



Effects of transcranial direct current stimulation on the working memory of post-stroke people: an integrative review

Edson Meneses da Silva Filho¹, Jéssica Andrade de Albuquerque², Karime Andrade Mescouto¹, Rodrigo Pegado de Abreu Freitas³

ABSTRACT

Background: Stroke is a chronic disease that is becoming more common in all the world causing damage to people affected, for instance, cognitive deficits. The Transcranial Direct Current Stimulation (tDCS) is a form of treatment that modulates specific areas of the nervous system. **Objective:** The objective of this integrative review was to analyze the effectiveness of Transcranial Direct Current Stimulation (tDCS) on the working memory (WM) in post-stroke patients. **Method:** This review included articles that analyzed the effects of tDCS on human beings with a diagnosis of stroke and used as outcomes: verbal, visual, spatial or auditory WM. The assessment of studies eligibility was performed by two independent researchers from 8 databases: Cochrane Library via Wiley - CENTRAL, PubMed, LILACS, SCIELO, Web of Science, Scopus, CINAHL and PEDro following PRISMA guideline. **Results:** Three articles were included in the qualitative synthesis presenting a total of 66 participants (32 male and 34 female), 36 ischemic stroke and 30 hemorrhagic stroke with an average time of 42 days. Interventions were done on the areas F3/F4 (dorsolateral part of the prefrontal cortex) and T3/T4 (temporal anterior lobe) with 2mA current intensity for 30 minutes duration. The outcomes analyzed: verbal, visual, spatial, and auditory WM showed significant improvements after the use of tDCS. **Conclusion:** The limitations of this review were study designs, number of participants, lack of standardized interventions and short period of follow-up. tDCS showed satisfactory results on the WM of post-stroke individuals, but it is needed to be cautious due to the methodological quality of the articles. It is registered in the Prospective Register of Systematic Reviews - PROSPERO with registration number CDR42016048050.

Keywords: Stroke; Transcranial Direct Current Stimulation; Memory

INTRODUCTION

Stroke is a disease that has a great impact worldwide specially in developing countries⁽¹⁾. Factors such as age, Alzheimer's, female gender and hypertension increase the risk for developing stroke⁽²⁾. In addition, silent infarcts have been associated with increased risk of symptomatic stroke and cognitive impairment⁽³⁾.

One of the locations associated with cognitive deficits in stroke is located in the Working Memory (WM). This type of memory is used for temporary storage of information, being responsible for various processes, such as comprehension, language, learning and consolidation of long-term memory⁽⁴⁾ and according to the classical model of Baddeley and Hitch⁽⁵⁾ it is composed of two other temporary memory, verbal and visuospatial, which are often affected after stroke.

Transcranial Direct Current Stimulation (tDCS) is a noninvasive and safe technique used to improve cognitive impairments, which acts by modulating specific areas of the central nervous

system that modifies neuronal electrical membrane potentials and its activity⁽⁶⁾. This technique has also been directed to the improvement of the WM functions in different populations, specifically stimulating the dorsolateral area of the prefrontal cortex of subjects⁽⁷⁻¹¹⁾. Although, there is a growing number of studies that use tDCS to improve patients cognitive functions, there are still insufficient searches in specific populations, such as post-stroke patients with WM impairment.

The knowledge about the proper use of tDCS in post-stroke people is important for professionals to manage this technique in a standardized manner, giving individuals the maximum benefits of treatment. It is hypothesized that tDCS shows satisfactory results on the WM in post-stroke individuals.

The question on which this review was based for the construction of the PICO was: Does the transcranial direct current stimulation interferes on the working memory of post-stroke adults? P – adults, stroke; I - transcranial direct

Corresponding author: Edson Meneses da Silva Filho. Rua Andrade Bezerra, 78, Centro – Timbaúba – PE, Brazil. CEP: 55870-000. Phone: 0055 81 9 9470 6661.
Email: meneses.edson@yahoo.com.br

¹ Physiotherapist, master student in Science of Rehabilitation – Universidade Federal do Rio Grande do Norte - UFRN, Faculty of Health Sciences at Trairi, Santa Cruz, Rio Grande do Norte, Brazil.

Full list of author information is available at the end of the article.

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current stimulation; C - transcranial direct current stimulation (sham) or active control (cognitive training); O – working memory. The verbal WM was adopted as primary outcome, the visual, spatial and auditory WM were considered as secondary outcomes.

Thus, the purpose of this integrative review was to analyse the effects of transcranial direct current stimulation on the working memory of post-stroke individuals compared to any active or passive control.

MATERIALS AND METHODS

Protocol and registration

This review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)⁽¹²⁾ and it is registered in the Prospective Register of Systematic Reviews - PROSPERO with registration number CDR42016048050.

Eligibility criteria

This review included articles that showed the following criteria: studies with patients > 18 years of age with a diagnosis of stroke, without gender restriction, to be written in any language and year of publication showing the effects of transcranial direct current stimulation (tDCS) in post-stroke individuals and to have used as outcome verbal, visual spatial and auditory Working Memory (WM). Active tDCS (unilateral/bilateral, anodic/cathodic) or active tDCS associated with any cognitive training that influenced on the WM was compared to sham tDCS intervention or any active or passive control. It was considered as active tDCS, long term application (greater than 1 minute) on the injured hemisphere or bilateral and defined as sham tDCS, positioning the electrodes without current application or stimulus of short duration (less than 1 minute). This is considered a sufficient time for the current sensation on the scalp disappears⁽¹³⁾.

Search strategy

The search strategies were made according to the specificities (language, synonyms, truncation and descriptors) of the databases used to search the articles. The databases used for collection of the articles were the Cochrane Library via Wiley - CENTRAL, PubMed, LILACS, SCIELO, Web of Science, Scopus, CINAHL and PEDro. To identify more published, unpublished and ongoing studies a search was done in clinical trials registers, reference lists of included studies and was made contact with the authors, if needed. The last search was conducted on october 18, 2016.

Data collection and analysis

Initially, a simple search was done by two independent researchers in the databases mentioned with the insertion of descriptors and Boolean operators according to the

official language and accepted nomenclature (mesh). Then, a sensitized search was done through the inclusion of descriptor's synonyms and its categories.

Studies selection

The titles, abstracts and potentially relevant full texts were screened by the researchers. Articles that met inclusion criteria were stored and during the consensus meeting the researchers discussed which study would take part of this integrative review. A third investigator was contacted in case of disagreements.

Data collection process

Data were independently extracted from the included studies by both researchers. A formulary was created in order to obtain the largest possible number of data as: identification and study design, data randomization, sample (country, age and gender), stage of disease, intervention groups, allocation concealment, follow-up, blinding, statistical power, inclusion and exclusion criteria, outcomes, selective description and summary measures. The comparison among the data obtained was done in the consensus meeting. Authors were only contacted to elucidate any unclear information about the article.

Risk of bias assessment

The tool risk of bias table made by the Cochrane Collaboration was used for the analysis of risk of bias of the studies⁽¹⁴⁾. This analysis was done by two researchers independently and in the consensus meeting was discussed, evaluated and decided the risk of bias from each study. The third investigator was contacted, if there was some disagreement.

RESULTS

Articles Selection

A total of 3.549 articles were initially identified. After reading the titles/abstracts, 3.497 articles were excluded because they did not meet the inclusion criteria, remaining a total of 52 eligible articles. Ultimately, only 3 articles were suitable for quality assessment after reading the full texts, as represented in figure 1.

Characteristics of the articles

The description of all the studies, objectives, sample characteristics, interventions, outcomes and main results are in Table 1.

A total of 66 participants (32 male and 34 female), 36 ischemic stroke and 30 hemorrhagic stroke with an average time of 42 days⁽¹⁵⁻¹⁷⁾. The interventions were done on the areas F3/F4 (dorsolateral part of the prefrontal cortex) and T3/T4 (temporal anterior lobe) for stimulation in accordance with the international 10-20 system EEG⁽¹⁸⁾ with 2mA current intensity



for 30 minutes duration. The follow-up was pre/post treatment in all studies, but they differ in the session number. Yun et al.⁽¹⁵⁾ presented a total of 15 sessions being 3x/week, Jung et al.⁽¹⁶⁾ did only 2 sessions with a 48 hours interval and Park et al.⁽¹⁷⁾ didn't report the amount of sessions.

Risk of bias assessment

Park et al.⁽¹⁷⁾ did not describe properly the randomization, allocation concealment, blidind: searcher, participants and outcomes, however, the data were complete, there were

not selective description and other bias. Jung et al.⁽¹⁶⁾ did not randomize the sample. The allocation concealment, blidind searcher and participants were not described properly, besides bliding outcomes was not done. There was incomplete outcome data and other bias, but selective description did not occur. Yun et al.⁽¹⁵⁾ did not describe properly the randomization, allocation concealment, blidind: searcher, participants and outcomes, however, the data was complete, there was not selective description and other bias. The risk of bias of the articles is specified in Figure 2.

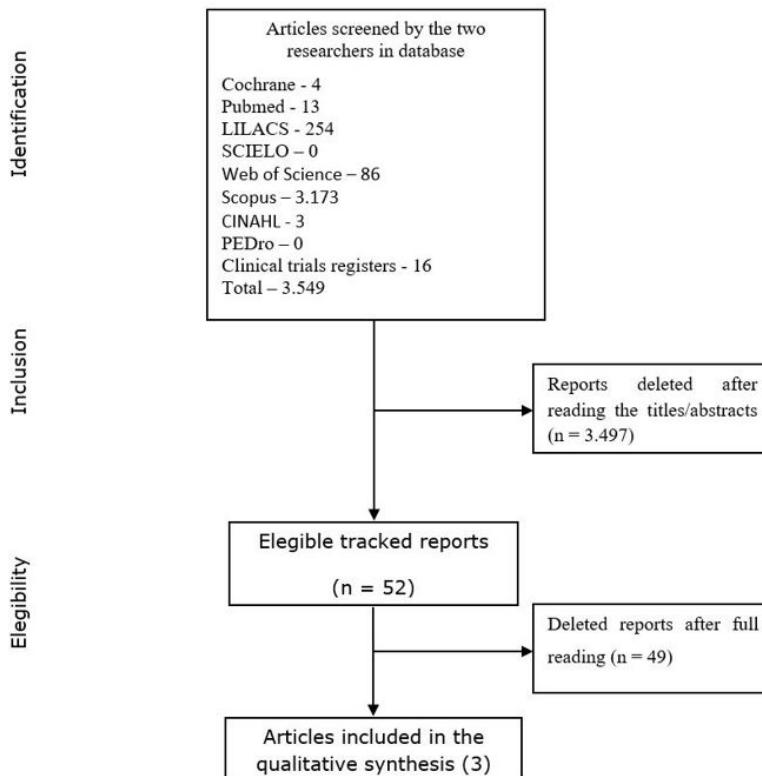


Figure 1. Flowchart of selected articles

Risk of bias table

	?	?	?	?	+	+	+
Yun, 2015	?	?	?	?	+	+	+
Jung, 2009	-	?	?	-	-	+	+

randomization
Allocation concealment
Blinding: searcher and participants
Incomplete outcome data
Selective description
Other bias

Park, 2013

⊕ Low risk of bias

? Undefined risk of bias

- High risk of bias

Figure 2. Bias risk analysis of the articles included in the review.

**Table 1.** Characterization of the studies.

References	Purpose	Characteristics of the Sample	Intervention/outcome	Main results
Yun, 2015 ⁽¹⁵⁾	To investigate, if transcranial direct current stimulation influences on the cognition of post-stroke individuals.	Sample: 45 individuals, 26 ischemic stroke and 19 hemorrhagic stroke with a mean of 40 days. 20 are male and 25 female with mean age: 62.7 years old.	There were 3 groups. Group 1: right anodic stimulation (temporal anterior lobe – T4), group 2: left anodic stimulation (temporal anterior lobe – T3) and group 3: sham. Current intensity: 2mA during 30 min, 5 times a week for 3 weeks. The outcomes: attention, verbal and visual working memory were analysed before and after the treatment.	Group 1: showed significant improvements in intragroup analysis on attention, verbal and visual working memory tests: Korean version of the Mini-Mental State Examination, backward digit span, forward visual span test, verbal learning test-delayed recall, Korean version of the modified Barthel Index. Group 2: showed significant improvements in intragroup analysis on tests: verbal learning test-delayed recall and Korean version of the modified Barthel Index.
Jung, 2009 ⁽¹⁶⁾	To investigate if the effects of anodic transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex affects the working memory in post-stroke patients.	Sample: 10 individuals, 4 ischemic stroke and 6 hemorrhagic stroke with a mean 60 days. 7 males and 3 females with a mean age: 47.9 years old.	Group 1: cognitive training plus anodic tDCS during 30 minutes, intensity: 2mA Group 2: cognitive training plus tDCS sham. After one session was given the wash-out period of 48 hours and after that, the groups reversed the treatments. The outcome analyzed was the working memory through tests: visual response time, visual recognition accuracy and visual accuracy.	In the intragroup analysis (pre/post treatment) the tests: visual accuracy and visual recognition accuracy improved significantly only in the group 1 (active tDCS). It was not done intergroup analysis.
Park, 2013 ⁽¹⁷⁾	To examine the synergistic effects of cognitive rehabilitation associated with bilateral anodic transcranial direct current stimulation over prefrontal cortex on cognition of post-stroke patients.	Sample: 11 patients. 6 ischemic strokes and 5 hemorrhagic strokes with mean of 27 days. 6 patients are males and 5 females with mean age: 65.6 years old.	Experimental group: bilateral anodic tDCS over the prefrontal cortex during 30 minutes, intensity: 2mA plus cognitive training Control group: sham tDCS plus cognitive training. It did not specify the number of sessions of each group only the mean: 17.8 days. The outcomes measured were attention, auditory and visual working memory, visual-motor coordination function.	In the intergroup analysis (post intervention) only the Auditory and visual continuous performance test and showed significant results.



DISCUSSION

This is the first integrative review of studies that analysed Transcranial Direct Current Stimulation (tDCS) in post-stroke individuals using as outcome the Working Memory (WM). Moreover, it is also important to mention that there are few studies that have used this type of intervention in post-stroke patients, thus justifying the small number of articles present in this review.

The three studies that adopted this approach showed undefined risk of bias, according to the methodological evaluation of this review. They showed different interventions, which differed in the number of sessions and study design, thus making difficult compare them. Other variables, such as intensity of current, stimulated area, stimulation time and methods used to measure the outcomes were similar, corroborating with protocols used by other authors in different populations that investigated the same outcomes^(19,20).

It is known that after stroke may occur a change in synaptic homeostasis, which affects individuals' cognition⁽²¹⁾. In the present study the verbal and visual WM showed significant improvements after the use of tDCS, supporting the results found in diverse population by other authors^(22,23). One possible explanation is that the modulation of membrane action potential induced by tDCS could limit this homeostasis lost, therefore maintaining the cognitive functions⁽²⁴⁾. A brief episode of strong synaptic activation after stimulation has demonstrated improvements in neural transmission and neuroplasticity, hence improving memory and learning⁽²⁵⁾.

The spatial WM showed significant results after the use of tDCS possibly because of neurons activation patterns enhancement, through the late time window that generated improvements in memory functionality⁽²⁶⁾. Another reason is based on the fact that some authors have found evidence of a separation of a WM information division of object and space in parietal and temporal lobe, while the dorsolateral part of the prefrontal cortex (DLPFC) was important for both types of information⁽²⁷⁾. In a study about temporal dynamics and interactions within many different areas it was found interferences after stimulation between the DLPFC and parietal areas on tasks involving spatial WM⁽²⁸⁾, so it is assumed that tDCS may have influenced the neural network associated with spatial WM both locally and in distant places⁽²⁹⁾.

Some authors have suggested that the DLPFC plays an important role in the planning and proper execution of motor response during WM based tasks^(30,31), in addition, the declarative memory⁽³²⁾, emotional⁽³³⁾, and attention⁽³⁴⁾ are also being used for cognitive rehabilitation with the tDCS. After stimulation of DLPFC area, significant results were found, through analysis of visual and spatial WM outcomes, being in accordance with previous studies on other populations⁽³⁵⁻³⁷⁾. Other areas such as posterior⁽³⁸⁾ and lateral parietal⁽³⁹⁾ are also being used as sites of stimulation, in an attempt to assist in cognitive performance after injury.

Some authors were able to observe improvements in auditory WM after stimulation^(40,41). Following a brain injury, individuals often have deficits in specific anatomical listening areas including Wernicke's and surrounding areas^(42,43). tDCS provides changes in cortical excitability and an increase of cognitive performance is observed when followed by specific training⁽⁴⁴⁾, therefore justifying the improvements found in WM auditory outcome. The result in the auditory continuous performance test presented in this review should be viewed with caution given that the pre-treatment groups were not homogeneous.

Among the limitations encountered by this review we can highlight the studies designs that made impossible conduct a meta-analysis. Also the number of participants, lack of standardized intervention and a small follow-up.

CONCLUSIONS

The use of transcranial direct current stimulation in post-stroke individuals demonstrated improvements on the working memory after treatment, but better design studies that have a longer follow-up, standardized intervention and a large sample are needed.

AUTHORS' CONTRIBUTION

EMSF, JAA and KAM participated in the idealization of the study, data collection, analysis/interpretation and article writing; EMSF and JAA participated in data collection; RPAF participated, in the condition of guiding, the idealization of the study, analysis, interpretation of data and article's writing.

CONFLICTS OF INTEREST

There is not

AUTHOR DETAILS

² Psychologist, PhD student in Social Psychologist – Universidade Federal da Paraíba - UFPB, João Pessoa, Brazil.

³ Physiotherapist (PhD), Universidade Federal do Rio Grande do Norte, Faculty of Health Sciences at Trairi, Santa Cruz, Rio Grande do Norte, Brazil.

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