Effects of transcranial direct current stimulation on working memory in healthy older adults: a systematic review

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Abstract:

This mini systematic review aimed to investigate the effects of transcranial direct current stimulation (tDCS) on working memory in older adults without cognitive impairment. The search was carried out in three different databases for all human trials published from 2005 to 2015, assessing the effects of tDCS on working memory in healthy older adults. The screening was conducted by two independent reviewers. Four studies were included. All studies combined anodal tDCS (applied to pre-frontal or parietal cortex) with working memory training. Anodal tDCS seems to be able to modulate working memory performance. Nonetheless, there is evidence that suggests that variables, such as level of education, working memory task and time of assessment can moderate the effect. Recommendations for futures studies are also provided.

INTRODUCTION

Aging is associated with structural and functional loss, affecting a wide range of cognitive skills, such as memory, language and executive function (1). These changes can have a negative impact on activities of daily living and quality of life and may result in disorders such as depression, mild cognitive impairment and dementia (e.g.: Alzheimer's disease and fronto-temporal dementia), ultimately becoming a significant burden on health-care systems (2). Hence, growing interest emerges in an attempt to promote healthy aging, optimizing cognitive skills and remediating cognitive impairment.

Among the cognitive skills affected by the aging process, working memory (WM) stands out due its notable decline throughout the individual's lifespan. The decline begins in the mid-20s and concerns both visuospatial and verbal aspects of WM (3). WM is a mental workspace in which information is maintained and processed over a short period of time while a task is being performed (4). WM is related to several higher order cognitive functions such as reading (5), mathematics (6), intelligence (7-9), prospective memory

(10, 11), processing speed (12), attention (13), perceptual organization (14) and general language (15).

The mechanisms underlying WM decline are unclear. Normal Functional brain alterations have been reported in healthy older adults; greater bilateral activation has been found in healthy older adults during a WM task compared to younger adults. This phenomenon is thought to represent a functional reorganization and compensation mechanism by the recruitment of additional resources in order to maintain cognitive performance (16, 17) . Also normal aging is followed by structural loss in brain tissue (18-20), mainly in prefrontal brain regions (21). Given the centrality of WM in these higher order cognitive functions and its substantial decline over aging, new strategies to reduce the impact of WM loss in this population are sorely necessary.

In the past few years, there has been a growing interest in non-invasive brain stimulation techniques (NIBS) and the development of new combined interventions that can be used as rehabilitation strategies. Transcranial direct current stimulation (tDCS) is one such

NIBS. Given the safety profile, high tolerability, affordable cost, and few side effects, tDCS has been widely used in both healthy and clinical populations (22, 23). The most common side effects associated with tDCS are itching, tingling, headache, burning sensation and discomfort (24). tDCS has already been shown to improve performance in several cognitive domains such as perception, attention, working memory, learning and decision making (25). tDCS changes cortical activity through weak electric currents, producing changes in membrane resting potential and hence in brain activity (26-28). In tDCS a weak current (1-2mA) is delivered through the scalp, for a duration of up to 30 minutes. tDCS modulates membrane excitability of neurons in the regions underlying the electrodes (29, 30). The direction of this modulatory effect depends on the stimulation polarity; anodal stimulation increases excitability, while cathodal stimulation decreases it (31). It is also notable that depending on the intensity, duration and research protocol, non-linear effects have also been reported (32).

There is evidence to suggest that the application of tDCS on the prefrontal cortex (PFC) (33-37), posterior PC (parietal cortex) (38) and cerebellum (39) may modulate WM. Specifically in older populations, there are several studies that report noninvasive brain stimulation such as tDCS can have positive effects on cognitive function in typical and pathological aging (40). Therefore, the aim of this review paper is to summarize the current literature on the effects of tDCS on WM performance improvement in healthy older adults.

METHODS

We conducted database searches using PubMed, Web of Science, and Science Direct to identify human trials, written in English, from 2005 to 2015. The search terms used were "transcranial direct current stimulation", "tDCS", "aging", "elderly", "older adults" and "working memory" (details about the search strategy can be found in Appendix A). Two authors independently examined the titles and abstracts in order to exclude articles that did not meet inclusion criteria. Subsequently, the two reviewers examined the full text independently in order to identify relevant papers.

The inclusion criteria for the review were (1) population: studies had to include at least one group of healthy participants aged over 55 years old; (2) intervention: tDCS, regardless of the number of sessions and if the stimulation is or is not associated with cognitive training; (3) assessment instrument – studies had to assess working memory both before and after intervention; (4) study design: studies had to be sham controlled trials published in a peer reviewed journal.
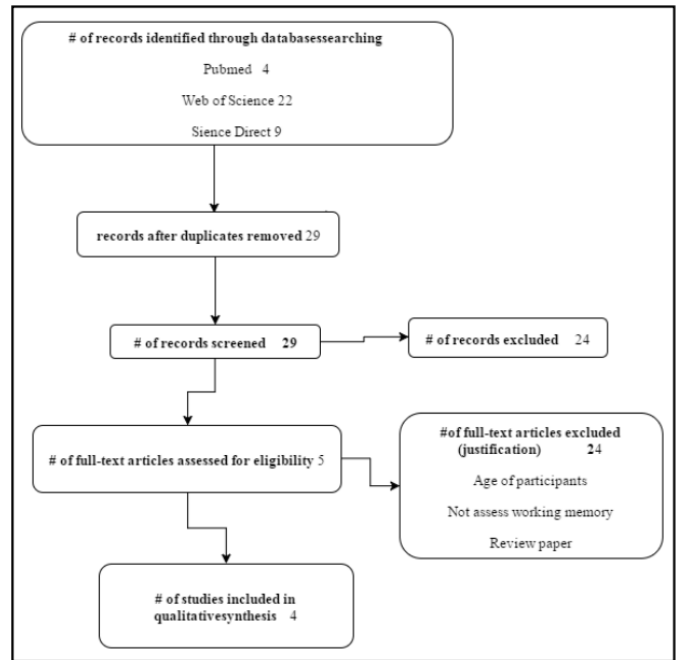

Fig. 1. Flowchart for identifying eligible studies.

RESULTS

Included Studies

The results of the screening carried out by the two independent authors were exactly the same, with no disagreements. A total of 29 papers were found in the search after eliminating duplications across search engines. Twenty-four articles were excluded in the initial screening due to age of participants, assessment (some of the studies did not assess working memory) and study design (some of them were literature review papers). We reviewed the full text of the remaining five articles and one of the papers was excluded due to low age of participants. Finally, four articles were included in the systematic review.

Table 1 summarizes the characteristics of the studies. In terms of the methodological quality of the included studies, random allocation was explicitly described for three trials (41-43). There was one paper that did not describe the randomization method or how participants were allocated to the experimental/placebo group (44). Two studies were single-blind designs (42, 43) and two were double-blind designs (41, 44). All studies used a sham-controlled design and carried out a screening phase using the Mini-Mental State Examination (MSSE) to ensure that participants were cognitively healthy older adults. In three of the studies participants

Author (year)	Type of study	N	Age (years)	Current density (mA/cm2)	Offline online task	# of arms	Anodal electrode[1]	Cathodal electrode	Size (active/ return in cm2)	Number of sessions / duration	Follow-up	Primary outcomes	Secondary outcomes	Main results
Berryhill & Jones (2012)	Rand. Placebo Single-Blind	25*	56-80	0.043	Offline (however participants performed practice trials online)	Cross-Sectional (1)	F4 F3	CL cheek	35/35	3³ (1 session for each condition: F3/F4/sham) 10 min	No	Verbal and visual 2-back	n/a¹	- No significant effect before divide the group in two samples according to the level of education. - tDCS was uniformly beneficial across sites and WM tasks in older adults with more education. - In the low education group, tDCS impaired visual WM performance and had no effect on verbal WM
Jones et al (2015)	Rand. Placebo Single - Blind	72**	55-73	0.043	Offline (however participants performed practice trials online)	4 *Sham *PFC *PC *PC alternating with PFC	F4' P4 F4/P4	CL cheek	35/35	10 10 min	Yes 1 month after training	Visuospatial WM task and Ospan	Stroop, digit span (forward and backward) and spatial 2-back	-The current flow to identify the spatial extent of brain stimulation after anodal tDCS to PFC and PC sites were modeled. tDCS to the PFC supplied current to PFC regions and also to orbitofrontal and ventral temporal regions. The PC stimulation target PC and posterior occipital and ventral temporal regions. There was considerable overlap of current flow in both areas - Both active and control tDCS groups (PFC, PC, PFC/PC and sham) showed equivalent improvement immediately after 10 sessions of training. However only the active tDCS group maintained significant improvements at follow-up a month later on trained and non-trained tasks. -All active tDCS groups (PFC, PC, PFC altering with PC) resulted in equivalent benefits -The more challenging and adaptive task (recall and Ospan tasks) showed great gains compared to recognition tasks - The largest transfer effect was observed in the most difficulty near transfer task, the spatial 2-back. The two other near transfer measures, the Stroop task and the digit span showed no transfer effects.
Park et al (2014)	Rand. Placebo Double-Blind	40 (20 sham / 20 active) * 27 females	>=65	0.08	online	2 *Anodal bilateral (F3 and F4) * Sham	F3 and F4 (bilateral)*	Nondominant arm	25/25	10 30 min	Yes (7 and 28 days)	Accuracy and response time in a 2-back verbal WM task and digit span forward	Verbal learning test, visual span test, CPT, word-color test, trail making test,	-Accuracy of the verbal WM task increased significantly for up to 28 days. -The reaction time of the verbal WM task was significantly shortened in the real stimulation group only in the last day of stimulation -Improvement in digit span forward in the active group observed only 7 days after stimulation - No improvement in the other transfer measures
Seo et al (2011)	No information about rand. Placebo Double-Blind	24 (12 sham/ 12 active) *10 females	65-78	0.08	online	2 *'F3 * Sham	F3	Left arm	25/25	1 30 min	No	Accuracy and response time on a verbal 2-back and visuospatial WM task	n/a	- Improvement of the verbal WM performance observed in the active group - For reaction time, there was not a significant effect of tDCS -No difference in visuospatial working memory performance

Rand.: Randomized; n/a: not applicable; CL: contralateral. Electrodes positions refers to the International 10-20 EEG system (46). Jasper HH. The ten-twenty electrode system of the International Federation. Eletroencephalography and Clinical Neurophysiology; 1958. p. 371-5.

Table 1. Characteristics of the studies included in the review

were right handed subjects (42-44) while in one of the studies handedness was not reported (41).

Intervention

Only two studies applied repeated sessions of tDCS (41, 43). In both of them tDCS was administered during 10 days. One study had a multiple outcome design; evaluating sham stimulation versus anodal tDCS to the left (F3) or right (F4) PFC in an intra-subject analysis and also the effect of educational level in a between-subject analysis(42). One study had a single session of tDCS (44). The duration of stimulation in two studies was 10 minutes (42, 43) and 30 minutes in the other two (41, 44). Two studies used a current density of 0.043 mA/cm2 (42, 43), while the other two used a 0.08 mA/cm2 current density (41, 44).

Furthermore, all studies combined cognitive training with tDCS. Two studies delivered stimulation while participants were engaged in a cognitive task (41, 44) while the other two studies used an "offline" design, in which participants performed the task after receiving tDCS (42, 43). However, in the two offline studies, participants performed practice trials while receiving stimulation. Additional add-on training was not reported in any of these papers.

The cognitive training tasks targeted both verbal and visuospatial subcomponents of working memory: verbal 2- back (42, 44); visual 2-back (42, 43);

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visuospatial WM task (43, 44) and Ospan (43). Park and colleagues (41) used the Korean CACT Program (45) although they did not provide details about the specific tasks composing the program. In all trials the difficulty level of the task was not adaptive.

In regards to treatment protocol, the electrode size used in most of the studies was 5x7cm, with the exception of Seo et al. (44) who used 5x5cm electrodes. All the studies used anodal stimulation, targeting the left or right dorsolateral prefrontal cortex (DLPFC) (F3, F4) or right PC (P4). In all studies, reference electrodes were placed in an extracephalic region (cheek or arm). One study presented a follow-up assessment 1 month after training (43) while Park et al (41) performed a follow-up after 7 and 28 days.

Outcome measures

Several outcome measures were used in the selected studies. Verbal 2 back (41, 42, 44), visual 2-back (42, 43), visuospatial WM task (43, 44), Ospan (43), Stroop (43), digit span forward (41, 43), digit span backward (41), verbal learning test (41), visual span test (41), Continuous Performance Test (CPT) (41), word-color test (41) and trail making test (41).

In general, the literature indicated that tDCS had a positive effect on working memory by improving verbal and visual working memory performance. Interestigly, Berryhill and Jones (42) did not find significant effect of anodal tDCS on WM, when comparing to sham, immediately after stimulation. However, subgroup analysis demonstrated that older adults with higher levels of education had significant improvement in working memory performance after stimulation, having no difference between the stimulation in F4 and F3 or between verbal and visual tasks. In the group of lower educational levels, the stimulation had negative effects on visual WM performance and had no effects on verbal WM. Jones et al. (43) modulated the current flow to identify the spatial extent of brain stimulation after anodal tDCS to the PFC and PC and they found that tDCS to the PFC supplied current to PFC regions and also to orbitofrontal and ventral temporal regions. The PC stimulation targeted PC and posterior occipital and ventral temporal regions. There was considerable overlap of current flow in both areas. They have also identified that both active and control tDCS groups (PFC, PP, PFC/PP and sham) showed equivalent improvement immediately after 10 sessions of training. However only the active tDCS group maintained significant improvements at the 1-month follow-up for both trained and non-trained tasks. All active tDCS groups (PFC, PC, PFC altering with PC) resulted in equivalent improvements. Jones and colleagues also reported that

the more challenging and adaptive tasks (recall and Ospan tasks) showed greater improvements when compared to recognition tasks. The largest transfer effect was observed in the most difficult near transfer task, the spatial 2-back. The two other near transfer measures, the Stroop task and the digit span showed no transfer effects. Park et al. (41) showed that improvedverbal WM accuracy was sustained for up to 28 days, after 10 sessions of computer-based cognitive training combined with bilateral anodal tDCS of the PFC (F3 and F4). The reaction time of the verbal WM task was significantly shortened in the real stimulation group only in the last day of stimulation and not in the follow up. They also reported a near transfer effect, namely improvement in digit span forward in the active group that was observed only 7 days after stimulation.. Finally, Seo et al. (44) failed to find differences in visual working memory performance following tDCS, but they reported verbal WM improvements in the active group. There was no significant effect of tDCS in reaction time in both visuospatial and verbal working memory performance.

Adverse effects

Two studies reported the following adverse effects: minimal skin discoloration on the arms for a few days (41) and transient aching and redness on the arm (44).

Variables mediating the tDCS effect

Berryhill and Jones (42) demonstrated that the educational level has been a potential effect modifier, with participants with higher levels of education benefiting more from the intervention. Modality of working memory (verbal or visual) can also be influenced differently bu tDCS Seo et al (44) found positive effect of intervention only on verbal WM performance of the active group, having no difference in visuospatial WM performance. Berryhill and colleagues (42) reported impairment in visual working memory of lower educational group. Time of assessment can also mediate the effects. Jones et al. (43) reported that both active (PFC,PP, PFC/PP) and sham tDCS groups showed equivalent improvement immediately after 10 session of training. However only the active tDCS group maintained significant improvements on trained and non-trained tasks at follow-up a month later.

DISCUSSION

The aim of this paper was to review the literature on tDCS effects on the WM performance of healthy elderly people. We found four papers that met our criteria. Most of the studies were randomized and included sham controlled

blinded trials. The included studies showed that WM training administered with anodal tDCS over the PFC and PC can enhance WM, and these positive effects can be transferred to tasks similar to those used in the WM training.

In the elderly, the effects of tDCS on WM seem to have a similar pattern to the one showed with young adults, in which anodal tDCS over the left DLPC improves WM (47). However, this enhancement was found only in the verbal component of working memory, as was the case in Seo et al (44). Indeed, Berryhill and colleagues (42) reported an impairment in visual WM performance after stimulation in older people with lower educational level, which was more evident during stimulation of the right PFC (F4). Richmond et al. (47) argue that this absence of results and negative effects of tDCS on visuospatial WM could be due to stimulation of the left hemisphere, since the left side is associated with verbal contents and the right side is responsible for visuospatial processing (48).

The WM task used in training can be adaptive; the difficulty level adapts to match the participant ability, and it can be increased throughout training according to the improvement of the participant's proficiency. All the studies in this review adopted a non-adaptive WM task; the task had the same level of difficulty for all participants, and was not adjusted according to the performance of the subject. One meta-analysis of WM training in an elderly population (49) failed to recognize a difference between adaptive and non-adaptive training paradigms, which suggests that utilizing an adaptive structure of WM training not improve the quality of working memory training.

Finally, a neuroimaging study showed that a single session of anodal tDCS administered to the left inferior frontal gyrus can temporarily reverse changes in brain activity and connectivity in older adults (50). In that study, a decrease in bilateral hyperactivity related to the intervention was observed, suggesting a "youth-like" connectivity pattern during resting state fMRI (50).

In one of the studies (42), tDCS was beneficial in older adults if they had a higher level of education. However, in the study by Berryhill and Jones, the group with relatively lower education was in school for an average 13.5 years (comparing to 16.9 on the higher level of education). These effects may be due to differences on cognitive reserve. Thus, older adults with higher educational level may present differences in the flexibility and adaptation of cognitive networks (51). It would be interesting to further examine the effect of educational level within groups with lower educational level or even with illiterate participants. Additionally, it is important to verify if other variables such as genetic factors, gender, age and personality can mediate the intervention effect.

Half of the studies included in this review had an online cognitive training (41, 44), which means that the training was performed simultaneously with application of tDCS. The other half of the studies used an offline design, meaning that the task was carried out after stimulation (42, 43). However, in the two offline studies, participants performed practice trials while receiving tDCS. Both kinds of stimulation (online and offline) showed similar results, which would be expected since the physiological effects of tDCS have been reported to last for more than one hour after several minutes of stimulation, and the participants of the offline studies performed the practice trial during stimulation (31). Nevertheless, it is worth pointing out that there is evidence that online and offline tDCS can have differential effects. For instance, anodal tDCS over the motor cortex increases motor learning when applied during the task, while offline tDCS has the opposite effect (52). Moreover, online anodal tDCS over the left DLPFC is more effective on skill acquisition following two days of WM training than offline tDCS (53). In line with this finding, a neuroimaging study reported greater brain activation during stimulation compared to the period following stimulation (54). Further studies should explore the effects of tDCS timing during WM training in elderly people.

Repetitive sessions of tDCS are thought to boost the effects of stimulation, since single stimulation has relatively short after-effects (27, 31). The main assumption underlying the effects of repetitive sessions is that it will change the mechanisms of synaptic plasticity, such as longterm potentiation (LTP) and long term depression (LTD) (55-59) LTP is activity-dependent plasticity that induces an increase of synaptic transmission, while LTD reduces the efficacy of synaptic transmission (60). Therefore, the use of repetitive sessions of tDCS may induce learning in the neural networks which will ultimately benefit cognitive training (61). Among the papers analyzed, we identified only two studies showing the effect of repeated tDCS sessions on WM in older people (41, 43) which is in line with findings reported with younger people (45, 62-68). In both studies (41, 43) participants received intervention five days a week for 2 weeks. There is no concrete evidence of the optimal sessions frequency and duration of tDCS tDCS, however the cumulative effects of motor cortical excitability in daily sessions of anodal tDCS seem to be greater compared to sessions separated by a two day interval (69). Similar results were found in stroke patients in which the cumulative effects of motor function

was associated with five daily sessions, but not associated with weekly sessions of tDCS(70). Additionally, tDCS has been reported to have different effects depending on the duration of stimulation. Three minutes have been reported as the minimum required time to induce an after-effect; and longer periods (i.e. more than 30-min) have produced mixed results (32, 71). There is also the possibility that the baseline level of cortical activity in a given neural network can modify subsequent modification to that network (72). Although it is costlier and logistically difficult to carry out studies with multiple sessions compared to single sessions, investment in this area is warranted and may significantly contribute to development of this field. This would go a long way to validate the effectiveness of this type of intervention, as well as standardize the tDCS intervention protocol in terms of the number of sessions, interval between sessions and duration of stimulation.

The optimized site of tDCS is another issue that needs consideration. Based on computer modeling, the largest effects induced by tDCS polarity are elicited beneath the stimulation electrode (73). However, tDCS over different stimulation locations (such as bi-hemispheric, unihemispheric, prefrontal, parietal, prefrontal alternating with parietal and right and left) can lead to similar effects on WM. It is important to have active stimulation targeting an area that is not related to WM in order to determine whether similar effects can be observed by stimulating any given area of brain (43). Moreover, as most of tDCS effects so far have been on the verbal subcomponent of WM, it will be important to test different targets in order to increase other subcomponents, such as the visual.

Finally, our results provide evidence of the safety of tDCS in elderly people, as only minor adverse effects were reported among studies.

CONCLUSION

In sum, anodal tDCS over the PC and PFC seems to improve WM in healthy elderly subjects, and those improvements can be sustained up to one month postintervention. However, better parameters of stimulation are still required before mainstream use.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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