Modulation of pain-descending inhibitory pathway using transcranial direct current stimulation priming protocols in healthy subjects: systematic review

Modulação da via inibitória descendente da dor usando protocolos de priming de estimulação transcraniana por corrente contínua em indivíduos saudáveis: revisão sistemática

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ABSTRACT

BACKGROUND AND OBJECTIVES: Priming is a phenomenon in which brain activity can shift in an inhibitory or excitatory direction, potentially increasing synaptic efficiency in response to a previous input. Transcranial direct current stimulation (tDCS) is a neuromodulation technique that has been extensively investigated as an alternative treatment in pain processing changes. Priming techniques can improve pain relief mechanisms in healthy subjects. However, no systematic reviews have been published that summarize these findings. The objective of this review was to identify and evaluate studies that used tDCS as priming or testing protocols and investigate its effects on the descending inhibitory pathway of pain in healthy people.

CONTENTS: Two independent reviewers searched Medline, Embase, CINAHL, Web of Science, PsycINFO, PEDro, Scopus, and Cochrane databases until January 2024 for studies using tDCS as a priming or testing protocol in healthy subjects to assess changes in the pain descending pathway. Four studies were eligible. Two studies showed that cathodic tDCS increases pain threshold when applied before 1Hz rTMS (repetitive transcranial magnetic stimulation), and this may be mediated by homeostatic metaplasticity mechanisms. Two studies have shown that anodal tDCS combined with exercise can activate central pain control mechanisms; the use of both at the same time may have resulted in a synergistic effect and greater analgesia.

CONCLUSION: The priming approach of cathodal or anodal tDCS appears to change the pain threshold in healthy people, however, the effect is reliant on the test stimulus used and may increase or reverse the intended effect.

Keywords: Diffuse noxious inhibitory control, Repetition priming, Transcranial direct current stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: *Priming* é um fenômeno no qual a atividade cerebral pode mudar em uma direção inibitória ou excitatória, aumentando potencialmente a eficiência sináptica em resposta a um estímulo anterior. A estimulação transcraniana por corrente contínua (ETCC) é uma técnica de neuromodulação extensivamente investigada como uma alternativa de tratamento para alterações no processamento da dor. As técnicas de *priming* podem melhorar mecanismos de analgesia, no entanto, nenhuma revisão sistemática foi publicada sumarizando esses achados. O objetivo desta revisão foi identificar e avaliar estudos que utilizaram ETCC como protocolos *priming* ou teste e investigar seus efeitos na via inibitória descendente da dor em pessoas saudáveis.

CONTEÚDO: Dois revisores independentes consultaram nas bases de dados Medline, Embase, CINAHL, *Web of Science*, *PsycINFO*, PEDro, Scopus e Cochrane, até janeiro de 2024, estudos que utilizaram ETCC como *priming* ou teste em indivíduos saudáveis para avaliar alterações na via descendente da dor. Quatro estudos foram elegíveis. Dois estudos mostraram que a

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HIGHLIGHTS

- This systematic review provides important insights into the use of a non-invasive neuromodulation strategy as a potential priming technique to pain relief.
- Metaplasticity mechanisms are possible mediators of the priming phenomena.
- Priming tDCS effects depend on the parameters and type of subsequent intervention.

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tDCS catódica aumenta o limiar de dor quando aplicada antes da rTMS (estimulação magnética transcraniana repetitiva) de 1 Hz, podendo ser mediada por mecanismos de metaplasticidade homeostática. Dois estudos demonstraram que a tDCS anódica combinada ao exercício pode ativar mecanismos centrais de controle da dor; o uso concomitante teve efeito sinérgico, resultando em maior analgesia.

CONCLUSÃO: A abordagem de *priming* da ETCC catodal ou anodal parece alterar o limiar da dor em pessoas saudáveis, entretanto, o efeito depende do estímulo de teste utilizado e pode aumentar ou reverter o efeito pretendido.

Descritores: Controle inibitório nociceptivo difuso, Estimulação transcraniana por corrente contínua, *Priming* de repetição.

INTRODUCTION

The descending pain inhibitory pathway is an endogenous analgesic mechanism that arises in the periaqueductal gray matter (PAG), which has reciprocal communication with the rostral ventromedial medulla (RVM), locus coeruleus (LC), and dorsal reticular subnucleus (DRS)[1]. Nociceptive afferents reach the PAG, which, through direct serotonergic and noradrenergic neuronal projections with the RVM, triggers inhibition of the nociceptive stimulus[2]. However, this pathway may change in both healthy and unhealthy people, serving as a predictor of pain chronification and poor treatment response[3].

Individuals suffering from chronic pain may experience morphophysiological changes in cortical and subcortical structures as a result of the pain[4-6], affecting regions such as the PAG and impairing pain inhibition mediated by the descending inhibitory pathway[7,8]. These changes could be linked to maladaptive neuroplasticity in various cortical areas involved in pain processing[9,10]. In this regard, studies utilizing neuromodulation techniques for pain control[11], cortical function modulation[12], and the neuroplasticity process have been developed[13].

The transcranial direct current stimulation (tDCS) technique can promote reversible and long-lasting changes in cortex excitability by changing neuronal transmembrane potential, with anodal tDCS mostly triggering neuronal depolarization and increasing cortical excitability, and cathodal tDCS hyperpolarizing the neuronal membrane and decreasing cortical excitability[14].

tDCS is a non-pharmacological, non-invasive, and safe neuromodulation technique that has been extensively studied as an alternative or complementary therapy option for a variety of health issues, including pain processing modifications[15,16]. It acts on neurophysiological mechanisms to enhance or decrease cortical excitability, inducing lasting or reversible changes and targeting specific brain areas[14]. Age, gender, application timing, and sleep are just a few variables that can influence tDCS effects[17], which are also affected by previous neuronal activity[18].

Although tDCS may activate the pain mechanisms system[19], its effect appears to be insufficient when applied in healthy individuals[16]. On the other hand, when combined with another neuromodulatory technique, tDCS's analgesic effect can be enhanced. For example, in patients with chronic low back pain (CLBP), tDCS combined with peripheral electrical stimulation (PES) results in significant clinical pain relief that can last up to three months[20]. These approaches may be related to the priming phenomenon, which involves preparing the brain by modulating excitability in an inhibitory or excitatory manner, thereby increasing synaptic efficiency based on a preceding stimulus[21].

There is evidence that the priming phenomenon can occur during a combination of neuromodulatory techniques via homeostatic or non-homeostatic metaplasticity buttons, which regulate the cortical excitability threshold, shifting it towards long-term potentiation (LTP) or long-term depression (LDP)[22]. Homeostatic controls are bidirectional, adjusted based on previous neuronal activity, and reliant on N-methyl D-Aspartate (NMDA) receptor activation and increased intracellular calcium[18]. Non-homeostatic switches, which are associated with voltage-gated calcium channels, are also linked to the prolongation of the metaplastic effect[21,23]. As a result, prior use of a technique such as the priming protocol can enhance the effect of the subsequent intervention known as testing. These findings show that priming phenomena using neuromodulatory techniques can enhance analgesic effects.

Previous systematic reviews have investigated the effects of various priming protocols with noninvasive neuromodulation techniques on primary motor cortex excitability. These reviews have shown that the effects vary depending on the type of priming used. Specifically, using an inhibitory priming technique followed by an excitatory test stimulus can increase cortical excitability, in the same way that equal stimuli provide a reversal effect[18,23]. However, no systematic reviews were conducted to summarize the effect of tDCS as priming or test protocols on clinical outcomes of the descending pain inhibitory pathway, including pain threshold and conditioned pain modulation (CPM). The primary goal of this review was to identify and assess studies that used tDCS as priming and testing protocols, as well as to investigate their effects on the descending inhibitory pathway of pain in healthy people.

CONTENTS

This literature review was carried out in accordance with the PRISMA Guidelines[24] and was registered in PROSPERO under the identification number CRD42023412986. Two independent authors (RSRJ and AMCB) conducted database searches in the following databases: PubMed, Embase, CINAHL, Web of Science, PsycINFO, Physiotherapy Evidence database (PEDro), Scopus, and the Cochrane Database of Systematic Reviews. In cases of disagreement, a third reviewer (FAH) was brought in to help make the decision. Additional references were found by searching the reference lists of the articles. The Rayyan software was utilized to remove duplicates and filter out titles and abstracts. This application employs a semi-automated procedure to streamline the evaluation of articles for review[25].The articles were chosen for analysis after duplicates were removed. The following terms were used as keywords, and MeSH terms: "Transcranial Direct Current Stimulation", and "Repetition Priming" OR "Priming", and "Descending pain inhibitory pathway". None filter was applied in the search strategy and all keywords were

inserted into the database search page, enclosed in quotation marks. The complete strategy is available in the table 1.
Papers were included if they met the following criteria: Clinical trials; involved human subjects without pain, neurodegenerative, musculoskeletal, psychiatric, or neurological disorders; used tDCS like a priming protocol; and had outcome measures regarding changes in the descending inhibitory pathway of pain.
Exclusion criteria: (1) Neither priming nor the test protocol included NIBS, and (2) the mean results did not assess changes in the descending pain inhibitory pathway.

Data extraction
Following the inclusion of articles, both authors, (RSRJ and AMCB), extracted the subsequent information from each article: study design, sample size, priming intervention and test protocol characteristics, method of assessing pain threshold and CPM, and results (Table 1). The obtained data was inputted into an Excel spreadsheet and subsequently incorporated into the text. Disagreements in interpretation were settled through discussion and mutual agreement.

Quality assessment
Two independent researchers (RSRJ and AMCB) reviewed each included article and assigned a quality score based on the PEDro scale[26], with a third reviewer (FAH) arbitrating any disagreements. The PEDro scale includes several items that are rated on a 'yes/no' basis to assess for each article the external and internal validity. The PEDro scale yields total scores ranging from 0 to 10, with a higher PEDro score indicating higher quality (Table 2).

RESULTS

The initial search yielded 1130 articles, of which 4 were deemed appropriate for inclusion in this review (Figure 1).

Characteristics of the studies
Four clinical trials were included, with 61 healthy participants aged 20 to 30 years old. Two of the four articles included in the results synthesis used transcranial direct current stimulation (tDCS) as a priming strategy previously used with transcranial magnetic stimulation (TMS). Prior application of cathodal tDCS increased cold pain thresholds from 11.5±52 °C to 5.8±3.8 °C and heat pain thresholds from 45.9±1.6 °C to 47.8±1.0 °C (21), as well as pressure pain thresholds from 365.73±90.92 KPa to 405.07±97.44 KPa (22) in relation to the groups that received anodal and sham tDCS priming.
The authors[27] conducted a study where they found that anodal tDCS followed by isometric contraction exercise reduced the intensity of experimental pain caused by the application of Intramuscular Injection of nerve growth factor (NGF). The pain intensity decreased from 0.83±0.94 to 0.33±0.49 immediately after the exercise and 0.42±0.51 fifteen minutes after the intervention in the wrist flexion movement. In the wrist extension movement, the pain intensity decreased from 1.25±0.87 to 0.92±0.51 immediately after the exercise and 0.92±0.51 fifteen minutes after the intervention. These reductions were observed in comparison to a group that received sham-tDCS. However, there were no statistically significant changes in PPT and CPM[27].
The study[28] found that the addition of anodal tDCS to aerobic exercise (AE) resulted in an 83.4% rise in pain threshold. This increase was significantly higher compared to the tDCS (40.7%) and AE/sham tDCS (51.5%). Furthermore, the tDCS/AE group saw earlier and more significant changes in pain threshold compared to the sessions of tDCS and AE/sham tDCS (28). To verify changes in pain perception, all studies used at least one quantitative sensory test (Table 1).

Study quality
All clinical trials included in the review were assessed using the PEDro scale[19] and had an average of 7.75 indicating good methodological quality and a low risk of bias (Table 2). Two studies did not clearly report or describe the method of randomization and group allocation (29,30). Three trials failed to blind the therapists and the evaluator to the delivery or evaluation of the intervention (28–30). Furthermore, despite the risk of bias mentioned, the authors' findings did not take these issues into account.
PEDro criteria: (1) Eligibility criteria were specified; (2) Subjects were randomly allocated to groups (in a crossover study, subjects

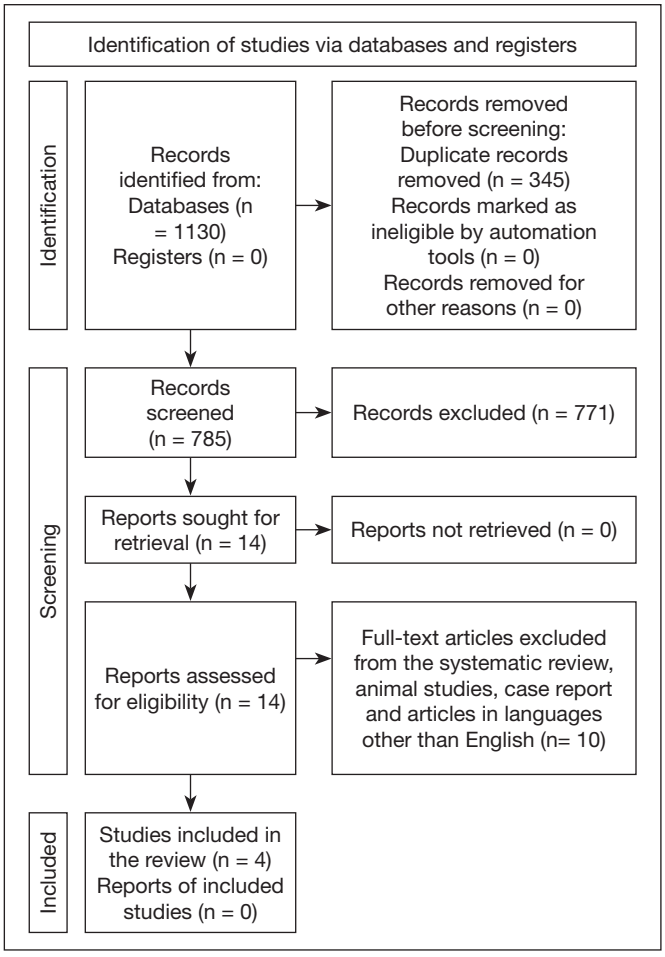

Figure 1. Flowchart of studies included in this review[24].

Table 1. Characteristics of the included studies

Authors	Study design	Subjects	tDCS priming	Application site	Test protocol	Pain threshold	CPM	Adverse effects	Results
Moloney and Witney[29]	Sham-controlled, single-blind study	n = 12 (men)	a-tDCS; 1mA; 25cm²; 10min c-tDCS; 1mA;-25cm²; 10min	A= Left M1 C= Right SO	rTMS; 1Hz; RMT90; M1; 15 min	Thermal stimuli; palmar thenar eminence; 1° to 32°C; 4 times	NA	NR	Priming a-tDCS ↓ CPT Priming c-tDCS ↑ CPT and HTP
Moloney and Witney[30]	Sham-controlled, single-blind study	n =15 (men)	a-tDCS;1mA; 25 cm²;10min. c-tDCS;1mA; 25 cm²;10min	A= Left M1 C= Right SO	rTMS; 1Hz; RMT90; M1; 15 min	Algometer; palmar thenar eminence of the hand; 4 times	NA	NR	Priming a-tDCS no effect PPT Priming c-tDCS ↑ PPT
Borovskis et al.[27]	Double-blind randomized sham-controlled trial	n = 24 (10 men)	a-tDCS;1mA; 25 cm²;10min	A= Left M1 C= Right SO	IHE; 25%±5% MVC; 3 min;	Algometer; Right and Left ECRB, TA muscle bellies; 3 times	Algometer in right ECRB; left hand immersed in cold water; 2 min	NR	Priming a-tDCS ↓ NRS but doesn't affect PPT and CPM
Sato et al.[28]	Single-blind experimental study with a cross-over	n = 10 (6 men)	a-tDCS;2mA; 35 cm²; 20min	A= Left M1 C= Right SO	AE on the cycle ergometer; 20 min	Algometer; nail of the middle finger on the right side	NA	NR	Priming a-tDCS/AE ↑ PPT Priming sham-tDCS/AE and a-tDCS doesn't affect PPT significantly

tDCS = Transcranial direct current stimulation; a-tDCS = anodal tDCS; c-tDCS = cathodal tDCS; rTMS = Repetitive transcranial magnetic stimulation; RMT = Resting motor threshold; M1 = Primary motor cortex; SO: Supraorbital; A = Anodal; C = Cathodal; PPT = Pressure pain threshold; CPM = Conditioned pain modulation; QTS = Quantitative sensory testing; AE = Aerobic exercise; CPT = Cold pain threshold; HPT = Heat pain threshold; ECRB = Extensor carpi radialis brevis; TA = Tibialis anterior; IHE = Isometric handgrip exercise; MVC = maximum voluntary contraction; NRS = Numeric Rating Scale; NA = Not assessed; NR = Not reported.

Table 2. Study quality and outcomes

PEDro Scale Criteria												
Studies	1	2	3	4	5	6	7	8	9	10	11	Total
Moloney and Witney[29]	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	7
Moloney and Witney[30]	Y	N	Y	Y	Y	N	N	Y	Y	Y	Y	7
Borovskis et al.[27]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	9
Sato et al.[28]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8
Mean												7.75

were randomly assigned an order in which treatments were received); (3) Allocation was concealed; (4) The groups were similar at baseline regarding the most important prognostic indicators; (5) There was blinding of all subjects; (6) There was blinding of all therapists who administered the therapy; (7) There was blinding of all assessors who measured at least one key outcome; (8) Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; (9) All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat"; (10) The results of between-group statistical comparisons are reported for at least one key outcome; (11) The study provides both point measures and measures of variability for at least one key outcome; Y = Yes; N = No.

DISCUSSION

The purpose of this systematic review was to identify and assess studies that used tDCS as priming and testing protocols, as well as to investigate their effects on the descending inhibitory pathway of pain in healthy people. The findings show that cathodal tDCS priming enhances analgesic responses and highlights the crucial role of metaplasticity mechanisms. The studies included in this review employed various priming strategies and evaluated pain thresholds as well as CPM.

According to the synaptic modification model[31], metaplastic mechanisms regulate cortical excitability and can be classified as either homeostatic or non-homeostatic. This model suggests the existence of a bidirectional sliding threshold that adjusts based on presynaptic neuronal activity, promoting Long-Term Potentiation (LTP) or Long-term depression (LTD). Considering that tDCS is a neuromodulation technique dependent on neuronal activity, the choice of the priming stimulus, whether inhibitory or excitatory, can significantly affect the subsequent effects of the test stimulus.

Next, we present the different types of priming protocols identified in this review and discuss their repercussions on pain perception in healthy individuals.

Priming tDCS over rTMS

Two studies involving the application of tDCS before 1 Hz rTMS (transcranial magnetic stimulation) were conducted. In

a clinical trial, pain thresholds were evaluated in healthy individuals before and after tDCS priming followed by 1 Hz rTMS. The study revealed that the group receiving cathodic tDCS in primary motor cortex (M1) experienced an increase in cold and heat thermal pain thresholds[29]. The inhibitory preconditioning session caused by cathodic tDCS may be responsible for the increase in pain thresholds observed in the cathodic tDCS-1Hz rTMS protocol.

According to the metaplastic theory, the reduction in cortical activity caused by the cathodic tDCS inhibitory preconditioning session may facilitate a general increase in cortical excitability following the subsequent low frequency rTMS stimulation, resulting in elevated cortical excitation. Increasing M1 excitability may increase PAG activity, which is linked to the antinociceptive descending pathways[29]. As a result, pain threshold and pain relief can be modulated.

The second study demonstrated that priming the primary motor cortex (M1) before 1 Hz rTMS stimulation modulates pain thresholds and analgesia[30]. In this experiment, the group that received cathodal tDCS had a significant increase in their pressure pain threshold. The anodic tDCS group, on the other hand, showed a decrease in cortical excitability with no effect on PPT. Previous research has shown that the effects of both tDCS and rTMS techniques are dependent on the state of neuronal activity[18]. When two inhibitory techniques are used together, they produce a contrasting effect that leads to increased cortical excitability, which can be mediated by metaplasticity's homeostatic mechanisms[23]. Moreover, the activation of regions involved in the emotional processing of pain, such as the anterior cingulate cortex in the basal ganglia or insula, may have been indirectly influenced by M1 stimulation. This indicated that tDCS affects a complex pain-processing network, leading to higher pain thresholds and decreased pain intensity[32].

Taken together, these results suggest that an anterior stimulus may potentiate or suppress the subsequent stimulus. For instance, providing an anterior excitatory stimulus (tDCS anode) followed by an inhibitory stimulus (1 Hz rTMS) activates the inhibitory effect. This may explain the decrease in thermal pain thresholds into the group that received the anode stimulus[29]. In other words, the plastic changes observed in the two clinical trials may be related to brain function, which can be altered by tDCS[18,21]. Combining tDCS and rTMS can result in significant clinical benefits, and understanding the underlying mechanisms can aid in the optimization of treatment strategies[30].

Priming tDCS over exercises

Two studies examined the combination of tDCS with exercise. The authors[27] investigated the effects of anodic tDCS on experimentally induced muscle soreness prior to isometric manual pressure exercises[27]. The Numerical Rating Scale (NRS), pressure pain threshold, and conditioned pain modulation were used as assessment tools in the study. The findings revealed an immediate decrease in NRS scores following the intervention, with greater significance observed in the anodic tDCS group compared to the sham group.

There were no significant differences between the groups in terms of pressure pain threshold or CPM. The authors proposed that while anodic tDCS during exercise accelerates the onset of hypoalgesia, this effect may be mediated by cortical and diencephalic regions rather than descending inhibitory pain pathways[27]. The potential synergism between tDCS mechanisms and exercise, such as strength training, which promotes analgesia, could explain the analgesic effects[33-35]. The effects of tDCS priming can increase corticomotor excitability and enhance the effects of subsequent techniques.

The second study found that combining anodic tDCS with aerobic exercise (AE) increased the pressure pain threshold, implying that anodic tDCS may have facilitated analgesic effects via a central pain control mechanism. The same findings were found in people with fibromyalgia[36], where the tDCS/AE combination had a significant analgesic effect. Because both tDCS[37,38] and AE[39] can activate central pain control mechanisms, using both at the same time may have resulted in a synergistic effect, resulting in greater analgesia[27].

However, when anodic tDCS was performed before exercise, there was no change in the pain threshold, contradicting the priming perspective, which would have anticipated a reverse effect favoring cortical inhibition. On the other hand, when tDCS was used at the same time as exercise, changes in the pressure pain threshold were seen. This demonstrates that exercise and tDCS work in tandem[28], and that the synergistic analgesic effects found may be mediated by mechanisms other than homeostatic metaplasticity.

Limitations and future perspectives

It is important to highlight some limitations of the present review. The lack of quantitative analysis, the heterogeneity of protocols and the small sample size of the included articles could somehow limit the study's conclusion. The included studies mostly evaluated only male individuals, so future studies can be conducted with people of both genders. Thus, there is a need for larger controlled trials that perform assessment blinding, which could increase the power of results.

Furthermore, only one study includes a test and conditioned stimulus to evaluate the CPM test, a mechanism that allows researchers to measure the response of the descending pain inhibitory pathway. Second, different priming and testing protocols, as well as pain assessment methods, were used. Finally, the included studies differ significantly in terms of assessment methods and intervention protocols. These limitations underscore the important need for additional tDCS research to assess the efficacy of priming techniques for improving the descending pain inhibitory system.

CONCLUSION

In healthy people, using tDCS as a priming method can modulate descending inhibitory pathway activity, and raise pain threshold. The findings of this systematic review suggest that the priming phenomenon may enhance the descending pain inhibitory system in healthy people when cathodal tDCS is

used before 1 Hz rTMS. However, no priming studies were found that attempted to improve the efficacy of tDCS. Priming and testing protocols must be carefully adjusted to ensure that the effects are accentuated rather than reversed, while also accounting for the shift in homeostatic metaplasticity.

AUTHORS' CONTRIBUTIONS

Raquel Sales Rocha-Jacob
Data Collection, Project Management, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision
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Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision
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Data Collection, Methodology, Writing - Preparation of the original
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Data collection, Methodology, Writing - Preparation of the original
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Data Collection, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Supervision

REFERENCES

1. Ong WY, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. Mol Neurobiol. 2019;56(2):1137-66.
2. Harrison R, Gandhi W, van Reekum CM, Salomons TV. Conditioned pain modulation is associated with heightened connectivity between the periaqueductal grey and cortical regions. Pain Rep. 2022;7(3):e999.
3. Ramaswamy S, Wodehouse T. Conditioned pain modulation--A comprehensive review. Neurophysiol Clin. 2021;51(3):197-208.
4. Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci. 2004;24(46):10410-5.
5. Cauda F, Palermo S, Costa T, Torta R, Duca S, Vercelli U, et al. Gray matter alterations in chronic pain: a network-oriented meta-analytic approach. Neuroimage Clin. 2014;4:676-86.
6. Yang S, Chang MC. Chronic pain: structural and functional changes in brain structures and associated negative affective states. Int J Mol Sci. 2019;20(13). Available from: http://dx.doi.org/10.3390/ijms20133130
7. Coulombe MA, Lawrence KS, Moulin DE, Morley-Forster P, Shokouhi M, Nielson WR, et al. Lower functional connectivity of the periaqueductal gray is related to negative affect and clinical manifestations of fibromyalgia. Front Neuroanat. 2017;11:47.
8. Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. Neuroimage Clin. 2014;6:100-8.
9. Thoma P, Drämel N, Grothe M, Lotze M, Fleischmann R, Strauss S. Impaired pain processing at a brainstem level is involved in maladaptive neuroplasticity in patients with chronic complex regional pain syndrome. Int J Mol Sci. 2022;23(23). Available from: http://dx.doi.org/10.3390/ijms232315368.
10. Eldufani J, Elahmer N, Blaise G. A medical mystery of complex regional pain syndrome. Heliyon. 2020;6(2):e03329.
11. Baptista AF, Fernandes AMBL, Sá KN, Okano AH, Brunoni AR, Lara-Solares A, et al. Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC2-NIN-CP). Pain Rep. 2019;4(1):e692.
12. Schoellmann A, Scholten M, Wasserka B, Govindan RB, Krüger R, Gharabaghi A, et al. Anodal tDCS modulates cortical activity and synchronization in Parkinson's disease depending on motor processing. Neuroimage Clin. 2019;22:101689.
13. Flöel A. tDCS-enhanced motor and cognitive function in neurological diseases. Neuroimage. 2014;85 Pt 3:934-47.
14. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527 Pt 3(Pt 3):633-9.
15. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128(1):56-92.
16. Gurdiel-Álvarez F, González-Zamorano Y, Lerma-Lara S, Gómez-Soriano J, Sánchez-González JL, Fernández-Carnero J, et al. Transcranial Direct Current Stimulation (tDCS) Effects on Quantitative Sensory Testing (QST) and nociceptive processing in healthy subjects: a systematic review and meta-analysis. Brain Sci. 2023;21;14(1). Available from: http://dx.doi.org/10.3390/brainsci14010009.
17. Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol. 2010;588(Pt 13):2291-304.
18. Hurley R, Machado L. Using tDCS priming to improve brain function: can metaplasticity provide the key to boosting outcomes? Neurosci Biobehav Rev. 2017 Dec;83:155–9.
19. Pacheco-Barrios K, Cardenas-Rojas A, Thibaut A, Costa B, Ferreira I, Caumo W, et al. Methods and strategies of tDCS for the treatment of pain: current status and future directions. Expert Rev Med Devices. 2020;17(9):879-98.
20. Hazime FA, Baptista AF, de Freitas DG, Monteiro RL, Maretto RL, Hasue RH, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: a randomized, double-blind, factorial clinical trial. Eur J Pain. 2017;21(7):1132-43.
21. Müller-Dahlhaus F, Ziemann U. Metaplasticity in human cortex. Neuroscientist. 2015;21(2):185-202.
22. Karabanov A, Ziemann U, Hamada M, George MS, Quartarone A, Classen J, et al. Consensus Paper: probing homeostatic plasticity of human cortex with non-invasive transcranial brain stimulation. Brain Stimul. 2015;8(5):993-1006.
23. Hassanzahraee M, Zoghi M, Jaberzadeh S. How different priming stimulations affect the corticospinal excitability induced by noninvasive brain stimulation techniques: a systematic review and meta-analysis. Rev Neurosci. 2018;29(8):883-99.
24. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Rev Esp Cardiol. 2021;74(9):790-9.
25. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
26. Moseley AM, Herbert RD, Sherrington C, Maher CG. Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). Aust J Physiother. 2002;48(1):43-9.
27. Borovskis J, Cavaleri R, Blackstock F, Summers SJ. Transcranial direct current stimulation accelerates the onset of exercise-induced hypoalgesia: a randomized controlled study. J Pain. 2021;22(3):263-74.
28. Sato G, Osumi M, Nobusako S, Morioka S. The effects of transcranial direct current stimulation combined with aerobic exercise on pain thresholds and electroencephalography in healthy adults. Pain Med. 2021;22(9):2057-67.
29. Moloney TM, Witney AG. Transcranial direct current stimulation (tDCS) priming of 1Hz repetitive transcranial magnetic stimulation (rTMS) modulates experimental pain thresholds. Neurosci Lett. 2012;534:289-94.
30. Moloney TM, Witney AG. Pressure pain thresholds increase after preconditioning 1 Hz repetitive transcranial magnetic stimulation with transcranial direct current stimulation. PLoS One. 2014;9(3):e92540.
31. Cooper LN, Bear MF. The BCM theory of synapse modification at 30: interaction of theory with experiment. Nat Rev Neurosci. 2012;13(11):798-810.
32. Naegel S, Biermann J, Theysohn N, Kleinschnitz C, Diener HC, Katsarava Z, et al. Polarity-specific modulation of pain processing by transcranial direct current stimulation - a blinded longitudinal fMRI study. J Headache Pain. 2018;19(1):99.
33. Galdino GS, Duarte IDG, Perez AC. Participation of endogenous opioids in the antinociception induced by resistance exercise in rats. Braz J Med Biol Res. 2010;43(9):906-9.
34. Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. Front Hum Neurosci. 2013;7:628.
35. Kidgell DJ, Stokes MA, Pearce AJ. Strength training of one limb increases corticomotor excitability projecting to the contralateral homologous limb. Motor Control. 2011;15(2):247-66.
36. Mendonca ME, Simis M, Grecco LC, Battistella LR, Baptista AF, Fregni F. Transcranial direct current stimulation combined with aerobic exercise to optimize analgesic responses in fibromyalgia: a randomized placebo-controlled clinical trial. Front Hum Neurosci. 2016;10:68.
37. Mehta S, McIntyre A, Guy S, Teasell RW, Loh E. Effectiveness of transcranial direct current stimulation for the management of neuropathic pain after spinal cord injury: a meta-analysis. Spinal Cord. 2015;53(11):780-5.
38. Ji Y, Ni X, Zheng K, Jiang Y, Ren C, Zhu H, et al. Combined effects of transcranial direct current stimulation and aerobic exercise on inhibitory control function in healthy young adults: an event-related potential study. Brain Cogn. 2023;173:106090.
39. Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. Pain. 2014;155(1):158-67.