



## ***THE INFLUENCE OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON FUNCTIONAL RECOVERY AFTER STROKE: A SYSTEMATIC REVIEW***

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### **ARTIGO DE REVISÃO**

#### **ABSTRACT**

**INTRODUCTION:** Stroke is the third leading cause of death in the world and second in Brazil, whose main characteristics are global or focal disorders of brain functions, involving cognitive and mainly physical limitations, including motor, sensory changes, ataxias, apraxias and aphasias. Transcranial Direct Current Stimulation (ETCC) is a non-pharmacological treatment that has demonstrated relevant benefits in the rehabilitation of patients. **OBJECTIVE:** to verify the effects of ETCC on the functional capacity of post-stroke patients, focusing on efficacy and results in the face of individuals' motor disorders. **METHOD:** The searches were performed in the databases PeDRO, Cochrane, PubMed and MEDLINE. Eligible studies included at least one of the population outcomes  $\geq 18$  years, resulting from the intervention, therapeutic efficacy and Motor activity. **RESULTS:** Seven were selected according to the inclusion and exclusion criteria, published between 2015 and 2020. **CONCLUSION:** ETCC, applied in isolation, can be an effective technique to improve motor deficits after stroke, including injured upper limb function, lower limb strength, unilateral neglect, mobility and Daily Living Activities. It is suggested to carry out further studies for the standardization of a treatment protocol, as well as to verify the best moment of its application in the post-stroke patient.

**Keywords:** Transcranial Direct Current Stimulation; Stroke; Motor Activity; Efficacy.

## A INFLUÊNCIA DA ESTIMULAÇÃO TRANSCRANIANA POR CORRENTE CONTÍNUA NA RECUPERAÇÃO FUNCIONAL APÓS AVC: UMA REVISÃO SISTEMÁTICA

### RESUMO

**INTRODUÇÃO:** O Acidente Vascular Cerebral (AVC) é a terceira causa de morte no mundo e segunda no Brasil, cujas principais características são distúrbios globais ou focais das funções encefálicas, envolvendo limitações cognitivas e principalmente físicas, incluindo alterações motoras, sensoriais, ataxias, apraxias e afasias. A Estimulação Transcraniana por Corrente Contínua (ETCC) é um tratamento não farmacológico que tem demonstrado benefícios relevantes na reabilitação de pacientes.

**OBJETIVO:** verificar os efeitos da ETCC na capacidade funcional de pacientes pós AVC, com foco na eficácia e resultado frente às desordens motoras dos indivíduos. **MÉTODO:** As buscas foram realizadas nas bases de dados PeDRO, Cochrane, PubMed e MEDLINE. Os estudos elegíveis incluíram pelo menos um dos desfechos de população  $\geq 18$  anos, resultado da intervenção, eficácia terapêutica e atividade Motora. **RESULTADOS:** Sete foram selecionados segundo os critérios de inclusão e exclusão, publicados entre 2015 a 2020. **CONCLUSÃO:** A ETCC, aplicada isoladamente, pode ser uma técnica eficaz na melhora de déficits motores pós AVC, incluindo função de membro superior lesionado, força de membro inferior, negligência unilateral, mobilidade e Atividades de Vida Diária. Sugere-se a realização de mais estudos para a padronização de um protocolo de tratamento, bem como para verificar o melhor momento de sua aplicação no paciente pós AVC.

**Palavras-chave:** Estimulação Transcraniana por Corrente Contínua; Acidente Vascular Cerebral; Atividade Motora; Eficácia.

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## **INTRODUCTION**

The Cerebrovascular Accident (CVA), also known as a stroke, corresponds to an acute abnormality in the Central Nervous System (CNS), occurring when there is a decrease or blockage in the blood supply to the brain for a period exceeding 24 hours, causing lesions<sup>1</sup>. Considered a global public health problem and one of the most prevalent neurological diseases<sup>2</sup>, stroke ranks as the third leading cause of death worldwide and the second in Brazil, accounting for approximately 68 thousand deaths per year<sup>1,3</sup>.

Stroke has two classifications: ischemic stroke (IS), which accounts for the majority of cases, involves vascular obstruction to a region of the brain; and hemorrhagic stroke (HS), where vascular rupture leads to blood leakage into the brain or the subarachnoid space<sup>1</sup>. The disease's main characteristics include global or focal disturbances of brain functions, encompassing cognitive and primarily physical limitations, including motor, sensory, ataxias, apraxias, and aphasias affecting up to 80% of individuals<sup>1,2</sup>. The impairment can be unilateral or bilateral, resulting in hemiparesis or hemiplegia when affecting one side of the body, as well as quadriparesis or quadriplegia, affecting both the upper and lower limbs<sup>4</sup>. Spasticity, an alteration in muscle tone that creates resistance to movement and involuntary movements, is a significant aspect of motor changes<sup>1</sup>.

In-hospital management of IS involves thrombolytic therapy, dependent on a therapeutic window of up to 4 hours and 30 minutes after the onset of symptoms. For HS, treatment focuses on preventing or treating to minimize sequelae, which can occur through clinical-medication and/or surgical means<sup>1</sup>. Non-pharmacological actions have also been employed to minimize cognitive and functional deficits, involving the collaboration of various professionals such as Speech Therapists, Psychologists, and Physiotherapists<sup>1,5</sup>.

Among non-pharmacological strategies, Transcranial Direct Current Stimulation (tDCS) stands out, demonstrating significant benefits in the rehabilitation of patients, especially when combined with adjunct therapies such

as physiotherapy and cognitive training<sup>4</sup>. tDCS is a non-invasive technique capable of modulating cortical neuronal excitability, inducing neuroplasticity mechanisms without directly affecting neurons, reducing the possibility of adverse effects<sup>4,6</sup>. The application involves fixing two silicone electrodes wrapped in saline-soaked sponges and a device providing direct current, lasting 3 to 20 minutes, and low amperage ranging from 0.4 to 2mA<sup>6</sup>.

After a stroke, various events occur in the brain, from changes in membrane excitability to synaptic modifications and the formation of new neuronal networks<sup>6</sup>. Given this, the use of tDCS in stroke rehabilitation makes sense, considering the direct correspondence between the functional changes resulting from the injury and the areas stimulated by tDCS. However, there are still limitations regarding the real effects of its use in individuals affected by stroke<sup>4</sup>.

Therefore, the present study aimed to investigate the effects of tDCS on the functional capacity of post-stroke patients, with a focus on efficacy concerning the motor disorders of individuals.

## **METHOD**

This is a systematic review of secondary studies: Systematic Reviews, Guidelines, and Meta-Analyses published between 01/2015 and 09/2020 in the English language. Electronic databases PeDRO, Cochrane, PubMed, and MEDLINE were used to search the literature, employing the descriptors identified in the Medical Subject Headings (MESH), appropriately applied to each electronic database. The search strategy and search terms are described in Supplementary Material 1.

Supplementary Material 1 - Method

CONCEPT	MeSH TERMS	KEY WORDS
Stroke	Stroke [MeSH]	Stroke
Transcranial Direct Current Stimulation	Transcranial Direct Current Stimulation [MeSH]	Transcranial Direct Current Stimulation OR tDCS OR Transcranial Electrical Stimulation
Efficacy	Efficacy [MeSH] OR Effectiveness [MeSH] OR Evaluation of Results of Therapeutic Interventions [MeSH] OR Evaluation of the Efficacy-Effectiveness of Interventions [MeSH] OR Comparative Effectiveness Research [MeSH]	Efficacy OR Effectiveness OR Treatment Outcome
Result	Negative results [MeSH] OR Treatment Outcome [MeSH] OR Evaluation of Results of Therapeutic Interventions [MeSH] OR Patient Outcome Assessment [MeSH] OR Effectiveness [MeSH]	Results analysis OR Evaluation of Results of Therapeutic Interventions OR Treatment Outcome OR Results of Health Interventions
Motor Activity	Motor Activity [MeSH] OR Motor Skills Disorders [MeSH] OR Somatosensory Disorders [MeSH] OR Motor Disorders [MeSH]	Motor Activity OR Motor Control OR Motor Function OR Functionality
Study Design	Systematic Review [MeSH] OR Meta-Analysis [MeSH] OR Practice Guidelines as Topic [MeSH]	Systematic Review OR Meta-Analysis OR Guidelines

The article search yielded results from PeDRO (19 articles), Cochrane (5 articles), PubMed (12,541 articles), and MEDLINE (6 articles). Articles identified through the search strategy (Supplementary Material 2) were subsequently selected after applying filters for each database (Supplementary Material 3).

Supplementary Material 2 – Search Strategies

USED IN THE PUBMED DATABASE
SEARCH
1. (Systematic Review/ OR Meta-Analysis/ OR Guidelines).pt
2. (Transcranial Direct Current Stimulation). ti, ab
3. Strategy 1 AND 2
4. (Efficacy/ OR Negative Results /OR Motor Disorders/). ti, Ab
5. Strategy 3 AND 4
6. (Stroke). ti, Ab
7. Strategy 5 AND 6
USED IN THE COCHRANE DATABASE
SEARCH
1. (Stroke). ti, Ab
2. (Transcranial Direct Current Stimulation). ti, Ab
3. Strategy 1 AND 2



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USED IN PEDro DATABASE

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SEARCH TERM

1. (Transcranial Direct Current Stimulation). ti, Ab
  2. (Systematic Review).pt
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USING MEDLINE DATABASE

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SEARCH TERM

1. (Systematic Review/ OR Meta-Analysis/ OR Guidelines).pt
  2. (Transcranial Direct Current Stimulation). ti, Ab
  3. Strategy 1 AND 2
  4. (Efficacy/ OR Negative Results/ OR Motor Disorders). ti, Ab
  5. Strategy 3 AND 4
  6. (Stroke). ti, Ab
  7. Strategy 5 AND 6
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Abbreviations: ti, title; ab, abstract; pt, publication type

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Supplementary Material 3 – Filters

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USED IN THE PUBMED DATABASE

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FILTERS

- I. Article Type
    - Guideline
    - Meta-Analysis
    - Systematic Review
  - II. Publication Date
    - 5 years
  - III. Species
    - Humans
  - IV. Language
    - English
- 

USED IN THE COCHRANE DATABASE

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FILTERS

- I. Custom Range
    - 01/2015 to 09/2020
- 

USED IN PEDro DATABASE

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FILTERS

- I. Method
  - II. Systematic Review
  - III. Published Since
  - IV. 01/01/2015
- 

USED IN MEDLINE DATABASE

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FILTERS

- I. Publication Year Range
    - Past 5 Years
- 

The selection process involved reading titles and abstracts according to the following inclusion criteria: Stroke; Utilization of Transcranial Direct Current Stimulation (tDCS); Intervention in humans aged 18 years or older; Intervention outcome; Therapeutic efficacy; Motor activity; Analysis of at least one outcome; Systematic Reviews; Meta-Analyses; Guidelines.

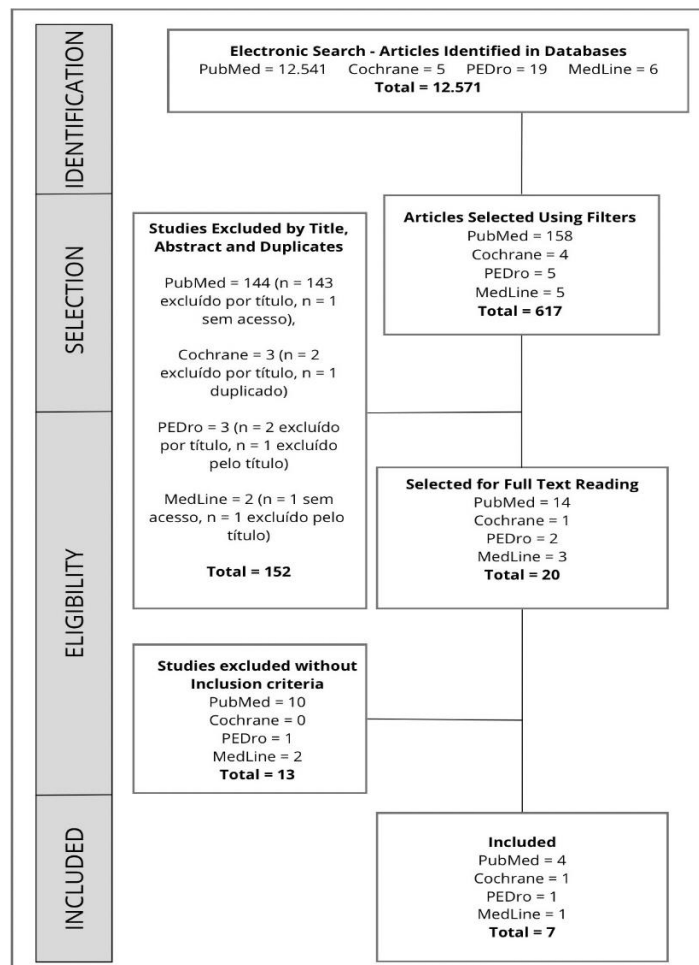
Articles that did not meet the eligibility criteria, those using combined techniques, and those published before the year 2015 were excluded, as described in Table 1.

Data extraction was carried out by two independent researchers, and after the selection and full reading of the chosen articles, the study characteristics were summarized in a table for final analysis and the preparation of this systematic review.

## RESULTS

Out of 12,571 articles found, 20 were selected and fully read. Thirteen were discarded for not meeting eligibility criteria, leaving seven articles for inclusion (Figure 1).

Figure 1. Flowchart of the methodological Search.



Therefore, this review includes seven articles, comprising three systematic reviews, two systematic reviews with meta-analysis, and two meta-analyses.

Table 1. Details of the Studies.

Author/Year	Kind of study	Efficiency	Treatment Results	Motor disorders	Conclusion
<b>Fregni et al. (2020)</b> <sup>7</sup>	Systematic review	Yes	Improvement of motor function in acute, subacute and chronic stroke.	Injured UL and fine motor function (subacute and chronic stroke), paresis (acute and chronic stroke).	The use of tDCS in stroke is recommended.
<b>García-Rudolph et al. (2019)</b> <sup>8</sup>	Systematic Review with Meta-analysis	Yes	Functional improvement in patients with subacute stroke.	ADL dysfunction.	Small and moderate effects on improving ADLs in stroke.
<b>Denissen et al. (2019)</b> <sup>9</sup>	Systematic review	Inconclusive	Stimulation of different regions of the brain may have a different impact on post-stroke falls.	Fall risk	Little evidence on the use of tDCS to reduce falls after stroke
<b>Fan et al. (2018)</b> <sup>10</sup>	Systematic Review with Meta-analysis	Yes	Reduction in the level of unilateral neglect after stroke	Unilateral negligence	tDCS has effects on unilateral neglect. However, more studies are needed to find the ideal protocol.
<b>Li et al. (2018)</b> <sup>11</sup>	Systematic Review with Meta-analysis	Yes	It improves strength and mobility, but has no significance	Gait speed, mobility, balance, MI strength.	It may have beneficial effects on lower limb mobility and muscle



				on gait speed and balance.		strength in stroke patients. More studies are also needed.
<b>Elsner et al. (2017)<sup>12</sup></b>	Meta-analysis	Yes	There is evidence of the use of cathodal tDCS in improving ADLs and UL function. There is no evidence of other tDCS.	ADL's and MS function.		It suggests that cathodal tDCS is the most promising for improving ADLs and MS function in stroke. It suggests improving the methodological quality of studies.
<b>Chhatbar et al. (2016)<sup>13</sup></b>	Meta-analysis	Yes	There is evidence of improved function in MS.	MS function.		Evidence on improvement in MS function, revealing a dose-response relationship*.

Table 1 presents the characteristics and key findings of the articles. In general, six out of seven studies supported tDCS as a potentially effective therapy<sup>7,8,10-13</sup>.

## DISCUSSION

This systematic review revealed a low number of clinical studies in this topic. Although the selected studies had robust methodologies, the results were heterogeneous in their outcomes, making it challenging to draw definitive conclusions. One methodological issue to be noted regarding the use of tDCS is the standardization of application parameters, which varied across studies,

potentially stimulating different brain regions and consequently producing different effects.

Fregni et al. (2020) demonstrated that anodal tDCS in the affected area and cathodal in the unaffected area is likely effective for motor rehabilitation in subacute stroke (Level B). In the Bilateral montage, tDCS is possibly effective for motor rehabilitation in subacute stroke (Level C)<sup>7</sup>. García-Rudolph et al. (2019), in their Systematic Review with Meta-Analysis, included tDCS intervention in 5 Meta-Analyses, showing small to moderate effect sizes without heterogeneity<sup>8</sup>.

Fan et al. (2018) revealed statistically significant differences in tDCS compared to the control group (-0.51; 95% CI, -1.02 to -0.01; P = 0.04) in reducing post-stroke unilateral neglect<sup>10</sup>. Li et al. (2018) demonstrated a significant effect of tDCS on mobility (SMD 0.44, 95% CI: 0.01 to 0.87, P = 0.04) and lower limb muscle strength (SMD 1.54, 95% CI: 0.29 to 2.78, P = 0.02). However, no significant effect was found in walking speed (SMD 0.39, 95% CI: -0.06 to 0.85, P = 0.09), walking endurance (SMD 0.28, 95% CI: -0.28 to 0.84, P = 0.33), and balance function (SMD 0.44, 95% CI: -0.06 to 0.94, P = 0.08)<sup>11</sup>.

Elsner et al. (2017) provided evidence of a cathodal tDCS effect on improving Activities of Daily Living (ADL) capacity (standardized mean difference, SMD = 0.42; 95% CI 0.14 to 0.70). However, regarding arm function, measured by the upper extremity Fugl-Meyer assessment (FM-UE), there was no improvement post-stroke<sup>12</sup>.

Chhatbar et al. (2016) demonstrated a large effect in bihemispheric tDCS (Hedge's  $g = 1.30$ , 95% CI = [-0.14, 2.75], P = 0.08), but a mild to moderate effect size was found with anodal (Hedge's  $g = 0.21$ , 95% CI = [-0.72, 1.14], P = 0.65) and cathodal (Hedge's  $g = 0.43$ , 95% CI = [-0.23, 1.08], P = 0.20). It also revealed that studies recruiting individuals with chronic stroke showed a larger effect size (Hedge's  $g = 1.23$ , 95% CI = [0.20, 2.25], P = 0.02), while those with acute stroke showed a smaller effect size (Hedge's  $g = 0.18$ , 95% CI = [-0.30, 0.66], P = 0.07)<sup>13</sup>.

Denissen et al. (2019) revealed uncertainty about tDCS reducing the number of falls compared to the control group (risk ratio 0.30, 95% CI 0.14 to 0.63; 60 participants), even though only one study was found for this comparison. Therefore, it suggests that the evidence is of low quality, and more evidence is needed for tDCS to be introduced in fall prevention intervention<sup>9</sup>.

To date, there is no Level A recommendation achieved for any clinical indication<sup>14</sup>. However, Fregni et al. (2020) showed a Level B recommendation with anodal ipsilesional and cathodal contralesional tDCS in subacute stroke. It also presented a Level C recommendation for Bilateral montage, with evidence that tDCS is possibly effective for motor rehabilitation in subacute stroke<sup>7</sup>. Additionally, Chhatbar et al. (2016) showed bihemispheric montage as advantageous<sup>13</sup>. Therefore, recommendations in this work should not be misinterpreted, as overall tDCS demonstrated results in all types of montages and consistently proved beneficial despite heterogeneity among studies.

According to Elsner et al. (2017), different effects of tDCS on the rehabilitation of Activities of Daily Living (ADLs) using cathodal tDCS<sup>8,12</sup>, although not presenting heterogeneity in the quantification of effects, were small to moderate. This superiority of cathodal tDCS can be explained by Di Pino et al. (2014), who demonstrated evidence that responses to different tDCS protocols to promote functional recovery post-stroke may involve inhibitory or excitatory application in the affected or unaffected hemisphere.

From a marker of microstructural defect in affected motor pathways, it was evident that patients with extensive corticospinal tract lesions responded poorly to inhibitory stimulation (cathodal) of the unaffected hemisphere, while patients with smaller lesions responded well<sup>15</sup>, as there may be a change in the balance between neuron excitation and inhibition, and this hyperexcitability may be a sign of resetting neuron activity in the affected area due to homeostatic mechanisms<sup>16</sup>, providing a conducive environment for axonal sprouting signal in the infarcted area<sup>16</sup>. In this regard, Chhatbar et al. (2016), in their Meta-analysis,

showed that bihemispheric tDCS use can simultaneously decrease (cathodal) and increase (anodal) neural activity in the affected and unaffected areas, respectively.

This demonstrates that there is still no standardization of how to apply the technique, and the patient's profile may influence the choice of protocol. In this sense, Fregni et al. (2020) show us that parameters, density, and duration of stimulation are factors that change the outcome, and there is no systematic measurement of how these factors interact, so it is also important to consider the severity of the stroke when planning such factors<sup>7</sup>. Similar findings were found by other authors, suggesting the need for standardization of tDCS application protocols for result reliability<sup>5,6,17</sup>.

An interesting finding reveals the use of tDCS to improve unilateral neglect, characterized by the inability to notice, associate, or respond to events from the contralateral hemibody or hemispace to the brain injury<sup>18</sup>, or even as a disorder of attention, perception, and action post-stroke<sup>18</sup>. As demonstrated in the study by Oliveira et al. (2014), where tDCS use showed statistically significant improvements in unilateral neglect compared to a control group<sup>18</sup>. These studies align with Li et al. (2018) and Elsner et al. (2017), showing a significant improvement in mobility and lower limb strength<sup>11</sup> and ADLs<sup>12</sup>. However, these same studies did not observe significant improvements in walking speed, endurance, and balance<sup>11</sup> and improvement in the affected upper limb function<sup>12</sup>. Regarding falls, Denissen et al. (2019) showed little certainty that tDCS use could prevent falls or even reduce their occurrence, thus characterizing it as low-quality evidence<sup>9</sup>.

This study has limitations that must be acknowledged. The included studies used different and distinct evaluation methods, as despite the eligibility criteria being described, the articles did not have all variables equal and presented reasonably homogeneous results<sup>7-13</sup>, leading to restrictions in analyzing post-tDCS intervention effects, inducing an isolated result from each article. However,



this should not interfere with the result or the importance of our study and future studies.

## **CONCLUSIONS**

tDCS, applied in isolation, can be an effective technique in improving post-stroke motor deficits, including affected upper limb function, lower limb strength, unilateral neglect, mobility, and ADLs. It is suggested that further studies be conducted for the standardization of a treatment protocol, as well as to determine the optimal timing of its application in post-stroke patients.

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