SMART are hierarchical in nature, with each new strategy building upon the previous one. Through strategic reasoning, meanings are transformed from concrete-based into abstract gist-based. In addition to conventional CT, four studies utilized computerized programs for training delivery [26,30,31,32]. Regarding the timing of cognitive training, seven studies provided online cognitive training concurrently with tDCS stimulation [26,27,28,29,31,32,33], while two studies implemented tDCS prior to CT [24], and after CT [25]. One study did not specify the timing of CT relative to tDCS [30].

Coupling Effect of tDCS and Cognitive Training
In total, six studies suggested that coupling tDCS with CT may have a positive impact on cognitive function in individuals with cognitive impairment. Among these studies, two focused on subjects with MCI and reported statistically significant improvements in recognition memory [25] and enhanced object location memory training success [27]. In addition, two studies targeted individuals with fronto-temporal dementia and demonstrated beneficial coupling effects on picture naming ability [29], and comprehension of communicative intentions [28]. Another study focused on individuals with AD and found an enhancement effect on working memory [30]. Finally, one study included a mixed population of subjects with MCI or AD and reported positive effects on working memory and speed of processing [32].
However, four studies have reported non-significant or negative results regarding the coupling of tDCS with CT. For instance, Gonzalez et al. (2021) targeted subjects with MCI and found

no significant difference between groups, despite all groups demonstrating significant improvement in domain-specific cognitive outcomes [26]. Another study on patients with MCI reported a negative effect of the combined intervention, with significant enhancement in executive function and episodic memory only found in the sham-controlled group and not in the active tDCS group [24]. Besides, Cotelli et al. (2014) targeted the population with AD and found that both the active tDCS group and sham-controlled group showed significant memory enhancement effects, indicating that the coupled intervention was not superior to CT alone [31]. Finally, a study investigating a mixed population of MCI and AD reported non-significant improvement in global cognition [33].

Meta-analysis

Four studies were included in the meta-analysis [25,26,30,31], which revealed a statistically significant small to medium effect size for the immediate effect of coupling tDCS with CT in enhancing cognitive function (0.28 [95%CI, 0.02, 0.55], p=0.04) (Fig. 2a). However, the long-term effect size was non-significant (0.17 [95%CI, -0.09, 0.44], p=0.20). No evidence of heterogeneity was found in both short-term and long-term effect (Fig. 2b).

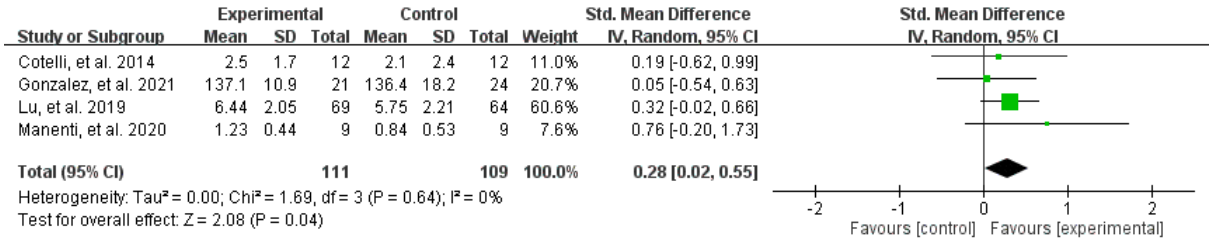

Fig. 2a. Forest plot showing the coupling effect of tDCS with cognitive training on memory in short term. Significant standardized effect size of 0.28 was found (p=0.04).

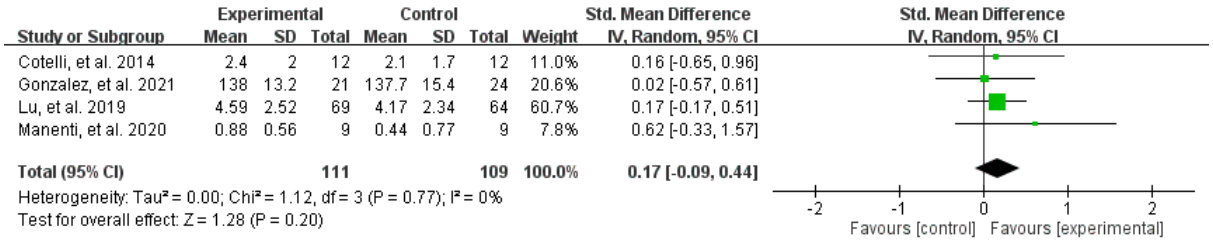

Fig. 2b. Forest plot showing the coupling effect of tDCS with cognitive training on memory in long term. Non-significant standardized effect size of 0.17 was found (p=0.20).

Methodological quality

The assessment of methodological quality using PEDro scale is summarized in Table 2. The evaluated studies exhibited a range of scores from 7 to 10 on a 10-point scale, with an average score of 8.3. It is particularly noteworthy that deductions in the scoring were predominantly due to the deficiencies in allocation concealment and the binding of therapists.

Table 2. Methodological-quality assessment using Physiotherapy Evidence Database Scale.

	1	2	3	4	5	6	7	8	9	10	11	Total

Rodella et al., 2022	1	1	0	1	1	1	1	1	1	1	1	**9**
Cotelli et al., 2014	1	1	0	1	1	1	1	1	1	1	1	**9**
Das et al., 2019	1	1	1	1	1	1	0	1	1	1	1	**8**
Manenti et al., 2020	1	1	1	1	1	1	1	1	1	1	1	**10**
Roncero et al., 2017	1	0	0	1	1	1	1	1	1	1	1	**8**
Lu et al., 2019	1	1	1	0	1	0	1	1	1	1	1	**7**
Inagawa et al., 2019	1	1	0	1	0	0	1	1	1	1	1	**7**
Cotelli et al., 2018	1	1	0	1	1	0	1	1	1	1	1	**8**
Gonzalez et al., 2021	1	1	1	1	1	0	1	1	1	1	1	**9**
de Sousa et al., 2020	1	1	0	1	1	0	0	1	1	1	1	**7**

Scale of the criterion score: 0 = no; 1 = yes.

The PEDro scale criteria are: (1) Eligibility criteria specified; (2) Random allocation; (3) Allocation concealment; (4) Groups similar at baseline; (5) Subject blinding; (6) Therapist blinding; (7) Assessors blinding; (8) Less than 15% dropouts; (9) Intention-to-treat analysis; (10) Between group statistical comparisons; (11) Point measures and variability data

Discussion

This systematic review and meta-analysis set out to assess the synergistic influence between tDCS and CT on the cognitive function of patients with MCI or dementia, both in the short and long term. An synthesis of data from selected studies yielded a significant positive short-term effect from the combined intervention. This immediate impact could be attributed to the direct current's capacity to alter the neuronal membrane potential, leading to cortical excitation and potentially facilitating the learning process inherent in cognitive training. This immediate effect of brain stimulation was illustrated by Monte-Silva et al. (2013), who discovered that a solitary stimulation session of 10-13 minutes could induce a modulatory effect lasting for an hour [36]. Consequently, it is plausible that the synergy between tDCS and CT could potentially ameliorate the compromised cognition in patients with MCI or dementia in the short term.

Although the initial outcomes of this intervention show promise in the short term, it is imperative to thoroughly examine its long-term implications. Previous research has demonstrated that repeated sessions of tDCS can induce a cumulative after-effect that lasts for up to a week or even longer [37,38], indicating its potential to induce more lasting neuroplastic changes in individuals with impaired cognitive function. In accordance with the principles of LTP, multiple intervention sessions may be necessary to induce more extensive neuroplastic changes. The majority of studies included in this review employed multiple intervention sessions, ranging from two to twenty sessions. Although the meta-analysis did not yield statistically significant long-term effects, the consistent use of multiple sessions in the study designs is noteworthy. Several recent studies have adopted an extended intervention framework to observe the long-term effects of tDCS on participants' cognition. For example, Im et al. (2019) implemented a 6-month home-based daily stimulation protocol to enhance global cognition and regional cerebral metabolic rate for glucose in patients with AD [39], suggesting a prolonged stimulation protocol involving consecutive daily sessions may bring promising results. This notion is in-line with another study, which provided insights that twenty daily administration of the combined intervention may be more beneficial over only two to three sessions administered weekly [40]. These emerging evidence suggest that achieving a clinically desirable long-term outcome may require an extended and continuous intervention approach.

This study sought to investigate the optimal intervention protocol. However, due to substantial variability among stimulation parameters and the diverse nature of CT, formulating a definitive statement regarding effective protocols proves challenging. Most studies have targeted the left DLPFC for memory enhancement, resonating with prior research suggesting that the neural

architecture of global cognition and memory is densely concentrated within the white matter fiber tracts bridging the left DLPFC and inferior parietal cortex [41]. Advanced voxel-based lesion-symptom mapping studies further substantiate this theory by revealing that the white matter tracts in left DLPFC form an integrated system that undergirds human memory processing [42]. Therefore, exploring the role of DLPFC in patients with compromised cognition is of significant value.

The systematic review has revealed insights into the polarity-dependent effects of tDCS on cognitive function in patients with cognitive impairments. While anodal tDCS has been thought to augment the effect of CT, it may exert the opposite effect in certain circumstances, as emerging evidence suggests a more complex interaction. Das et al. (2019) observed increased cerebral blood flow (CBF) in the right middle frontal cortex (MFC) [24], which is distant from the inferior frontal gyrus (IFG) — the intended target region. This finding, derived from neurophysiological imaging, raises questions about the specificity of tDCS effects. Moreover, behavioral measures indicated that the sham-controlled group experienced significant enhancements in executive functions and episodic memory, which was not found in the experimental group. These results imply that anodal tDCS may not always exert a facilitatory effect on the intended neural region and could inadvertently influence adjacent, non-stimulated areas. This concept is further supported by Yun et al. (2016), who suggested that the neural alterations induced by tDCS might span a more extensive network than the focal stimulation site, reflecting the intricate interconnectivity of cerebral hemispheres [43]. The increased CBF in the MFC might signify a non-localized effect originating from the IFG, hinting at the necessity for the concurrent application of tDCS and CT.

Corroborating this, several included literatures indicate that a simultaneous application of tDCS and CT could be more beneficial. Roncero et al. (2017) found that concurrent interventions led to greater and more persistent cognitive enhancements [29]. Lu et al. (2019) revealed that greater improvement was found in domain-specific cognitive function when the two modalities were conducted at the same time [30], and de Sousa et al. (2020) reported that tDCS administered during CT produced better cognitive outcomes [27]. The collective evidence suggests a synergistic effect when CT and tDCS are delivered concurrently, potentially due to the co-activation of task-related and stimulation-related neural networks. This dual activation may enhance neuroplasticity in targeted regions, leading to more effective cognitive improvement in patients with MCI or dementia. This review's analysis, which includes several key studies [27,29,30], reveals the intricate yet promising interplay between tDCS and CT.

This study also underscores the potential differences in the benefits of the combined intervention among individuals with differing cognitive performances. While individuals with MCI and dementia both exhibit cognitive impairment, the severity and impact on daily functioning can vary significantly between the two conditions. Therefore, it is crucial to consider the level of cognitive impairment when selecting participants for intervention. One of the included articles suggested that patients with higher cognitive function at baseline might benefit more from combined interventions [33], as they may possess a greater residual neuronal function to promote plastic change, which may be unachievable in late-stage AD. This concept aligns with the findings of a previous RCT, which showed that tDCS was ineffective in patients with moderate to severe dementia with apathy [44]. Although formulating a definitive statement about the optimal population from the current study may be challenging due to the limited number of articles included, this concept merits careful consideration.

There are several limitations in the present study that warrant acknowledgment. First, only a small number of articles were included in the study, which may underpower the result in the meta-analysis. Future trials should strive to recruit larger sample sizes to ensure significantly powered results. Second, there was variation in the assessment tools used in the studies, which may lead to a deviation in the result. Future studies might consider employing standardized,

repeatable, and comprehensive cognitive assessment tools, such as the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [45]. Third, clinical heterogeneity was observed among the population in the studies, as the stage of cognitive decline varied among subjects. Although the Mini-Mental State Examination was used in some studies to screen for MCI and dementia, future studies should incorporate other disease-specific scales, such as the Dementia Rating Scale [46], to further differentiate the severity of the diagnosis. This could minimize heterogeneity and enhance the validity and generalizability of the results.

In conclusion, this study sought to assess the potential synergistic impact of tDCS paired with CT on enhancing cognitive functions in individuals diagnosed with MCI or AD. The meta-analytic findings indicate a favorable influence of this combined intervention on memory performance in the short term. However, the evidence does not substantiate sustained long-term benefits. Nevertheless, the results may be underpowered due to the small number of articles included. Additionally, the heterogeneity among the studies complicates the determination of an optimal treatment regimen. Future studies should increase the sample size, consider concurrent interventions, prolong the intervention period, and use standardized outcome measures to provide more robust evidence. Lastly, we found a recent study published at the time this manuscript was completed [47], that RCT was not included due to the time eligibility criteria.

Conflict of Interest Statement

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author's Contributions

C.K.Y is responsible for designing the study, collecting the data, conducting data analysis and writing the manuscript. C.K.H contributed in screening the articles, assessing the risk of bias and writing the manuscript.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

We are grateful to all the scholars worldwide who conducted research in the field of combating cognitive decline in neurodegenerative disease.

References

1. Anderson ND. State of the science on mild cognitive impairment (MCI). CNS Spectrums. 2019 Jan 17;24(1):78–87. doi:10.1017/s1092852918001347
2. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment. Archives of Neurology. 1999 Mar 1;56(3):303. doi:10.1001/archneur.56.3.303
3. Prince M. World alzheimer report 2015: The global impact of dementia: An analysis of prevalence, incidence, cost and trends [dissertation]. World Alzheimer report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. [London]: Alzheimer's Disease International; 2015.

4. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. Alzheimer's Research & Therapy. 2014;6(4):37. doi:10.1186/alzrt269
5. Belleville S. Cognitive training for persons with mild cognitive impairment. International Psychogeriatrics. 2008 Feb;20(1):57–66. doi:10.1017/s104161020700631x
6. Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clinical Neurophysiology. 2016 Feb;127(2):1031–48. doi:10.1016/j.clinph.2015.11.012
7. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: State of the art 2008. Brain Stimulation. 2008 Jul;1(3):206–23. doi:10.1016/j.brs.2008.06.004
8. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. The Journal of Neuroscience. 2009 Apr 22;29(16):5202–6. doi:10.1523/jneurosci.4432-08.2009
9. Rozisky, J. R., Antunes, L. C., Brietzke, A. P., de Sousa, A. C., and Caumo, W. (2016). "Transcranial direct current stimulation and neuroplasticity," in *Transcranial Direct Current Stimulation (tDCS): Emerging Used, Safety and Neurobiological Effects*, ed L. Rogers (New York, NY: Nova Science Publishers Inc), 1–26.
10. Stafford J, Brownlow ML, Qualley A, Jankord R. AMPA receptor translocation and phosphorylation are induced by transcranial direct current stimulation in rats. Neurobiology of Learning and Memory. 2018 Apr;150:36–41. doi:10.1016/j.nlm.2017.11.002
11. Ferrucci R, Mameli F, Guidi I, Mrakic-Sposta S, Vergari M, Marceglia S, et al. Transcranial direct current stimulation improves recognition memory in alzheimer disease. Neurology. 2008 Aug 12;71(7):493–8. doi:10.1212/01.wnl.0000317060.43722.a3
12. Boggio PS, Ferrucci R, Mameli F, Martins D, Martins O, Vergari M, et al. Prolonged visual memory enhancement after direct current stimulation in alzheimer's disease. Brain Stimulation. 2012 Jul;5(3):223–30. doi:10.1016/j.brs.2011.06.006
13. Kuo M-F, Nitsche MA. Effects of transcranial electrical stimulation on cognition. Clinical EEG and Neuroscience. 2012 Jul;43(3):192–9. doi:10.1177/1550059412444975
14. Cruz Gonzalez P, Fong KN, Brown T. The effects of transcranial direct current stimulation on the cognitive functions in older adults with mild cognitive impairment: A pilot study. Behavioural Neurology. 2018;2018:1–14. doi:10.1155/2018/5971385
15. Bahar-Fuchs A, Martyr A, Goh AM, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. Cochrane Database of Systematic Reviews. 2019 Mar 25; doi:10.1002/14651858.cd013069.pub2
16. Hill NTM, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. American Journal of Psychiatry. 2017 Apr;174(4):329–40. doi:10.1176/appi.ajp.2016.16030360
17. Majdi A, van Boekholdt L, Sadigh-Eteghad S, Mc Laughlin M. A systematic review and meta-analysis of transcranial direct-current stimulation effects on cognitive function in patients with Alzheimer's disease. Molecular Psychiatry. 2022 Feb 3;27(4):2000–9. doi:10.1038/s41380-022-01444-7

18. Liberati A. The prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Annals of Internal Medicine. 2009 Aug 18;151(4). doi:10.7326/0003-4819-151-4-200908180-00136
19. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the pedro scale for rating quality of randomized controlled trials. Physical Therapy. 2003 Aug 1;83(8):713–21. doi:10.1093/ptj/83.8.713
20. Grober E, Buschke H. Genuine memory deficits in dementia. Developmental Neuropsychology. 1987 Jan;3(1):13–36. doi:10.1080/87565648709540361
21. Borenstein M, Hedges LV, Higgins JPT, Rothstein H. Introduction to meta-analysis. Hoboken, NJ: John Wiley & Sons, Inc; 2021.
22.Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods. 2010 Apr;1(2):97–111. doi:10.1002/jrsm.12
23. Gignac GE, Szodorai ET. Effect size guidelines for individual differences researchers. Personality and Individual Differences. 2016 Nov;102:74–8. doi:10.1016/j.paid.2016.06.069
24. Das N, Spence JS, Aslan S, Vanneste S, Mudar R, Rackley A, et al. Cognitive training and transcranial direct current stimulation in mild cognitive impairment: A randomized pilot trial. Frontiers in Neuroscience. 2019 Apr 12;13. doi:10.3389/fnins.2019.00307
25. Manenti R, Sandrini M, Gobbi E, Binetti G, Cotelli M. Effects of transcranial direct current stimulation on episodic memory in amnestic mild cognitive impairment: A pilot study. The Journals of Gerontology: Series B. 2018 Nov 5;75(7):1403–13. doi:10.1093/geronb/gby134
26. Gonzalez PC, Fong KNK, Brown T. Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial. Annals of Physical and Rehabilitation Medicine. 2021 Sept;64(5):101536. doi:10.1016/j.rehab.2021.101536
27. de Sousa AV, Grittner U, Rujescu D, Külzow N, Flöel A. Impact of 3-day combined anodal transcranial direct current stimulation-visuospatial training on object-location memory in healthy older adults and patients with mild cognitive impairment. Journal of Alzheimer's Disease. 2020 May 5;75(1):223–44. doi:10.3233/jad-191234
28. Cotelli M, Adenzato M, Cantoni V, Manenti R, Alberici A, Enrici I, et al. Enhancing theory of mind in behavioural variant frontotemporal dementia with transcranial direct current stimulation. Cognitive, Affective, & Behavioral Neuroscience. 2018 Jul 11;18(6):1065–75. doi:10.3758/s13415-018-0622-4
29. Roncero C, Kniefel H, Service E, Thiel A, Probst S, Chertkow H. Inferior parietal transcranial direct current stimulation with training improves cognition in anomic alzheimer's disease and frontotemporal dementia. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2017 Mar 24;3(2):247–53. doi:10.1016/j.trci.2017.03.003
30. Lu H, Chan SS, Chan WC, Lin C, Cheng CP, Linda Chiu Wa L. Randomized controlled trial of TDCS on cognition in 201 seniors with mild neurocognitive disorder. Annals of Clinical and Translational Neurology. 2019 Sept 17;6(10):1938–48. doi:10.1002/acn3.50823
31. Cotelli M, Manenti R, Brambilla M, Petesi M, Rosini S, Ferrari C, et al. Anodal tDCS during face-name associations memory training in alzheimer's patients.

Frontiers in Aging Neuroscience. 2014 Mar 19;6. doi:10.3389/fnagi.2014.00038
32. Rodella C, Bernini S, Panzarasa S, Sinforiani E, Picascia M, Quaglini S, et al. A double-blind randomized controlled trial combining cognitive training (CORE) and neurostimulation (tdcs) in the early stages of cognitive impairment. Aging Clinical and Experimental Research. 2021 Jun 22;34(1):73–83. doi:10.1007/s40520-021-01912-0
33. Inagawa T, Yokoi Y, Narita Z, Maruo K, Okazaki M, Nakagome K. Safety and feasibility of transcranial direct current stimulation for cognitive rehabilitation in patients with mild or major neurocognitive disorders: A randomized sham-controlled pilot study. Frontiers in Human Neuroscience. 2019 Sept 6;13. doi:10.3389/fnhum.2019.00273
34. Mudar RA, Chapman SB, Rackley A, Eroh J, Chiang H, Perez A, et al. Enhancing latent cognitive capacity in mild cognitive impairment with Gist Reasoning Training: A pilot study. International Journal of Geriatric Psychiatry. 2016 Apr 25;32(5):548–55. doi:10.1002/gps.4492
35. Mudar RA, Nguyen LT, Eroh J, Chiang H-S, Rackley A, Chapman SB. Event-related neural oscillation changes following reasoning training in individuals with mild cognitive impairment. Brain Research. 2019 Feb;1704:229–40. doi:10.1016/j.brainres.2018.10.017
36. Monte-Silva K, Kuo M-F, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. Brain Stimulation. 2013 May;6(3):424–32. doi:10.1016/j.brs.2012.04.011
37. Mondino M, Jardri R, Suaud-Chagny M-F, Saoud M, Poulet E, Brunelin J. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. Schizophrenia Bulletin. 2015 Aug 24;42(2):318–26. doi:10.1093/schbul/sbv114
38. Carlson HL, Ciechanski P, Harris AD, MacMaster FP, Kirton A. Changes in spectroscopic biomarkers after transcranial direct current stimulation in children with perinatal stroke. Brain Stimulation. 2018 Jan;11(1):94–103. doi:10.1016/j.brs.2017.09.007
39. Im JJ, Jeong H, Bikson M, Woods AJ, Unal G, Oh JK, et al. Effects of 6-month at-home transcranial direct current stimulation on cognition and cerebral glucose metabolism in Alzheimer's disease. Brain Stimulation. 2019 Sept;12(5):1222–8. doi:10.1016/j.brs.2019.06.003
40. Pallanti S, Grassi E, Knotkova H, Galli G. Transcranial direct current stimulation in combination with cognitive training in individuals with mild cognitive impairment: A controlled 3-parallel-arm study. CNS Spectrums. 2022 Sept 12;28(4):489–94. doi:10.1017/s1092852922000979
41. Barbey AK, Colom R, Solomon J, Krueger F, Forbes C, Grafman J. An integrative architecture for General Intelligence and executive function revealed by lesion mapping. Brain. 2012 Mar 6;135(4):1154–64. doi:10.1093/brain/aws021
42. Chiang M-C, Barysheva M, Shattuck DW, Lee AD, Madsen SK, Avedissian C, et al. Genetics of brain fiber architecture and intellectual performance. The Journal of Neuroscience. 2009 Feb 18;29(7):2212–24. doi:10.1523/jneurosci.4184-08.2009
43. Yun K, Song I-U, Chung Y-A. Changes in cerebral glucose metabolism after 3 weeks of noninvasive electrical stimulation of mild cognitive impairment patients.

Alzheimer's Research & Therapy. 2016 Dec;8(1). doi:10.1186/s13195-016-0218-6
44. Suemoto CK, Apolinario D, Nakamura-Palacios EM, Lopes L, Paraizo Leite RE, Sales MC, et al. Effects of a non-focal plasticity protocol on apathy in moderate alzheimer's disease: A randomized, double-blind, sham-controlled trial. Brain Stimulation. 2014 Mar;7(2):308–13. doi:10.1016/j.brs.2013.10.003
45. 1. DUFF K, HUMPHREYSCLARK J, OBRYANT S, MOLD J, SCHIFFER R, SUTKER P. Utility of the RBANS in detecting cognitive impairment associated with alzheimer's disease: Sensitivity, specificity, and positive and negative predictive powers. Archives of Clinical Neuropsychology. 2008 Sept;23(5):603–12. doi:10.1016/j.acn.2008.06.004
46. Vitaliano PP, Breen AR, Russo J, Albert M, Vitiello MV, Prinz PN. The clinical utility of the Dementia Rating Scale for Assessing Alzheimer Patients. Journal of Chronic Diseases. 1984 Jan;37(9–10):743–53. doi:10.1016/0021-9681(84)90043-2
47. Lau CI, Liu M-N, Cheng F-Y, Wang H-C, Walsh V, Liao Y-Y. Can transcranial direct current stimulation combined with interactive computerized cognitive training boost cognition and gait performance in older adults with mild cognitive impairment? A randomized controlled trial. Journal of NeuroEngineering and Rehabilitation. 2024 Feb 16;21(1). doi:10.1186/s12984-024-01313-0

Table 1. Characteristics of The Reviewed Studies

Participant Characteristics	**tDCS montage and parameters**	**Detail of cognitive training**	**Mode of intervention**	**Outcome measures**	**Assessment sequence**	**Effect of the**
MCI or Mild AD N=33 (16E; 17C) Mean age: E 71.62 ± 5.65 C75.13 ± 4.76	An: L DLPFC Cat: R Deltoid 2mA 30 min	Computerized CT: CoRe software that involved 11 tasks targeting logical execution, processing speed, working memory, and episodic memory functions	Concurrent tDCS + CT 4 sessions/week for 3 weeks	MMSE, Logical Memory Test immediate-delayed recall, Rey's 15 words test immediate delayed recall, Rey Complex Figure delayed recall ; Raven's Matrices 1947, Frontal Assessment Battery, FAS, Rey Complex Figure copy ; Verbal Span, Digit Span, Corsi's block-tapping test span; Trail Making Test; BDI, SF-36; ADL, IADL, CRIq only in baseline Ax	Baseline Immediate post-Tx 24 weeks follow up	**Effective** - Improved in and attention at both post-T assessment -Stable MMS up, while shar
Mild to moderate AD N=36 12 tDCS + CT [A]; 12 sham + CT [B]; 12 tDCS + motor training [C]) Mean age:	An: L DLPFC Cat: R Deltoid 2mA 25 min	Individual computerized memory training: Over 10 days of training, 20 face-name pairs were learned Motor training: walking,	Concurrent tDCS + CT 5 sessions/week for 2 weeks	Picture naming task, BADA ; RBMT, Rey auditory verbal learning test; Rey-osterrieth, complex figure-copy; Trail making test-A, Trail making test-B	Baseline 2 week post-Tx 12 weeks follow up 24 weeks follow up	**Ineffective** - Both the tD + CT group improved pe weeks compa + motor traini

A 76.6 ± 4.6 B: 74.7 ± 6.1 C: 78.2 ± 5.2		coordination and balance training				
MCI N=22 (12E; 10C) Mean age: E62.58 ± 8.43 C63.3 ± 7.38	An: L inferior frontal gyrus Cat: R deltoid 2mA 20 min	SMART cognitive training group that focused on cognitive strategies	Separated, tDCS immediately prior to CT Total 8 sessions in 4 weeks	Test of Strategic Learning, Controlled Oral Word Association, Delis-Kaplan executive function system, Selective Auditory learning task, Multifactorial Memory Questions, California Verbal Learning Task, Logical Memory, Imaging: fMRI for cerebral blood flow	Baseline Immediate post-Tx 12 weeks follow up	**Ineffective** - tDCS+CT blood flow to cortex but l executive fun memory
MCI N=18 (9E:9C) Mean age: E 75.3 ±4.8 C 75.3±2.2	An: L DLPFC Cat: R supra-orbital area 1.5mA 15 min	Word learning with spatial contextual reminder	Separated, tDCS 10 min after CT Single session	Percentage of words correctly answered, MMSE, Raven's Colored Progressive Matrices, Verbal Fluency, Token Test, Rey-Osterrieth Complex Figure Copy, Trail Making Test A, Trail Making Test B, AVLT, Story Recall, Rey-Osterrieth Complex Figure Recall, Digit Span, CRIq	1 day Post-Tx 28 days follow up	**Effective** - Active recognition m sham
AD or frontotemporal dementias N=10 (5:5 crossover) Mean age: 67.4±5.94	An: L inferior parieto-temporal region Cat: R fronto-orbital area 2mA 30 min	Picture naming training	Concurrent tDCS+CT 10 active session 10 sham session	Performance in a trained picture naming tasks and untrained list; digit span, verbal fluency, MoCA, MMSE; Interview for carer for change in mood, cognition and day to day function	Baseline Immediate Post-Tx 2 weeks follow up	**Effective** - Significantl real stimulatio lasting at lea stimulation - A small incr picture-namin span for real t
AD N=201 69 tDCS-working memory training[A] ; 64 sham-working memory training [B]; 68tDCS-control cognitive training[C]) Mean age: A 74.2±6.7 B 74.5±6.6 C 73.4±6.1	An: L lateral temporal cortex Cat: R upper limb 2mA 20 min	Computerized working memory training: Adaptive N-back Controlled cognitive training: click the mouse when detected the stimuli	Not mentioned about the timing of delivering tDCS and CT Total 12 session in 4 weeks	Reaction time, ADAS-Cog, Logical memory, 10 min word list learning test, CVFT, Trail making test; Chinese Neuropsychiatric inventory	Baseline Immediate Post-Tx 4 weeks follow up 8 weeks follow up	**Effective** - Cognitive found across t weeks interve Combined tD showed sign improvement delayed reca memory capa

nild or major neurocognitive lisorders N=22 (7E : 13C) Mean age: E 76.6±5.7 C 76.2±7.7	An: L DLPFC Cat: R supra-orbital ridge 2mA 20 min	Calculation and language training	Concurrent tDCS+CT 2 sessions/ day Consecutive 5 days	Attrition rate to measure safety, ADAS-Cog, MMSE, FAB, CDR	Baseline Immediate Post-Tx 2 weeks follow up	**Ineffective** - No statist improvement ADAS-cog a follow up
ronto-temporal lementia N=16 (8:8 crossover) Mean age: 64.9±8.6	An: Medial frontal cortex Cat: Inion 1.5 mA 10 min	Theory of mind training;	Concurrent tDCS+CT Single session of tDCS Single session of sham	Reaction time and accuracy of test in each session	Baseline Immediate Post-Tx	**Effective** - Significan accuracy imp comprehensio communicativ active stimula
MCI N=67 (21 tDCS+ct [A]; 24 sham+ct [B]; 21 ct alone [C]) Mean age: A: 69.8±5.3 B:71.0±6.2 C:70.6±5.4	An: L DLPFC Cat: contralateral brachioradialis muscle 1.5mA 30 min	computerized CT: 'Neuron Up' which consist of customizable training materials to enable cognitive rehabilitation	Concurrent tDCS+CT 3 sessions/week for 3weeks	MoCA, Digit Span Test, Trail Making Test A and B, RBMT-3 Cognitive training task-specific outcomes: errors, completion time and reaction time depending on nature of task	Baseline Immediate Post-Tx 6 weeks follow up	**Ineffective** - tDCS comb not superior t CT and CT alo domain-specif outcomes, bu comparatively
MCI N=18 (8:8) Healthy ndividuals N=36 (16:16) Mean age: MCI: 70±6 Healthy ndividuals: 69±7	An: R temporo-parietal cortex Cat: L supraorbital area 1 mA 20 min	Visuo-spatial memory training using object location memory paradigm	Concurrent tDCS+CT daily session in 3 days	CERAD, MMSE, TMT, Digit span, Verbal Fluency, Regensburger Verbal Fluency Test, MWT, PANAS, BDI, WHOQoL, PSQI, SVF120, Percentage correct scores and recall performance	Baseline Immediate Post-Tx 4 weeks follow up	**Effective** - CT+tDCS success only i - Relative per similar in compared to H - Suggested a online, but a offline perfo patients. - Indicated between performers ar from tDCS

AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; An, AnodeBDI, Beck Depression Inventory; C, Control group; Cat, Cathode; CDR, Clinical Dementia Rating; CRIq, Cognitive Reserve Index questionnaire; CT, Cognitive training; DLPFC, Dorsolateral prefrontal cortex; E, Experimental group; FAB, Frontal Assessment Battery; FAS, Fatigue Assessment Scale; L, Left; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; R, Right; RBMT, Rivermead Behavioural Memory Test; RCT, randomized controlled trial; Tx, Treatment