Journal of
Modern Rehabilitation

January 2025, Volume 19, Number 1

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

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

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

Use your device to scan and read the article online

Citation Chu KY, Cheng KH. 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. 2025; 19(1):1-13. http://dx.doi.org/10.18502/jmr.v19i1.17504

http://dx.doi.org/10.18502/jmr.v19i1.17504

Article info:
Received: 10 Mar 2024
Accepted: 25 Jul 2024
Available Online: 01 Jan 2025

Keywords:
Rehabilitation; Cognitive dysfunction; Transcranial direct-current stimulation; Cognitive training; Neuroscience

ABSTRACT

Introduction: We aimed 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 the memory of individuals with mild cognitive impairment (MCI) or dementia and to explore the optimal treatment protocol.

Materials and Methods: Following the preferred reporting items for systematic reviews and meta-analyses (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 (ES) of 0.28 was found for the short-term effect (95% CI, 0.02%, 0.55%). However, the long-term effect was non-significant, with an ES of 0.17 (95% CI, -0.09%, 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.

*** Corresponding Author:**
Chu Ka Yin.
Address: *Department of Occupational Therapy, Wong Tai Sin Hospital, Hong Kong, China.*
Tel: *+85 (93) 460047*
E-mail: *ckyinchu@gmail.com*

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 burden our healthcare system with an estimated 2 trillion dollars [3]. Over the last decade, drug trials that aimed at curbing cognitive decline, particularly in Alzheimer disease (AD), have yielded insignificant results. One plausible explanation is that pathophysiological alterations start 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 toward 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 (ES) for this intervention [5].

Besides CT, novel neuromodulation techniques, such as transcranial direct-current stimulation (tDCS), have drawn researchers' attention. tDCS is a safe, economical, and noninvasive 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 gamma-aminobutyric acid (GABA) [8]. Accumulation of these transient effects may further induce long-term potentiation (LTP) or depression (LTD), which are the crucial components of neuroplasticity supporting 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 can modify the cerebral physiology underlying cognition, enhancing cognitive performance in individuals with MCI or dementia [13]. Specific neural circuits are activated with increased neuronal firing when cognitive stimuli engage them, 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 supports the role of CT in combating cognitive decline [15, 16], as well as tDCS [17]. However, evidence on the combined effect of both therapies has remained 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.

Materials and Methods

This research adhered to the preferred reporting items for systematic reviews and meta-analyses (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 literature search was conducted across PubMed, Medline, CINAHL and EMBASE databases. 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 and operators: (“tDCS” OR “transcranial direct current stimulation”) AND (“cognitive rehabilitation” OR “cognitive enhancement” OR “cognitive training” OR cognitive therapy”) AND (“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: study subjects had a confirmed diagnosis of MCI

or dementia, the study was an RCT, the treatment group underwent both tDCS and CT and the control group received sham tDCS or no brain stimulation. The exclusion criteria were as follows: Unavailability in full text, non-English publications, studies involving alternative brain stimulation techniques, and 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, details of CT, mode of intervention, time points 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 patients with MCI and dementia [20]. The most conservative outcome was selected in multiple memory-related outcomes across studies [21]. Numerical data, including the Mean±SD and sample size, were treated as continuous variables and processed in RevMan software, version 5.4 to calculate the ES. 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]. ES calculation was expressed as the standardized mean difference with a 95% confidence interval (CI), differentiated into small, medium, and large effects according to Cohen's convention (d=0.2; d=0.5; d=0.8) [23]. The I^2 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. The difference between the two groups at follow-up evaluation relative to baseline was calculated for the long-term effect. Data from the most distant follow-up session were used for this calculation.

Results

Study selection

We identified 542 articles from databases: 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 that were further selected for meta-analysis. The selection process is shown in Figure 1.

Characteristics of the studies

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

The study designs varied, with three studies examining MCI using a parallel design [24-26] 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]. 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 the short-term effects of 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. The cognitive domains assessed varied across studies and the study characteristics are 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

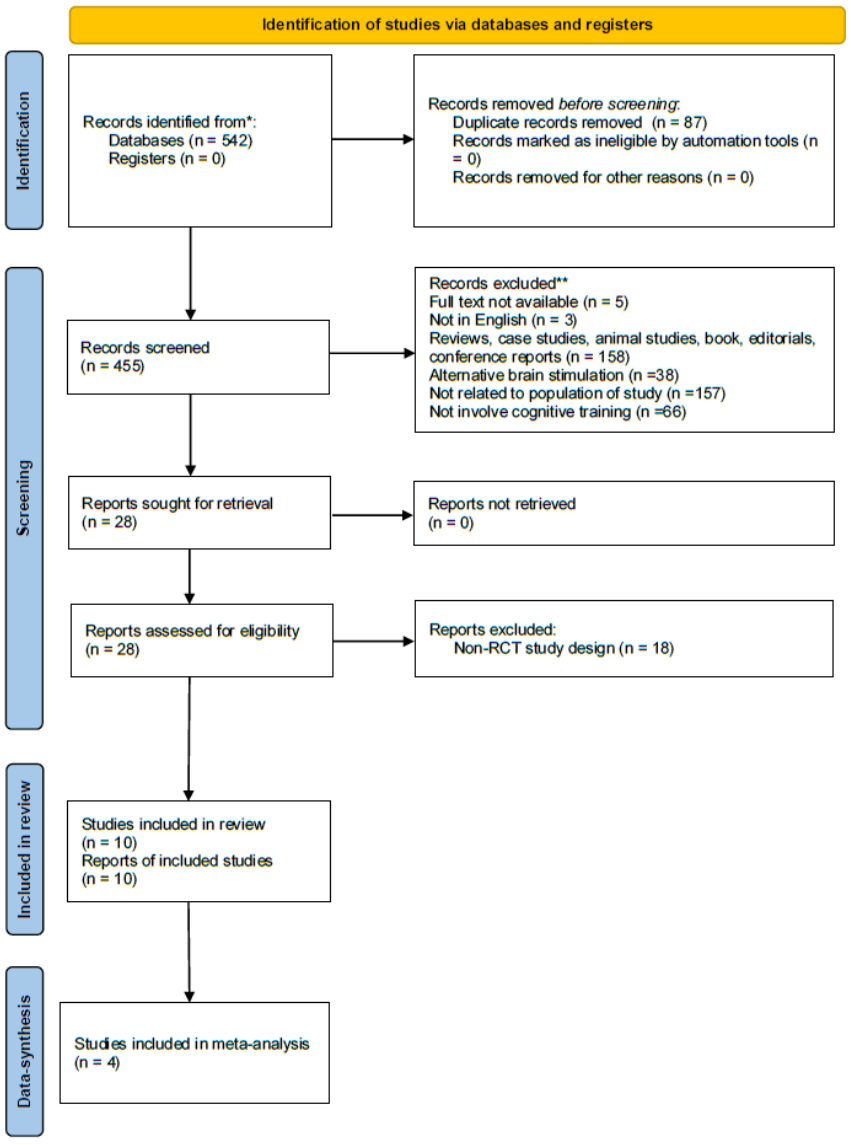

Figure 1. Flowchart of study selection process

RCT: Randomized controlled trial.

JMR

left inferior temporoparietal region [29], medial frontal cortex [28] and right temporoparietal cortex [27], respectively, to enhance multiple cognitive domains. Current intensity ranged from 1 to 2 mA, with 2 mA being the most frequently used. Stimulation duration varied from 10 to 30 minutes, with 20 minutes being the 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 CT

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 CT [24], adopting the strategic memory advanced reasoning training (SMART) protocol, which consisted of 8 hourly group sessions. As previously illustrated in studies that have adopted the same protocol [34, 35], the cognitive strategies featured in SMART are hierarchical, 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, 30-32]. Regarding the timing of CT, 7 studies provided online CT concurrently with tDCS stimulation [26-33], 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].

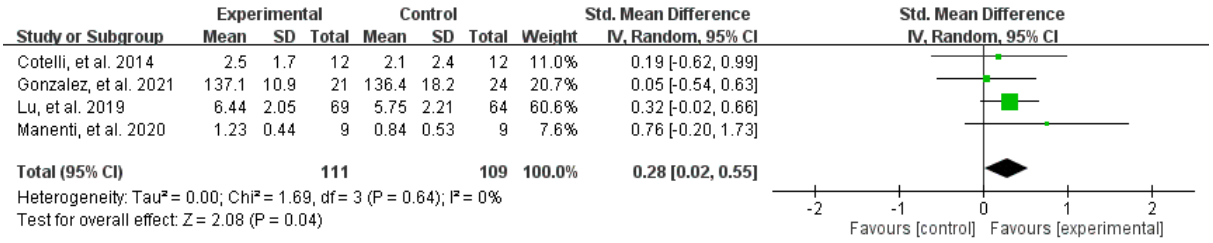

Figure 2. Forest plot showing the coupling effect of tDCS with cognitive training on short-term memory

Significant standardized effect size of 0.28 was found (P=0.04).

Coupling effect of tDCS and CT

In total, 6 studies suggested that coupling tDCS with CT may positively impact cognitive function in individuals with cognitive impairment. Among these studies, 2 focused on subjects with MCI and reported statistically significant improvements in recognition memory [25] and enhanced object location memory training success [27]. In addition, 2 studies targeted individuals with frontotemporal 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, 4 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 an adverse 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. targeted the population with AD and found that both the active tDCS group and the 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 ES for the immediate effect of coupling tDCS with CT in enhancing cognitive function (0.28: 95%CI, 0.02%, 0.55%; P=0.04) (Figure 2). However, the long-term ES was non-significant (0.17: 95% CI, -0.09%, 0.44%; P=0.20). No heterogeneity was found in short-term and long-term effects (Figure 3).

Methodological quality

The assessment of methodological quality using the 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.

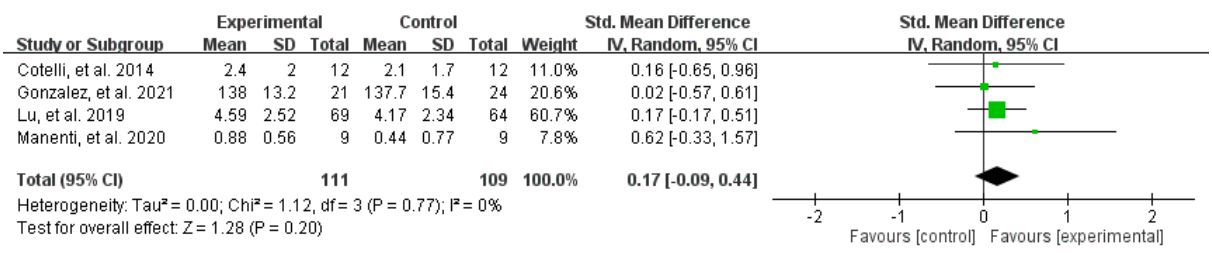

Figure 3. Forest plot showing the coupling effect of tDCS with cognitive training on long-term memory

A non-significant standardized effect size of 0.17 was found (P=0.20).

Table 1. Characteristics of The Reviewed Studies

Study and design (Ref.)	Participants Characteristics	tDCS Montage and Parameters	Detail of Cognitive Training	Mode of Intervention	Outcome Measures	Assessment Sequence	Effect of the Intervention
RCT parallel Rodella et al. (2022) [32]	MCI or Mild AD n=33 (16E; 17C) Mean age, y: E 71.62±5.65 C75.13±4.76	An: L DLPFC Cat: R Deltoid 2 mA 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 working memory and attention/processing speed at both post-Tx and follow-up assessment -The MMSE score was stable at follow-up, while the sham worsened.
RCT parallel Cotelli et al. (2014) [31]	Mild to moderate AD n=36 (12 tDCS+CT [A]; 12 sham+CT [B]; 12 tDCS+motor training [C]) Mean age, y: A 76.6]4.6 B: 74.7]6.1 C: 78.2]5.2	An: L DLPFC Cat: R Deltoid 2 mA 25 min	Individual computerized memory training: Over 10 days of training, 20 face-name pairs were learned Motor training: Walking, coordination, and balance training	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 tDCS +CT and sham+CT groups had significantly improved performances at 2 weeks compared with the tDCS+motor training
RCT parallel Das et al. (2019) [24]	MCI n=22 (12E; 10C) Mean age, y: E62.58]8.43 C63.3]7.38	An: L inferior frontal gyrus Cat: R deltoid 2 mA 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 - The tDCS+CT group increases blood flow to the R medial frontal cortex but blocks the benefit on executive function and episodic memory
RCT parallel Manenti et al. (2020) [25]	MCI n=18 (9E:9C) Mean age, y: E 75.3±4.8 C 75.3±2.2	An: L DLPFC Cat: R supraorbital area 1.5 mA 15 min	Word learning with a 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 tDCS enhanced recognition memory relative to sham

Study and design (Ref.)	Participants Characteristics	tDCS Montage and Parameters	Detail of Cognitive Training	Mode of Intervention	Outcome Measures	Assessment Sequence	Effect of the Intervention
RCT Crossover 2 months washout Roncero et al. (2017) [29]	AD or frontotemporal dementias n=10 (5:5 crossover) Mean age, y: 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 a carer for change in mood, cognition, and day-to-day function	Baseline Immediate Post-Tx 2 weeks follow up	Effective - Significantly more receiving real stimulation rather than sham lasting at least 2 weeks after stimulation - A small increase for untrained picture-naming items and digit span for real than sham
RCT parallel Lu et al. (2019) [30]	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 2 mA 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 sessions 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 enhancement was found across three groups after 4 weeks of intervention. The combined tDCS-WMT group showed significantly greater improvement than the sham in delayed recall and working memory capacity
RCT parallel Inagawa et al. (2019) [33]	mild or major neurocognitive disorders N=22 (7E: 13C) Mean age: E 76.6±5.7 C 76.2±7.7	An: L DLPFC Cat: R supraorbital ridge 2 mA 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 statistically significant improvement in MMSE and ADAS-cog at post Tx and follow-up
RCT Crossover 2 weeks washout Cotelli et al. 2018 [28]	fronto-temporal dementia N=16 (8:8 crossover) Mean age, y: 64.9±8.6	An: Medial frontal cortex Cat: Inion 1.5 mA 10 min	Theory of mind training;	Concurrent tDCS+CT A single session of tDCS A single session of sham	Reaction time and accuracy of the test in each session	Baseline Immediate Post-Tx	Effective - Significant and selective accuracy improvement in the comprehension of communicative intentions after active stimulation was observed

Study and design (Ref.)	Participants Characteristics	tDCS Montage and Parameters	Detail of Cognitive Training	Mode of Intervention	Outcome Measures	Assessment Sequence	Effect of the Intervention
RCT parallel Gonzalez et al. (2021) [26]	MCI n=67 (21 tDCS+ct [A]; 24 sham+ct [B]; 21 ct alone [C]) Mean age, y: A: 69.8±5.3 B:71.0±6.2 C:70.6±5.4	An: L DLPFC Cat: contralateral brachioradialis muscle 1.5 mA 30 min	computerized CT: 'Neuron Up' which consists 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 the nature of the task	Baseline Immediate Post-Tx 6 weeks follow up	Ineffective - tDCS combined with CT was not superior to sham tDCS with CT and CT alone in its effects on domain-specific cognitive outcomes, but it did provide comparatively larger effect sizes
RCT Counterbalanced Crossover 3 months washout de Sousa et al. (2020) [27]	MCI n=18 (8:8) Healthy individuals N=36 (16:16) Mean age, y: MCI: 70±6 Healthy individuals: 69±7	An: R temporal-parietal cortex Cat: L supraorbital area 1 mA 20 min	Visuospatial memory training using object location memory paradigm	Concurrent tDCS+CT daily session in 3 days	CERAD, MMSE, TMT, Digit span, verbal fluency, Regensburg 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 enhanced training success only in MCI patients -Relative performance gain was similar in MCI patients compared to HE under tDCS -It suggested a positive impact on online but a negative effect on offline performance in MCI patients. -Indicated an association between initially low-performers and greater benefit from tDCS

JMR

Abbreviations: AD: Alzheimer disease; ADAS-cog: Alzheimer disease assessment scale–cognitive subscale; ADL: Activities of Daily Living ; AVLT: Auditory verbal learning test; An: Anode; BADA: Battery for analysis of aphasic deficits; BDI: 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; MoCA: Montreal cognitive assessment; MWT: Multiple-choice vocabulary intelligence test; PANAS: Positive and negative affective schedule; RBMT, Rivermead behavioral memory test; RCT, randomized controlled trial; SF-36: Short form 36 health survey questionnaire; TMT: Trail making test; Tx: Treatment; tDCS: Transcranial direct-current stimulation; FAS: fatigue assessment scale has been mentioned in the abbreviation previously.

Journal of Modern Rehabilitation

Table 2. Methodological-quality assessment using physiotherapy evidence database scale

Authors (y)	1	2	3	4	5	6	7	8	9	10	11	Total
Rodella et al. (2022) [32]	1	1	0	1	1	1	1	1	1	1	1	9
Cotelli et al. (2014) [31]	1	1	0	1	1	1	1	1	1	1	1	9
Das et al. (2019) [24]	1	1	1	1	1	1	0	1	1	1	1	8
Manenti et al. (2020) [25]	1	1	1	1	1	1	1	1	1	1	1	10
Roncero et al. (2017) [29]	1	0	0	1	1	1	1	1	1	1	1	8
Lu et al. (2019) [30]	1	1	1	0	1	0	1	1	1	1	1	7
Inagawa et al. (2019) [33]	1	1	0	1	0	0	1	1	1	1	1	7
Cotelli et al. (2018) [28]	1	1	0	1	1	0	1	1	1	1	1	8
Gonzalez et al. (2021) [26]	1	1	1	1	1	0	1	1	1	1	1	9
de Sousa et al. (2020) [27]	1	1	0	1	1	0	0	1	1	1	1	7

Scale of the criterion score: 0: No; 1: Yes.

JMR

Note: The PEDro scale criteria comprise eligibility criteria specified, random allocation, allocation concealment, groups similar at baseline, subject blinding, therapist blinding, assessors blinding, less than 15% dropouts, intention-to-treat analysis, between-group statistical comparisons, and 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. A 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 CT. Monte-Silva et al. illustrated this immediate effect of brain stimulation and 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 some promise, it is imperative to examine its long-term implications thoroughly. Previous research has demonstrated that repeated sessions of tDCS can induce a cumulative after-effect that lasts up to one week or even longer [37, 38], indicating its potential to induce more lasting neuroplastic changes in individuals with impaired cognitive function. Following the principles of LTP, multiple intervention sessions may be necessary to induce more extensive neuroplastic changes. Most studies included in this review employed multiple intervention sessions, ranging from 2 to 20 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. 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 aligns with another study, which provided insights that 20 daily administration of the combined intervention may be more beneficial over only two to three weekly sessions [40]. This emerging evidence suggests 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 the 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. 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 indicate 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., 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 concurrently applying tDCS and CT.

Corroborating this, several studies indicate that a simultaneous application of tDCS and CT could be more beneficial. Roncero et al. found that concurrent interventions led to greater and more persistent cognitive enhancements [29]. Lu et al. revealed that greater improvement was found in domain-specific cognitive function when the two modalities were conducted simultaneously [30] and de Sousa et al. 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, 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 different 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 cognitive impairment level when selecting intervention participants. 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.

Study limitations

Several limitations in the present study warrant acknowledgment. First, only a few articles were included in the study, which may discourage the result of the meta-analysis. Future trials should strive to recruit larger sample sizes to ensure significantly powered results. Second, there were variations 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 study population, 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.

Conclusion

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 few 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 when this manuscript was completed [47], which found that RCT was not included due to the time eligibility criteria.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Study design, data collection, data analysis: Chu Ka Yin; Investigation and assessing the risk of bias: Cheng King Hei; Writing the manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors are grateful to all 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; 24(1):78-87. [DOI:10.1017/S1092852918001347] [PMID]

[2] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: Clinical characterization and outcome. Archives of Neurology. 1999; 56(3):303-8. [DOI:10.1001/archneur.56.3.303] [PMID]

[3] Alzheimer's Disease International (ADI). World alzheimer report 2015: The global impact of dementia: An analysis of prevalence, incidence, cost and trends [Internet]. 2015 [Updated 2024 December 25]. Available from: [Link]

[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] [PMID]

[5] Belleville S. Cognitive training for persons with mild cognitive impairment. International Psychogeriatrics. 2008; 20(1):57-66. [DOI:10.1017/S1041610207006310] [PMID]

[6] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related noninvasive brain stimulation tools. Clinical Neurophysiology. 2016; 127(2):1031-48. [DOI:10.1016/j.clinph.2015.11.012] [PMID]

[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; 1(3):206-23. [DOI:10.1016/j.brs.2008.06.004] [PMID]

[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; 29(16):5202-6. [DOI:10.1523/JNEUROSCI.4432-08.2009] [PMID]

[9] Rozisky JR, Antunes LC, Brietzke AP, de Sousa AC, Caumo W. Transcranial direct current stimulation and neuroplasticity. In: Rogers L, editor. Transcranial direct current stimulation (tDCS): Emerging used, safety and neurobiological effects. New York: Nova Science Publishers Inc; 2015. [Link]

[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; 150:36-41. [DOI:10.1016/j.nlm.2017.11.002] [PMID]

[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; 71(7):493-8. [DOI:10.1212/01.wnl.0000317060.43722.a3] [PMID]

[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; 5(3):223-30. [DOI:10.1016/j.brs.2011.06.006] [PMID]

[13] Kuo MF, Nitsche MA. Effects of transcranial electrical stimulation on cognition. Clinical EEG and Neuroscience. 2012; 43(3):192-9. [DOI:10.1177/1550059412444975] [PMID]

[14] Cruz Gonzalez P, Fong KNK, 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; 2018:5971385. [DOI:10.1155/2018/5971385] [PMID]

[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; 3(3):CD013069. [DOI:10.1002/14651858.CD013069.pub2] [PMID]

[16] Hill NT, 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; 174(4):329-40. [DOI:10.1176/appi.ajp.2016.16030360] [PMID]

[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; 27(4):2000-9. [DOI:10.1038/s41380-022-01444-7] [PMID]

[18] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. 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; 151(4):W65-94. [DOI:10.7326/0003-4819-151-4-200908180-00136] [PMID]

[19] Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of thePEDro scale for rating quality of randomized controlled trials. Physical Therapy. 2003; 83(8):713-21. [DOI:10.1093/ptj/83.8.713] [PMID]

[20] Grober E, Buschke H. Genuine memory deficits in dementia. Developmental Neuropsychology. 1987; 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; 2009. [Link]

[22] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods. 2010; 1(2):97-111. [DOI:10.1002/jrsm.12] [PMID]

[23] Gignac GE, Szodorai ET. Effect size guidelines for individual differences researchers. Personality and Individual Differences. 2016; 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; 13:307. [DOI:10.3389/fnins.2019.00307] [PMID]

[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; 75(7):1403-13. [DOI:10.1093/geronb/gby134] [PMID]

[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; 64(5):101536. [DOI:10.1016/j.rehab.2021.101536] [PMID]

[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; 75(1):223-44. [DOI:10.3233/JAD-191234] [PMID]

[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; 18(6):1065-75. [DOI:10.3758/s13415-018-0622-4] [PMID]

[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. 2017; 3(2):247-53. [DOI:10.1016/j.trci.2017.03.003] [PMID]

[30] Lu H, Chan SSM, Chan WC, Lin C, Cheng CPW, 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; 6(10):1938-48. [DOI:10.1002/acn3.50823] [PMID]

[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 ; 6:38. [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. 2022; 34(1):73-83. [DOI:10.1007/s40520-021-01912-0] [PMID]

[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; 13:273. [DOI:10.3389/fnhum.2019.00273] [PMID]

[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. 2017; 32(5):548-55. [DOI:10.1002/gps.4492] [PMID]

[35] Mudar RA, Nguyen LT, Eroh J, Chiang HS, Rackley A, Chapman SB. Event-related neural oscillation changes following reasoning training in individuals with mild cognitive impairment. Brain Research. 2019; 1704:229-40. [DOI:10.1016/j.brainres.2018.10.017] [PMID]

[36] Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated noninvasive brain stimulation. Brain Stimulation. 2013; 6(3):424-32. [DOI:10.1016/j.brs.2012.04.011] [PMID]

[37] Mondino M, Jardri R, Suaud-Chagny MF, 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. 2016; 42(2):318-26. [DOI:10.1093/schbul/sbv114] [PMID]

[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; 11(1):94-103. [DOI:10.1016/j.brs.2017.09.007] [PMID]

[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; 12(5):1222-8. [DOI:10.1016/j.brs.2019.06.003] [PMID]

[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; 28(4):489-94. [DOI:10.1017/S1092852922000979] [PMID]

[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; 135(4):1154-64. [DOI:10.1093/brain/aws021] [PMID]

[42] Chiang MC, 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; 29(7):2212-24. [DOI:10.1523/JNEUROSCI.4184-08.2009] [PMID]

[43] Yun K, Song IU, Chung YA. Changes in cerebral glucose metabolism after 3 weeks of noninvasive electrical stimulation of mild cognitive impairment patients. Alzheimer's Research & Therapy. 2016; 8(1):49. [DOI:10.1186/s13195-016-0218-6] [PMID]

[44] Suemoto CK, Apolinario D, Nakamura-Palacios EM, Lopes L, 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; 7(2):308-13. [DOI:10.1016/j.brs.2013.10.003] [PMID]

[45] Duff K, Humphreys Clark JD, O'Bryant SE, Mold JW, Schiffer RB, Sutker PB. 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; 23(5):603-12. [DOI:10.1016/j.acn.2008.06.004] [PMID]

[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; 37(9-10):743-53. [DOI:10.1016/0021-9681(84)90043-2] [PMID]

[47] Lau CI, Liu MN, Cheng FY, Wang HC, Walsh V, Liao YY. 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; 21(1):26. [DOI:10.1186/s12984-024-01313-0] [PMID]