Effects of Transcranial Direct Current Stimulation on Memory of Elderly People with Mild Cognitive Impairment or Alzheimer's Disease: A Systematic Review

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ABSTRACT

BACKGROUND: Transcranial direct current stimulation (tDCS) is one of the most studied non-invasive neuromodulation techniques, presenting itself as a promising technique for several pathologies, such as cognitive decline.

OBJECTIVES: The aim of this study was to conduct a systematic review of the effects of tDCS on the memory of elderly people with mild cognitive impairment or Alzheimer's disease, in order to describe the main protocols used, and to investigate the therapeutic effectiveness of this technique.

DATA SOURCES AND METHODS: 869 studies reporting controlled clinical trials were found in the databases PubMed, Web of Science, Lilacs, PsycArticles and Scielo, from which 13 met the expected requirements and were included in the final analysis.

RESULTS: There was a great variability in the stimulation protocols used in the studies; and methodological weaknesses were observed, such as absence of sample size calculation, and of information on effect sizes. Positive effects of tDCS were observed only in five studies, and the combination of stimulation and cognitive training did not seem to potentiate the effects of tDCS.

CONCLUSION: Although tDCS can be considered a technique with important therapeutic potential, more studies are needed to understand the acute effects of tDCS on memory of elderly people and the durability of these effects over time.

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KEYWORDS: Transcranial direct current stimulation, memory, cognitive training, elderly

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Introduction

The human aging process is accompanied by a reduction in cognitive capacity.[1] This reduction can manigest as barely noticeable behavioral alterations, or harm even basic daily activities, resulting in poor performance in several aspects, and affecting the life of the elderly in terms of social, emotional and psychological contexts.

According to Petersen,[2] the reduction in cognitive capacity is characterized by brief forgetfulness, such as loss of objects, forgetting information such as messages and schedules, and difficulty in memorizing situations. This reduction is defined as mild cognitive impairment (MCI), a term used to refer to both an age-related cognitive decline and an intermediate transition condition between normal cognition and dementia.[2,3] Although not characterized as a pathological condition and not classified by the Diagnostic and Statistical Manual of Mental Disorders (DSM - V), MCI is an important marker and signaling factor for possible future cases of dementia.[4] Dementias, on the other hand, are more accentuated cases of cognitive decline and, according to the American Psychiatric Association,[5] they are characterized by mental loss or deterioration, including damage to intellectual, thinking, language, and especially memory skills.

Dementia affects several aspects of cognition, strongly influencing behavior and the ability to perform simple tasks.[6] Currently, it is estimated that 50 million people worldwide have some type of dementia, with about 10 million new cases appearing annually, and Alzheimer's disease (AD) being the most common type and responsible for about 70% of cases.[6]

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The therapeutic potential of neuromodulation techniques based on electrical brain stimulation for cases of cognitive loss, such as MCI or dementia, has been investigated in the literature.[7-9] One of the forms of neuromodulation is the Transcranial Direct Current Stimulation (tDCS), which is a safe and painless low-intensity micro-electric current stimulation technique, whose efficiency for modulating cognitive functions such as attention, language, executive functions and memory has been demonstrated by several authors.[7,9-12] This technique has been shown to be effective when applied to healthy subjects aiming at the maintenance and preservation of cognitive activity, and also to individuals with cognitive decline and cases of dementia.[7,8,13]

Transcranial direct current stimulation aims to facilitate excitability (anodic stimulation) or inhibit (cathodic stimulation) cortical activity in a given area by modulating the resting membrane potential, inducing neural plasticity and modulating cognitive and motor functions associated with the stimulated cortical region.[14] In anodic stimulation, membrane depolarization occurs, which enhances the continuity of transmission of the electrical impulse. In the case of cathodic stimulation, there is a hyperpolarization of the membrane, which allows greater inhibition of cell activity. It alone does not generate the action potential due to its low intensity, but it can facilitate the conductivity of the ion channels so that neuromodulation/plasticity may occur.[15]

Another intervention that can help individuals who have some form of cognitive decline is cognitive training. The goal of this type of intervention is the improvement or preservation of specific cognitive domains, such as attention, memory and executive functions.[15] Studies show that this type of technique benefits healthy elderly people with MCI and also individuals with AD.[16-19] Many studies that use tDCS also use cognitive training as a complementary technique, in an attempt to achieve greater therapeutic efficacy.[20-22]

Transcranial direct current stimulation, combined or not with cognitive training, has been one of the most widespread and studied neuromodulation techniques, mainly due to its low cost and easy handling. The effects of tDCS on global and specific cognitive domains in elderly people have been already investigated in systematic literature reviews and meta analysis studies, with two studies reporting immediate and positive effects of tDCS,[23,24] and one showing inconclusive results.[25] According to the authors, the plurality in the use of techniques that involve tDCS, both in the type of assessed cognitive function and in the stimulation protocols compromises the understanding of the effects of this type of intervention. We hereby performed a systematic literature review on the effectiveness of tDCS on memory impairments in elderly people with MCI or AD. The present study expands on previous publications by investigating the effects of tDCS on specific memory domains, by presenting a risk of bias assessment and an extensive mapping of the protocols used with elderly people. This review was aimed to assist professionals and researchers in the area, with information that may be used to guide and advise clinical practice.

Method

This study is a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA[26] and was registered on the International Prospective Register of Systematic Reviews – PROSPERO platform (CRD-42020200573).

Articles search

The search was performed in the databases of Pubmed/Medline, Web of Science, Scientific Electronic Library Online (Scielo), Latin American and Caribbean Health Sciences Literature (Lilacs), and PsycArticles (APA), between July and August 2020, by two evaluators. The search terms were derived from the consultations of the Health Sciences Descriptors (DeCS) and Medicine's Controlled Vocabulary Thesaurus (MeSH). The selected keywords were: "transcranial direct-current stimulation OR tDCS" AND "memory" AND "mild cognitive impairment OR Alzheimer's disease".

Eligibility criteria

Controlled clinical trials written in the English language, published from 2010 onwards, were included in the research. The studies had to have investigated the effects of tDCS on the memory of elderly people with cognitive decline or Alzheimer's disease in comparison with sham tDCS applied in separate matched control groups. tDCS or sham tDCS could have been applied alone or combined with cognitive training. Participants could not have comorbidities other than MCI or AD. Diagnostic methods and the outcomes of each study are described in Table 1. Editorial letters, reviews, duplicates or documents that did not meet the objectives or that had a medium or high risk of methodological bias following the quality criteria presented in the risk-of-bias tool (Rob-2) were not included in this review.

Methodological analysis

The Rayyan[39] platform is an open source web application designed to manage and assist authors in systematic reviews. Through this platform, the screening and selection of articles from the abstracts was carried out by two independent researchers in a shielded manner. In cases of conflict, a third evaluator performed the tiebreaker according to the eligibility criteria. With a Kappa Reliability Index of .73, the results showed substantial reliability among evaluators. After selecting the articles, the risk-of-bias tool (Rob-2)[40] was used to assess the methodological quality of the studies. Rob-2 categorizes low risk of bias, high risk of bias studies or studies with caveats.

Data extraction

For data extraction, the Cochrane Collecting data tool - form for RCTs and non-RCTs[40] was used. Study characteristics were

Table 1. Diagnostic methods, screening instruments and outcomes.

STUDY	DIAGNOSTIC METHODS AND SCREENING INSTRUMENTS	OUTCOMES
Im et al[27]	Clinical Dementia Rating (CDR), DSM V, and the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) diganostic criteria	Cognitive performance and regional cerebral metabolic rate for glucose (rCMRglc)
Das et al[28]	Petersen's or Alzheimer's disease neuroimaging initiative (ADNI) diagnostic criteria	Cognitive performance
Cotelli et al[29]	NINCDS-ADRDA criteria	Cognitive performance
Khedr et al[30]	NINCDS-ADRDA criteria	Cognitive performance, Alzheimer's disease symptoms and neurophysiological measures
Bystad[31]	NINCDS-ADRDA criteria	Cognitive performance
Yun et al[32]	Petersen's criteria	Cognitive performance and cerebral glucose metabolism
Lu et al[33]	DSM-5 criteria, CDR, and the Cantonese Mini Mental State Examination (CMMSE)	Cognitive performance
Fileccia et al[34]	Medical diagnostic	Cognitive performance
Khedr et al[35]	NINCDS-ADRDA criteria	Cognitive performance, tau protein (TAU) levels, amyloid β 1-42 (Aβ 1-42) levels, and lipid peroxidase levels
Martin et al[36]	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Wechsler Test of Adult Reading (WTAR), and the Bayer-Instrumental Activities of Daily Living (Bayer-ADL)	Cognitive performance
Boggio et al[8]	NINCDS-ADRDA and DSM-IV criteria	Cognitive performance
Manor et al[37]	Trail Making Test Part A and B	Cognitive and mobility performance
Manenti et al[38]	Mini Mental State Examination (MMSE) and Everyday Memory Questionnaire (EMQ)	Cognitive performance

described, such as: objectives, bias, sample size, effect size, participant profile, randomization, blinding, intervention characteristics (assembly, electrode size, current and density, stimulated memory domain, effects, assessment tools, stimulation time, co-interventions) and results.

Results

Through the search strategies carried out in the databases, 869 studies were found, of which 62 duplicates were removed. 788 studies were excluded by type of publication, study design, type of intervention, language, and population. After analyzing the titles and abstracts of the studies, 19 articles were included by consensus among the evaluators for the analysis of methodological quality. In the methodological assessment carried out by Rob-2,[40] 13 articles had low risk of bias and were included for the final analysis, and 6 articles were excluded from the analysis, 2 with medium risk of bias and 4 with high risk of bias (Figure 1).

All reviewed studies[8,27-38] performed controlled clinical trials. The sample calculation was not performed in nine.[8,28-32,35,37,38] Random allocation occurred in all thirteen studies,[8,27-38] and all thirteen studies used sham stimulation for the control group. In twelve studies,[8,27-33,35-38] the researchers who performed the participant assessments were blinded, and in eight studies,[27-33,36] the researchers who performed the interventions were blinded.

Only four studies[33,36-38] used the calculation of the effect size to assess the effectiveness of the intervention. This measure showed a low effect size in one study[33] and a high effect size in the other three studies.[36-38] Finally, only two studies[33,36] met all the criteria used to assess the methodological quality and strength of evidence.

tDCS protocols and uses

Anodic stimulation was used in all studies included in this review. The intensity of 2 mA was the most common, having been used in twelve studies.[8,27-37] In one study[38] the amperage was 1.5 mA (Table 2).

Regarding the cortical regions that were stimulated, eigth studies[27,29,30,32,34,36-38] applied the anode in the area of the left dorsolateral prefrontal cortex (DLPFC) identified in the 10/20

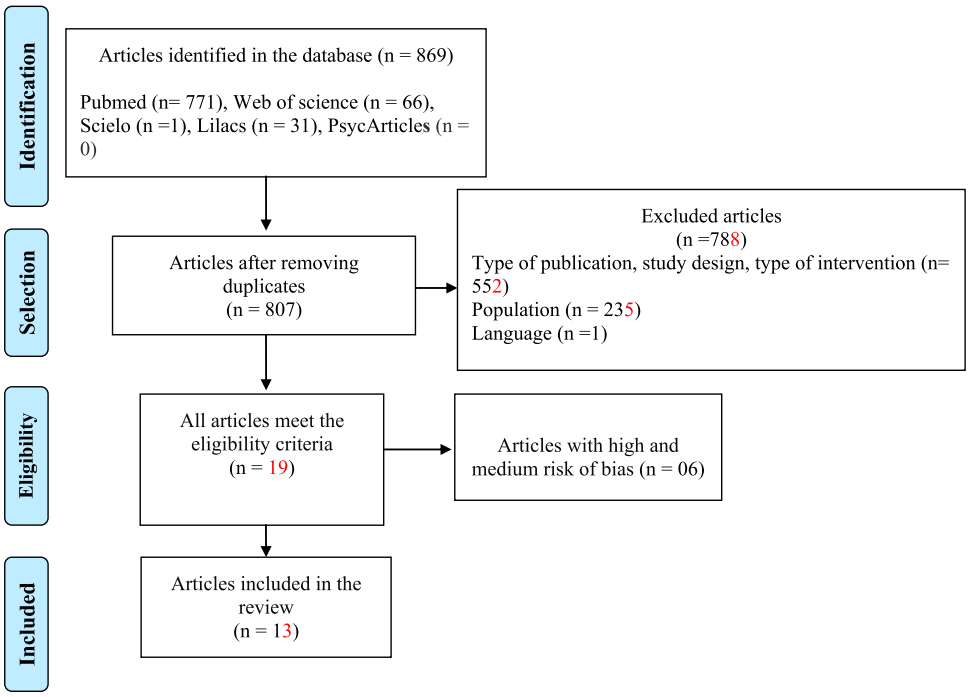

Figure 1. PRISMA flowchart. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, www.prisma-statement.org

system as F3; one study applied the anode in the area located between the intersection of T3-F3 and F7-C3, and the midpoint between F7-F3[28], and two studies[31,33] in the temporal region T3. In two studies, stimulation with two anode electrodes was performed in the regions T3 and T4[8] and in T3 and P3[35] (Table 2).

Concerning the electrode assembly, bipolar assembly was the most common, being reported in eightnine studies.[27,28,30-32,36-38] In this setup, both electrodes were placed over the brain and passed the same current on the anode and cathode.[14] In the remaining fivefour[8,29,33-35] studies, the monopolar assembly was used, when one electrode was placed on the scalp and the other one was placed extraencephalically, such as on the shoulder or deltoid muscle (Table 2). In short, bipolar anodic stimulation with an intensity of 2 mA, applied over the DLPFC (F3) region, was the most frequent in the analyzed studies, as shown in Table 2.

tDCS and cognitive training

Four studies[28,29,33,36] performed tDCS interventions combined with cognitive training. Of these, two[29,36] performed cognitive training at the same time (online) of the tDCS, two[28,33] immediately after the (offline) application of the tDCS. In other studies[8,27,30-32,34,35,37,38], tDCS was applied without any additional intervention.

When present, cognitive training was focused on memory and reasoning strategies[28]; face recognition[29]; short-term memorization[33]; short-term memorization and processing speed.[36] In the studies carried out by Cotelli et al,[29] Das et al,[28] Lu et al[33] and Martin et al,[36] positive effects of CT associated with memory were observed. However, when CT was combined with tDCS, the effects were not superior when compared to CT or tDCS applied alone.

Effects of tDCS on episodic memory. Episodic memory is defined as the ability to recall personal experiences or events.[41] From the selected articles, tree studies,[28,34,38] evaluated the effects of tDCS on episodic memory in patients with MCI. In only two studies[34,38] the therapeutic effects of tDCS were observed on this type of memory.

tDCS without cognitive training in patients with MCI. Anodic stimulation resulted in a significant improvement in the performance of participants in the RAVLT subtest, in the immediate recall part, and in the Brief Mental Deterioration Battery (BMDB), in the study by Fileccia et al[34]. However, in the episodic visual memory (delayed recall) subtest of the RAVLT, no significant differences were found between the tDCS and sham stimulation groups.[34]

Similarly, in the study by Manenti et al,[38] benefits of anodic tDCS were observed on episodic memory in patients with MCI. In this study, one of the evaluations consisted of the Word List test, presented on different days. There were differences in the number of words correctly recalled, with the group that received anodic stimulation showing better performance. This difference was not observed in the post-treatment (3 days), but only in the follow-up that took place after 30 days (Table 3).

Table 2. tDCS protocols.

STUDY	GROUPS	INTENSITY (MA)	ANODE	CATHODE	ONLINE/ OFFLINE TRAINING	ELECTRODES' SIZE	ASSEMBLY	DURATION, FREQUENCY AND TOTAL TIME OF SESSIONS	MAIN FINDINGS
Lu et al[33]	AS + CT FS + CT AS + CT	2.0	T3	Contralateral upper limb	Offline	5 × 7 cm	Monopolar	20 min, 3 x per week, 12 sessions	• All groups showed improvements in the N-Back task compared to baseline, with no difference between interventions
Fileccia et al[34]	AS FS	2.0	F3	Deltoid Muscle	N/A	7 × 5 cm (anode) 7 × 6 cm (cathode)	Monopolar	20 min, 5 x per week, 20 sessions	• The group that received AS showed improvements in the RAVLT: immediate recall, and in the brief mental deterioration battery compared to baseline, with. no difference between interventions
Khedr et al[35]	AS FS	2.0	T3-P3 T4-P4	Deltoid Muscle	N/A	35 cm^2	Monopolar	20 min (T3), 20 min (T4), 5 x per week, 10 sessions	• The group that received AS showed improvements in the Watch and MOCA tests compared to baseline and FS
Martin et al[36]	AS + CT FS + CT	2.0	F3	F8	Online	5 X 7 cm	Bipolar	30 min, 3 x per week, 15 sessions	• All groups showed improvements in the CVLT-II test at the post test, and improvements in the PAL and RVIP tests, in the follow-up (3 months) compared to baseline, with no difference between interventions
Im et al[27]	AS FS	2.0	F3	F4	N/A	6 cm in diameter	Bipolar	30 min, everyday, 6 months	• No effects of interventions related to memory were observed
Das et al[28]	AS + CT FS +CT	2.0	Center of the line connecting the intersection of T3-F3 and F7-C3, and the midpoint between F7-F3 on the left side	Contralateral shoulder	Offline	3 x 5 cm^2	Monopolar	20 min, 2 x per week, 8 sessions	• The group that received FS + CT showed improvements in the TOSL test compared to baseline. The group that received AS showed a worsening in the same test.
Cotelli et al[29]	AS + CT FS +CT AS +cCT	2.0	F3	Deltoid Muscle	Online	5 × 5 cm (scalp) 6 × 10 cm (deltoid)	Monopolar	25 min, 5 x per week, 10 sessions	• The groups that received AS + CT or FS + CT showed improvements in the FNAT test compared to baseline. No improvements were observed in the group that received AS +cCT.
Manenti et al[38]	AS FS	1.5	F3	Fp2	N/A	7 X 5 cm	Bipolar	15 min, 1 session	• The group that received AS showed improvements in the recognition task compared to baseline and FS

(Continued)

Table 2. Continued.

STUDY	GROUPS	INTENSITY (MA)	ANODE	CATHODE	ONLINE/ OFFLINE TRAINING	ELECTRODES' SIZE	ASSEMBLY	DURATION, FREQUENCY AND TOTAL TIME OF SESSIONS	MAIN FINDINGS
Boggio et al[8]	AS FS	2.0	T3-T4	Deltoid Muscle	N/A	35 cm^2 × (scalp) 64 cm^2 (deltoid)	Monopolar	30 min, 1 x per day, 5 sessions	• The group that received AS showed improvements in the VRT test compared to baseline and FS
Manor et al[37]	AS FS	2.0	F3	Fp2	N/A	35 cm^2	Bipolar	20 min, 5 x per week, 10 sessions	• The group that received AS showed improvements in the MOCA test, EF sub-item compared to baseline and FS
Yun et al[32]	AS FS	2.0	F3	F4	N/A	5 × 5 cm	Bipolar	30 min, 3 x per week, 9 sessions	• No effects of interventions related to memory were observed
Khedr et al[30]	AS CS FS	2.0	F3 (AS), Fp2 (CS)	Fp2 (AS), F3 (CS)	N/A	24 cm^2 (F3) 100 cm^2 (Fp2)	Bipolar	25 min, 10 days, 10 sessions	• The group that received CS, showed improvements in the WAIS compared to baseline and FS. No improvements were observed in the group that received AS
Bystad[31]	AS FS	2.0	T3	Fp2	N/A	35 cm^2	Bipolar	30 min, 6 sessions	• No effects of interventions related to memory were observed

AS: Anodic Stimulation; FS: Fictitious Stimulation; CT: Cognitive Training; cCT : control CognitiveTraining; N/A: Not applicable; EF: Executive Functions. C.S: Cathodal Stimulation;. RAVLT: Rey Auditory Verbal Learning Test; MOCA: Montreal Cognitive Assessment; CVLT - II: California Verbal Learning Task 2nd Edition; PAL: Paired Associates Learning; RVIP: Rapid Visual Information Processing; TOSL: Test of Strategic Learning; FNAT: Face Name Association task; VRT: Visual Recognition task; WAIS: Wechsler Adult Intelligence scale.

tDCS combined with cognitive training in patients with MCI. Das et al[28] used anodic stimulation combined with cognitive training focused on reasoning and memory strategies. The training took place in groups immediately after the tDCS sessions (off-line), lasting one hour. tDCS did not demonstrate episodic memory-related benefits at post-assessment or at follow-up (3 months, Table 3). On the contrary, the group of participants with MCI who received the sham stimulation and cognitive training showed better results in the assessment of episodic memory through the Selective Auditory verbal learning task (AVLT) and the TOSL. Meanwhile, the group that received anodic tDCS combined with cognitive training had worse post-treatment outcomes, indicating that tDCS had the opposite effect of "blocking" cognitive gains (Table 2).

Effects of tDCS on semantic memory

Semantic memory is defined as the ability to remember or learn new words or concepts.[32] Of the selected articles, three studies[27,31,36] evaluated the effects of tDCS on the semantic memory of patients with MCI or AD, and the benefits were observed only in the study by Martin et al.[36]

tDCS in AD patients without cognitive training. Studies carried out by Bystad[31] and Jamie Im et al[27] investigated the effects of tDCS on the semantic memory of patients with AD. In none of the studies, significant results were observed regarding the therapeutic effects of tDCS on this type of memory. In general, the results presented by the authors were not conclusive for the idea that tDCS could improve the semantic memory of elderly people with MCI or AD (Table 2).

tDCS combined with cognitive training in patients with MCI. With regard to the effects of tDCS on the semantic memory of patients with MCI, the study by Martin et al[36] applied anodic stimulation combined with cognitive training focused on memory strategies, such as categorization and organization of information. The combined application took place in the online format, which corresponds to the application of stimulation at the same time as the cognitive training. Improvement was observed in the groups that received anodic tDCS combined with CT and sham tDCS combined with CT, wih no differences between groups.[36]

Effects of tDCS on short-term memory

Short-term memory is defined as the ability to store, process and manipulate information for a short period of time: milliseconds, seconds or minutes.[32] From the reviewed articles, four studies[8,30,33,36] evaluated the effects of tDCS on short-term memory in elderly people with MCI or AD.

tDCS without cognitive training in AD patients. Khedr et al[30] evaluated the effects of anodic and cathodic stimulation on short-term memory performance in AD patients. In the WAIS, Arithmetic and Digit Span subtest scores, which specifically assesses short-term memory capacity, only the group that received cathodic stimulation showed improvement. These benefits persisted for up to 2 months after the intervention.

In the study by Boggio et al[8] the anodic tDCS, applied simultaneously in the T3 and T4 regions, with the extra-encephalic cathode, produced better performance in the short-term memory of elderly people with AD. This improvement was observed in the VR task (Table 2). No benefits in the VR task were observed in the follow-up performed one week and one month after the interventions (Table 3).

tDCS combined with cognitive training in patients with MCI. In the study carried out by Lu et al,[33] anodic stimulation was applied in the same group that performed cognitive training (offline) focused on short-term memory. Participants were divided into three groups: anodic tDCS with cognitive training, sham tDCS with cognitive training, anodic tDCS with control cognitive training. All groups showed improvements in the N-back task after treatment, but there was no difference between them. Likewise, in the specific assessment of working memory capacity, all groups showed improvements after the intervention. The tDCS group combined with cognitive training showed superior performance in this assessment, but with no significant difference when compared to the other groups. In the follow-up performed one and two months after the interventions, the improvements were still visible and superior when compared to the baseline (Table 3). The results suggest that tDCS combined with cognitive training or in isolation, as well as cognitive training alone, can benefit the short-term memory of elderly people with MCI.

In addition to assessing semantic memory, the study by Martin et al[36] also investigated the effects of anodic tDCS on short-term memory in elderly people with MCI. In the follow-up, carried out three months after the intervention, both groups, anodic tDCS with cognitive training and sham tDCS with cognitive training, showed improvements in the performance of the PAL and RVIP tests, which assess visual memory and working memory respectively, with no significant differences between groups. As in the study by Martin et al[36] the study by Lu et al[33] points out that tDCS and CT can benefit short-term memory in elderly people with MCI, but tDCS combined with cognitive training does not seem to be superior to cognitive training applied alone (Table 2).

Effects of tDCS on associative memory

Associative memory is defined as the ability to learn and remember information that was not previously related.[41] Only the study by Cotelli et al[29] evaluated the effects of tDCS on this type of memory. In the intervention, the anodic tDCS was applied together with the cognitive training aimed at recognizing faces.

Improvements were observed in the groups that received anodic stimulation with cognitive training and sham stimulation with cognitive training, but there was no difference between them. In the group that received anodic stimulation and control

Table 3. Follow-ups and long-term effects of interventions.

STUDY	POST-TEST FINDINGS	FOLLOW UP TIME	FOLLOW UP FINDINGS
Manor et al[37]	No effects on memory	Two weeks	No effects on memory
Manenti et al[38]	No effects on memory	Two weeks	Improvements in the Word List test
Boggio et al[8]	Improvement in the VRT task	One week and one month	No effects on memory
Khedr et al[30]	Improvement in the WAIS-III performance IQ score	One and two months	Improvement persisted in both follow-up assessments
Lu et al[33]	Improvement in the N-back task	One and two months	Improvement persisted in both follow-up assessments
Martin et al[36]	Improvements in the CVLT II task	Three months	Improvement in the CVLT II task persisted in the follow-up, when improvements in the PAL and RVPI tasks were also observed
Das et al[28]	No effects on memory	Three months	No effects on memory
Cotelli et al[29]	Improvement in the FNAT task	Three and six months	Improvement persisted in the follow-up performed 3 months after the intervention

cognitive training, no benefits were observed. The improvement in the first two groups was observed in the FNAT both at post-treatment and at the 3-month follow-up, but not at the 6-month follow-up, indicating that the effects of the intervention have limited durability. In the other tests performed (RAVLT and Rivermead Behavioral Memory test) no improvements were found.

These results indicate that tDCS combined with cognitive training or cognitive training applied alone can benefit the associative memory of elderly people with AD, but tDCS applied alone does not seem to be effective to improve this type of memory in the AD context.

Effects of tDCS on cognitive screening tests

According to Martins et al[36] screening tests are an important tool for detecting and monitoring cognitive declines. These tests are used to assess cognitive functions such as attention, memory, language, time-spatial orientation and executive functions. However, they do not specifically assess these constructs, they only result in general scores on one or more cognitive functions, being useful both for clinical practice and for empirical research. From the analyzed articles, three studies performed cognitive assessments only through screening tests, not using specific tests for the types of memory.

The study by Khedr et al[35] investigated the effects of anodic-monopolar stimulation without cognitive training in patients with Alzheimer's, and the results showed significant improvements in the MOCA and Clock tests. It is important to note that the study by Khedr et al[35] applied bilateral anodic stimulation in the T3-P3/T4-P4 regions. Only this study and the one by Boggio et al[8] performed double anodic stimulation with a cathode applied extracephalic (Table 2).

The study by Yun et al[32] used anodic stimulation in patients with MCI without cognitive training and showed improvements in the assessment of memory perception through the Multifactorial Memory Questionnaire (MMQ) tool. However, the MMSE, the CDR, the Hopkins Verbal Learning Test (HVLT), and the Rey Complex Figures Tests (RCFT) that served as baseline measures were not presented or discussed in the results.

Also regarding the positive effects of tDCS on screening tests, Manor et al[37] demonstrated that anodic stimulation, without cognitive training, benefits elderly people with MCI in the MOCA test - visuospatial executive function domain score, but these benefits did not persist in the follow-up performed two weeks after the intervention.

Follow-ups and durability of the tDCS Effects

Information about the durability of the tDCS effects is essential for the development and improvement of stimulation protocols, as it will help to define whether interventions need to be continuous and/or repeated over time. The duration of observed effects was assessed through follow-up in eight studies,[8,28-30,33,36-38] of which only five[29,30,33,36,38] reported significant long-term effects of the interventions. In general, this assessment consisted of reapplication of tests performed in the previous study evaluations. As shown in Table 3, the time interval between intervention, post-intervention assessment, and follow-up assessment varied between studies, as did the number of follow-up assessments.

Discussion

This systematic review evaluated the effects of tDCS on different memory domains of elderly people with MCI or AD, as well as described the tDCS protocols used in this population. The 13 articles selected from the search in the databases compared the effects of tDCS alone or combined with cognitive training with the effects of sham stimulation in separate control groups.

tDCS protocols

Anodic stimulation, with a current of 2 mA, was reported in most studies; however, the position and size of the electrodes varied greatly. The plurality in the stimulation protocols compromises the interpretation of the findings, and has already been described as an important limitation for the generalizability of the tDCS effects in previous literature reviews.[25]

Regarding the region of interest, there was a higher incidence of application in F3, with anodic tDCS in this area resulting in positive effects on the memory of the elderly.[29,36,38] On the other hand, the results presented by Cotelli et al,[29] Manenti et al,[38] Martin et al[36] have methodological weaknesses that limit the interpretation of these findings. In the studies by Martin et al[36] and Cotelli et al,[29] it is not possible to know whether the effects found in the experimental group were caused by tDCS or by the CT, as the designs of these studies do not allow for an isolated assessment of the effects of tDCS. In both studies, the effects of tDCS combined with CT were similar to those of CT combined with sham tDCS. Although these results are not conclusive, they indicate that the effects may be attributable to CT and not necessarily to tDCS, and/or that tDCS applied alone does not result in positive effects.

Another study that demonstrated positive effects of tDCS applied in F3 was that of Manenti et al,[38] whose results contrast with what has been reported in the literature on the durability of the tDCS effect. While it has been shown that the effects of a three-minute tDCS session can last only a few minutes after the session ends, Nitsche et al[14] and Manenti et al[38] reported improvements in the Word List test only at the follow-up, performed 30 days after the stimulation session. In addition, in this study, the MMSE and RAVLT were applied before the interventions, but not after. The RAVLT assesses the performance of episodic memory[42] and could have been useful to inform about the effects of tDCS specifically on this type of memory. The F3 area was also chosen for the application of tDCS by Manor et al[37] and Yun et al[32] However, the results of these studies did not demonstrate benefits of stimulation on the memory of the participants.

Other common area of stimulation, in the reviewed studies, was the T3[31] region that did not result in benefits on the participants' memory. On the other hand, bilateral anodic stimulation applied at T3-P3 or T4-P4, ie to homologous structures in both hemispheres, seems to be an important condition for the effects of tDCS to be observed on memory. Beneficial effects of this type of stimulation were observed by Khedr et al[35] and are believed to be due to the congruent and facilitatory effects that bilateral stimulation may have in integrative tasks that require both hemispheres to contribute to accomplish a task.[43]

Another important aspect regarding the tDCS protocols concerns the time and number of stimulation sessions. The application time in each tDCS session ranged between 20 and 30 minutes in most studies, which is the common recommendation in the literature.[44] However, the frequency with which stimulation was applied over time demonstrated once again the plurality in the intervention protocols. The studies performed applications once, twice, three or five times a week (Table 2), and it was not possible to infer that a higher weekly frequency of application of the tDCS promotes better effects on memories.

The total intervention time also varied considerably in the studies, with the minimum being just 15 minutes[38] and the maximum being 6 months.[27] This was another aspect that evidenced the plurality of protocols used, and did not seem to be associated with the observed effects.

tDCS and cognitive training

The combined use of tDCS with cognitive training (CT) has been recommended in the literature, however, the results of the effects of this combination were ambiguous. Based on the analyzed studies, it was not possible to conclude that cognitive training is capable of enhancing the effects of transcranial stimulation, nor vice versa.[28,29,33,36] Also, no significant differences were observed with regard to the condition when the CT was performed, whether in online[29,36] or offline[28,33] format. It is important to emphasize that the benefits' assessment of the combined use of CT and tDCS was compromised by methodological limitations, such as those observed in the studies by Martin et al[36] and Cotelli et al[29]

An important change to be tested in future studies is the combination of neuropsychological rehabilitation techniques with tDCS, as an alternative to cognitive training. Neuropsychological rehabilitation has been shown to be effective in the treatment of several neurological conditions. It has been demonstrated that neuropsychological rehabilitation effectively improves cognitive functions (working memory, prospective memory, attention and visuospatial functioning) of patients with traumatic brain injury or stroke.[45] In the context of dementia, compensatory and restorative rehabilitation techniques have effectively improved cognitive functions, including the memory of AD patients.[16] This results suggests that the combination of neuropsychological rehabilitation with tDCS may result in promising effects in elderly people with cognitive impairment.

CT is focused on the performance of specific tasks, and improvements are observed in tasks or tests that are not always generalizable to the individual's real life context. On the other

hand, in the neuropsychological rehabilitation process, the stimulation of cognitive functions is based on the work, educational and daily life activities' performance, as from activities that are part or complements of the elderly's life, which may have superior results than those of the CT.[16,46]

Effects of tDCS on memory

Memory benefits associated with the use of tDCS combined or not with CT were reported in eight studies in the post-intervention evaluation. However, a more detailed analysis of these studies revealed that in only five of them,[8,27,30,34,35] it is possible to conclude that the effects on memory were caused by the type of intervention performed.

These studies consisted of randomized clinical trials that had a group that was submitted only to tDCS or tDCS combined with the CT control, and whose results showed superior benefits compared to the other groups. An important limitation observed in two of these studies[27,35] concerns the fact that only screening tests (MMSE, MOCA, clock test) were used to assess the effects of the interventions. Specific tests to assess memory or other cognitive functions could have been used, and would have provided more accurate information about the type of memory benefited by tDCS.

Specific tests can also be important in cases where there is a contradiction among the results observed in the screening tests, as occurred in the study by Fileccia et al.[34] Although tDCS participants in that study showed improvements in the short battery of mental deterioration, no improvements were seen in the MMSE or the delayed recall subtest of the RAVLT. Similar results were observed in the study by Jamie Im et al,[27] in which the participants who received tDCS showed improvements in the screening test, but not in the test that specifically assessed semantic and visuospatial memory. These results suggest that the improvement detected by the screening evaluation must be associated with another cognitive function not evaluated by the specific tests.

It is important to note that studies such as Lu et al[33] and Khedr et al[35] suggest the potential need for extended periods of intervention with daily application of tDCS to achieve benefits on memory, however the results obtained by Im et al[27] after 6 months of intervention, did not show a positive effect of tDCS on semantic memory. A particularity of this study is related to the fact that the application of the tDCS took place at home, and was therefore subject to the influence of external factors to the study, such as application times, carrying out parallel activities, etc. In addition, it has been shown that the excitatory and inhibitory effects associated with electrode polarity (anode and cathode) can be altered by application time, current intensity and individual and collective characteristics (networks) of the cortical areas in which the current is applied,[45] which could also explain why the prolonged use of tDCS in this study did not generate the expected excitatory effects over time.

Although the literature indicates that anodic stimulation is the best way to generate excitatory effects and stimulate memory, there is still no consensus regarding the polarity of stimulation.[10,30] In the study by Khedr et al,[30] only cathodic stimulation was associated with benefits for the participants' memory, which is in agreement with other studies that have shown that cathodic stimulation can also fulfill this role.[43,47,48]. Furthermore, there is evidence that stimulation with anodic or cathodic current of 2 mA would be able to promote cortical excitability.[14,48] Further studies on the mechanisms underlying the action of tDCS on cortical activity are therefore needed in order to elucidate the specificities associated with each polarity.

Methodological limitations

In general, important methodological limitations were observed in the reviewed studies. The absence of sample calculation was verified in nine articles; and small samples size, less than 24 participants, prevailed in most studies. Such weaknesses reduce the external validity of the studies, and limit the possibility of performing a meta-analysis. In addition, only four studies provided information on the effect size,[33,36-38] which is the most reliable measure for evaluating the effectiveness of an intervention.

The methodological analysis revealed that the studies carried out so far are not sufficient to reach a scientific consensus on the action of tDCS in the memory of patients with MCI or AD. It is necessary that in future studies, researchers are careful with the design used and are aware of the methodological criteria that will allow the generalization of the study's findings.

Final Considerations

The use of tDCS showed great variability in the reviewed studies, with regard to the protocols and reported results. Although tDCS can be considered a technique with important therapeutic potential, the results do not allow us to conclude about the effectiveness of the technique for alleviating memory impairment in elderly people with MCI or AD. Future studies should investigate the acute effects of tDCS and the durability of these effects over time. Finally, the study of neural mechanisms related to tDCS, through neuroimaging techniques or electroencephalographic recording, may contribute to the standardization and refinement of stimulation protocols.

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