Effects of transcranial direct current stimulation on motor learning in healthy individuals: a systematic review

Efeitos da estimulação transcraniana por corrente contínua no aprendizado motor: uma revisão sistemática

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Abstract

Introduction: Transcranial direct current stimulation (tDCS) has been used to modify cortical excitability and promote motor learning. **Objective**: To systematically review published data to investigate the effects of transcranial direct current stimulation on motor learning in healthy individuals. **Methods**: Randomized or quasi-randomized studies that evaluated the tDCS effects on motor learning were included and the risk of bias was examined by Cochrane Collaboration's tool. The following electronic databases were used: PubMed, Scopus, Web of Science, LILACS, CINAHL with no language restriction. **Results**: It was found 160 studies; after reading the title and abstract, 17 of those were selected, but just 4 were included. All studies involved healthy, right-handed adults. All studies assessed motor learning by the Jebsen Taylor Test or by the Serial Finger Tapping Task (SFTT). Almost all studies were randomized and all were blinding for participants. Some studies presented differences at SFTT protocol. **Conclusion**: The result is insufficient to draw conclusions if tDCS influences the motor learning. Furthermore, there was significant heterogeneity of the stimulation

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parameters used. Further researches are needed to investigate the parameters that are more important for motor learning improvement and measure whether the effects are long-lasting or limited in time.

Keywords: Electric stimulation. Learning. Neuronal plasticity.

Resumo

Introdução: A estimulação transcraniana por corrente contínua (ETCC) tem sido usada para modificar a excitabilidade cortical e promover o aprendizado motor. Objetivo: Revisar sistematicamente os dados publicados para investigar os efeitos da estimulação transcraniana por corrente contínua sobre o aprendizado motor em indivíduos saudáveis. Métodos: Foram incluídos estudos randomizados ou quase randomizados que avaliaram os efeitos da ETCC sobre o aprendizado motor. O risco de viés foi avaliado por meio da ferramenta Cochrane Collaboration. As seguintes bases de dados eletrônicas foram utilizadas: PubMed, Scopus, Web of Science, LILACS, CINAHL, sem restrição de idioma. Resultados: Foram encontrados 160 estudos. Depois de ler o título e o resumo, 17 deles foram selecionados, mas apenas 4 foram incluídos. Todos os estudos envolveram adultos saudáveis e destros e avaliaram o aprendizado motor por meio do Jebsen Taylor Test ou do Serial Finger Tapping Task (SFTT). Quase todos os estudos foram randomizados e todos foram cegos para os participantes. Alguns estudos apresentaram diferenças no protocolo do SFTT. Conclusão: O resultado é insuficiente para tirar conclusões se a ETCC influencia o aprendizado motor. Além disso, houve uma significativa heterogeneidade dos parâmetros de estimulação utilizados nos estudos. Futuras pesquisas são necessárias para investigar quais são os parâmetros mais importantes para a melhoria do aprendizado motor e medir se os efeitos são duradouros ou limitados ao longo do tempo.

Palavras-chave: Estimulação elétrica. Aprendizado. Plasticidade neuronal.

Introduction

Since transcranial direct current stimulation (tDCS) was introduced by Nitsche and Paulus in 2000, it has been used to modify cortical excitability in a non-invasive and painless way (1, 2). Furthermore, tDCS has been shown to be effective for promoting motor learning in healthy subjects (3-5) and patients with brain disorders (6-8).

Modulating externally the brain excitability with the proposal of understand the mechanisms involved in motor learning has been largely employed in the last decade (9-16). Electrophysiological data demonstrate that changes of neuronal activity and excitability accompany the learning of new motor skill (17). As improving motor learning is the aim the therapy of many neurological and musculoskeletal conditions, tDCS has been pointed out as a therapeutic promise for enhancing clinical outcomes in these conditions (18). However, it is known that tDCS modulate the brain activity specific to the polarity, location of application and other parameters of stimulation (e.g. duration, intensity, size of electrode) (1, 14, 19). Then,

before using it in clinical practice, it is crucial to determine the best stimulation parameters required to increase motor learning, as well as to consider the effective ability of tDCS to improve motor learning.

Here, the studies addressing the effects of tDCS on motor learning over the non-dominant upper limb motor function in healthy individuals were systematically reviewed. Furthermore, the purpose of the current review was to investigate the parameters of stimulation recommended in these studies.

Methods

Literature research and Selection criteria

A literature research was performed using the following databases: PubMed, Scopus, Web of Science, LILACS, CINAHL, from their inception to January 2014.

The following key words were used: 'transcranial direct current stimulation', 'tDCS' or 'direct current stimulation', 'motor skill' or 'motor learning', 'upper extremity' or 'non-dominant upper extremity',

'healthy subjects', and any other associated variation. These terms were used in various combinations to find relevant studies. In addition to searching the database, the reference lists of all retrieved papers were searched for any related publications unidentified by the initial search strategy.

Two reviewers (AF and SR) screened independently the title and abstracts identified from the database research to assess whether they met the predefined inclusion criteria. The inclusion and exclusion criteria are listed in Table 1. Full text articles from the potentially relevant studies were reviewed to determine the studies to be included in the review. Differences of opinion between reviewers were resolved by consulting the opinion of a third reviewer (KMS).

Outcome measures

Randomized and quasi-randomized controlled clinical trials that evaluated the effects of tDCS on motor learning as primary or secondary outcome measures were included. The motor learning had to be assessed by a performance motor test done with non dominant upper limbs before and after tDCS, i.e., "off-line" studies.

Risk of bias assessment

The Cochrane Collaboration's tool (Reviewer's Handbook version 5.1.0) was used to assess the risk of bias of the included studies. Through five items, this tool evaluates selection, execution, detection and publication bias. In each item the evaluator considers a low, unclear or high risk of bias. In this systematic review, for each methodological procedure the "low risk of bias" was considered when the authors cited the item above the text, "high risk of bias" when the authors report that did not perform it and "unclear risk of bias" when it was not clear whether it was done.

Data extraction

The following data relevant to the aims of this study were extracted: (1) study design; (2) characteristics of subjects; (3) outcome measures and tDCS parameters; and (4) mean ± standard deviation (SD) of motor outcome before and immediately post intervention. Given the purpose of this review, only the data of non-dominant upper extremity were extracted.

Table 1 - Criteria for considering studies for the review

	Inclusion	Exclusion
Participants	Studies in which individuals were healthy and over 18 years of age.	
Intervention	Studies that involve tDCS as intervention of interest.	Studies in which there was combination of tDCS with other interventions (e.g., mental practice, mirror therapy, motor training, rTMS or PAS).
Comparison	Intervention vs. no treatment or sham treatment.	
Outcomes	A motor performance test done with non dominant upper extremity.	
A motor performance test done with non dominant upper extremity	Randomized or quasi-randomized. Blind (volunteers) clinical trials.	
Type of publications	Studies published in a peer-reviewed journal, regardless of the year of publication and the language.	

Note: tDCS = transcranial direct current stimulation; rTMS = repetitive transcranial magnetic stimulation; PAS = paired associative stimulation.

Results

Identification and selection of studies

The literature research of on-line databases identified 160 studies. After removal of the duplicates, the research yielded 87 citations. After the exclusion based on title and abstract, 17 potentially relevant articles were obtained and evaluated by two independent reviews (AF and SR), and five papers that met our eligibility criteria were analyzed. Two papers (15-16) resulted of the same study and the results obtained in one of them (15) were shown in the other (16) with a larger sample, so four studies were considered and included (Figure 1).

Risk of bias

All studies showed more than one type of bias (Figure 2). Just one study did not perform randomization (10) and all of them failed in reporting the concealment of treatment allocation (9, 10, 12, 16). Two studies did not mention if the evaluators were blinding (9, 16). Three studies failed in reporting if the outcome assessor was blinding (10, 12, 16). All studies presented selective reporting of outcomes (9-10, 12, 16).

TDCS protocol

The stimulation parameters of tDCS varied among studies and are summarized in Table 2. All studies included used stimulation intensity of 1mA and time duration over 15 min. The parameters of electrode size and tDCS type were heterogeneous among the studies. The cortical area stimulated was the primary motor cortex (M1) in all studies.

Overview of included studies

Table 3 shows the main characteristics of the studies included in the systematic review. In sum, 85 healthy, right-handed adults were evaluated. Sham treatment was given to 63 patients and 63 patients were submitted to active tDCS. All studies verified improvement in motor performance of non-dominant hand and investigated the upper extremity dominance was by the Edinburgh Handedness Inventory a sufficient means of assessment of the handedness aspect (20).
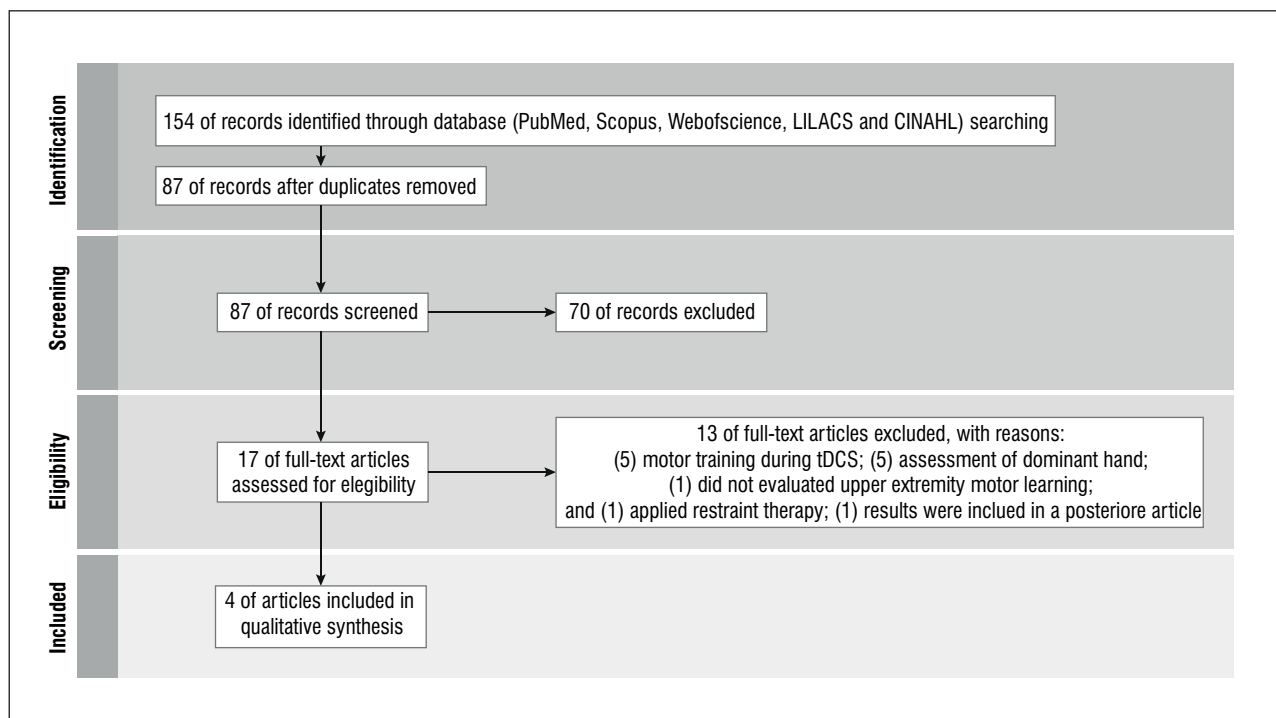
Figure 1 - Flowchart for the selection of studies

Note: tDCS = transcranial direct current stimulation.

		Randomization (selection bias)	Concealment of treatment allocation (selection bias)	Blinding of participants and evaluators (execution bias)	Blinding outcome assessor (detection bias)	Selective reporting of outcomes (publication bias)
	Low risk of bias (+)					
	Unclear risk of bias (?)					
	High risk of bias (-)					
Boggio et al. 2006		+	?	+	?	-
Vines et al. 2008a		+	?	?	-	-
Vines et al. 2008b		+	?	?	?	-
Tecchio et al. 2010		-	?	+	?	-

Figure 2 - Risk of bias of the included studies by Cochrane Collaboration's tool
Source: Handbook version 5.1.0 (22).

Table 2 - Parameters of tDCS protocol of the included studies

Study (country)	Current intensity (mA)	Electrode size (cm²) (Act/Ref)	Stimulation time (min)	tDCS type	Electrode placement
[12] (Brazil)	1	35/35	20	anodal Sham	- anode: right M1 - cathode: contralateral supraorbital area
[16] (USA)	1	16.3/30	20	anodal cathodal sham	- anode: right M1 or left M1 or contralateral supraorbital area - cathode: right M1 or left M1 or contralateral supraorbital area
[9] (USA)	1	16.3/30	20	dual-hemisphere anodal sham	- anode: right M1 - cathode: left M1 (dual-hemisphere) or contralateral supraorbital area (anodal)
[10] (Italy)	1	35/35	15	anodal sham	- anode: right M1 - cathode: ipsilateral arm

Note: Act = active; Ref = reference; min = minutes; tDCS = transcranial direct current stimulation; M1 = primary motor cortex.

Table 3 - Characteristics of included studies

Study (country)	Individuals (M/F)	Mean age (Y)	Dominant hand	Assessed	Assessment tool	Outcome (motor learning)
[12] (Brazil)	8 (0/8)	22.8	right	left hand	JTT	- anodal tDCS: improve 9.41% from baseline (p = 0.0004) - sham tDCS: improve 1.3% from baseline (p = 0.84)
[9] (USA)	16*	27.6	right	left hand	SFTT	- dual-hemisphere tDCS: improve 24% from baseline - anodal tDCS: improve 16% from baseline - sham tDCS: improve 12% from baseline - dual-hemisphere vs. anodal tDCS: p = 0.021 - dual-hemisphere vs. sham tDCS: p = 0.041 - anodal vs. sham tDCS: p > 0.05
[16] (USA)	17*	not reported	right	left hand	SFTT	- cathodal vs. anodal tDCS: p = 040** - cathodal vs. sham tDCS: p = 0.018** - anodal vs. sham tDCS: p > 0.09**
[10] (Italy)	47*	29	right	left hand	SFTT	- anodal tDCS: increase 11% from baseline (p = 0.011) sham tDCS: increase 5% (p = 0.665) - anodal vs. sham tDCS: p = 0.027

Note: M/F = male/female; tDCS = transcranial direct current stimulation; SFTT = serial finger time task; JTT = Jebsen Taylor Hand Functional Hand Test. * Did not report the relation of M/F. ** Study did not report the mean of the results obtained after the intervention.

Only one study (12) assessed the effects of tDCS on motor learning by Jebsen Taylor Hand Function Test (JTT). Three studies (9-10, 16) applied the serial finger tapping task (SFTT). The SFTT required subjects to press four numeric keys on a standard computer keyboard with the fingers, repeating a random or a sequential five element sequence "as quickly and as accurately as possible" for a period of 30s. The numeric sequence was displayed at the top of the screen at all times to exclude any working memory component to the task. Each key press produced a white dot on the screen, forming a row from left to right, rather than the number itself, so as not to provide accuracy feedback. The computer recorded the key press responses, and each 30s trial was automatically scored for the number of complete sequences achieved (speed) and the number of errors made (accuracy) a rest period of 30s between trials was applied (21). One study (10) modified the SFTT and submitted subjects to random and sequential nine-element series and given an accuracy feedback to the subjects.

Discussion

This systematic review suggests that tDCS affects motor learning process of the non-dominant upper extremity in healthy adults, but it was not conclusive concerning the tDCS parameters (current intensity, electrode size, stimulation time and type) to be applied for this. All studies included presented risk of bias and failed in reveled the effect size of tDCS on motor learning.

The main objective of a systematic review is to assess the studies risk of bias, irrespectively of the anticipated variability in either the results. For instance, the results may be consistent among studies but all the studies may be flawed (22).

Selection risk of bias were presented in all studies included, this type of bias refers to systematic differences between baseline characteristics of the groups that are compared. The only strength of randomization is that, if successfully accomplished, it prevents selection bias in allocating interventions to participants (22). Two studies (9, 16) did not report if the evaluators were blinding, so, it presented execution risk of bias. In all studies the outcome assessor was not blinding, it is considering a detection risk of bias and could affect the outcome measurements, considering that detection bias refers to systematic differences between groups in how outcomes are determined. All studies presented selective reporting of outcomes, setting up a publication risk of bias this type of bias is one of the most substantial biases affecting results from individual studies (23).

All studies were homogeneous regarding the population evaluated and assessed healthy, right-handed adults. Motor function was assessed by JTT or SFTT, tools recognized in the literature to be effective in measuring motor improvements (21, 24-26).

Two studies modified the original SFTT (9, 16). In these studies an accuracy feedback was given for the subjects during the execution of the task. In general, concurrent augmented feedback has been shown to effectively enhance learning in complex motor tasks (27). In musicians, the auditory feedback reinforced the serial reaction time task, a test similar of the SFTT, performance of the right hand (28). The differences between the results showed in the studies which applied the SFTT could be explained for providing or not accuracy feedback.

Differences in the tDCS protocol applied were identified. The effect of tDCS over the motor learning process was presented when current intensity of 1 mA was applied over the M1 during at least 15 min. In this review the best tDCS type (uni or dual-hemisphere) and electrode size to be used cannot be pointed out. TDCS effects depend of the current density (electrode size/current intensity), so the different results obtained in the included could be explained for the density current applied for each one.

Considering the result of this review, studies that investigate all the types of tDCS and assess motor learning at the same time are necessary to determine the best protocol able to promote motor learning in healthy subjects. The selective reporting of outcomes presented in the studies and the impossibility to calculate the effect size of the tDCS making impossible to conduct a meta-analysis.

This review showed as limitation the fact of have done the search only in electronic databases, so that potential studies that have not been published on these data bases were not selected for analysis and possible inclusion.

Conclusion

This review suggests that tDCS may affect motor learning mechanisms of the non-dominant hand. However, at the moment, the studies are insufficient to draw conclusions. In addition, all studies presented risk of bias and did not provide necessary information to calculate the effect size of the tDCS. Furthermore, there was significant heterogeneity of the parameters of stimulation used. Therefore, further research is needed to investigate which type of motor learning (explicit or implicit) is most likely to influence, and which stimulation parameters are more important for motor learning improvement. This information will be valuable in guiding future use of tDCS in clinical practice.

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