



## Alternate sessions of transcranial direct current stimulation (tDCS) reduce chronic pain in women affected by chikungunya. A randomized clinical trial



Clecio Gabriel De Souza <sup>a, b, 1, \*</sup>, Rodrigo Pegado <sup>a, h, 1</sup>, Jardson Costa <sup>c</sup>, Edgard Morya <sup>d, g, h, 1</sup>,  
Abraão Fontes Baptista <sup>e, g, h</sup>, Gozde Unal <sup>f</sup>, Marom Bikson <sup>f</sup>, Alexandre Hideki Okano <sup>e, g, h</sup>

<sup>a</sup> Federal University of Rio Grande Do Norte, Postgraduate Program in Rehabilitation Sciences, Santa Cruz, RN, Brazil

<sup>b</sup> Graduate Program in Collective Health, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil

<sup>c</sup> Faculty Estacio of Rio Grande Do Norte, Natal, RN, Brazil

<sup>d</sup> Edmond and Lily Safra International Neuroscience Institute, Santos Dumont Institute, Macaíba, RN, Brazil

<sup>e</sup> Universidade Federal do ABC, Center for Mathematics, Computing and Cognition, São Bernardo do Campo, SP, Brazil

<sup>f</sup> Department of Biomedical Engineering, The City College of New York, NY, USA

<sup>g</sup> Brazilian Institute of Neuroscience and Neurotechnology (BRAINN/CEPID-FAPESP), University of Campinas, Campinas, São Paulo, Brazil

<sup>h</sup> NAPeN Network (Rede de Núcleos de Assistência e Pesquisa em Neuromodulação), Brazil

### ARTICLE INFO

#### Article history:

Received 9 April 2020

Received in revised form

28 October 2020

Accepted 21 February 2021

Available online 3 March 2021

#### Keywords:

Chikungunya virus

Arthralgia

Chronic pain

Transcranial direct current stimulation

### ABSTRACT

**Context:** Thousands of people worldwide have been infected by the chikungunya virus (CHIKV), and the persistence of joint pain symptoms has been considered the main problem. Neuromodulation techniques such as transcranial direct current stimulation (tDCS) act on brain areas involved in the processing of chronic pain. It was previously demonstrated that tDCS for five consecutive days significantly reduced pain in the chronic phase of chikungunya (CHIK).

**Objective:** To analyze the effect of alternate tDCS sessions on pain and functional capacity in individuals affected by CHIK.

**Methods:** In a randomized clinical trial, 58 women in the chronic phase of CHIK were divided into two groups: active-tDCS (M1-S0, 2 mA, 20 min) and sham-tDCS. The Visual Analogue Scale (VAS) and the Brief Pain Inventory (BPI) were used to assess pain, while the Health Assessment Questionnaire (HAQ) assessed functional capacity. These scales were used before and after six sessions of tDCS in nonconsecutive days on the primary motor cortex, and at follow-up consultation 7 and 15 days after the last session. A repeated measures mixed-model ANOVA was used for comparison between groups (significant  $p$ -values < 0.05).

**Results:** A significant pain reduction ( $Z [3, 171] = 14.303$ ;  $p < 0.0001$ ) was observed in the tDCS group compared to the sham group; no significant difference in functional capacity was observed ( $Z [1.57] = 2.797$ ;  $p = 0.1$ ).

**Conclusion:** Our results suggest that six nonconsecutive sessions of active tDCS on M1 reduce pain in chronic CHIKV arthralgia.

© 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

### Introduction

Arboviruses are a group of viruses transmitted by vectors. The main current arboviral diseases circulating are dengue, zika, and chikungunya (CHIK) [1]. They have spread worldwide, especially in Latin America, where the high number of cases affected negatively the population [2]. The acute phase of CHIK presents symptoms such as fever, headache, muscle pain, and symmetric arthralgia, especially in the wrist and ankle joints. Approximately 50% of

\* Corresponding author.

E-mail addresses: [cleciogabriel@ufrn.edu.br](mailto:cleciogabriel@ufrn.edu.br) (C.G. De Souza), [rodrigopegado@gmail.com](mailto:rodrigopegado@gmail.com) (R. Pegado), [edgard.morya@isd.org.br](mailto:edgard.morya@isd.org.br) (E. Morya), [alexandre.okano@ufabc.edu.br](mailto:alexandre.okano@ufabc.edu.br) (A.H. Okano).

<sup>1</sup> These authors contributed equally to this work.

patients have chronic arthralgia for up to 6 years [3,4]. The disease is considered chronic when symptoms persist for over three months [3]. This phase accounts for a high rate of persistent and incapacitating arthralgia, resulting in a reduction of productivity and quality of life [4]. To date, there is no effective treatment for the CHIKV chronic pain [5–7], which may result of alterations in neural networks and central pain mechanisms, both related to pain perception, sensitization, and modulation [8].

In the last decades, non-pharmacological treatment strategies for chronic pain based on noninvasive neuromodulation techniques were developed to act on central pain processing, such as transcranial direct current stimulation (tDCS) [9,10]. tDCS applies a low-intensity sustained electric current on the scalp to produce acute or lasting changes in cortical excitability [11,12]. According to electrode montage, notably the anodal motor cortex (M1) and cathodal contralateral supra orbital area (SO) [13,14], a modulatory effect can be observed in brain areas responsible for pain processing [15–17].

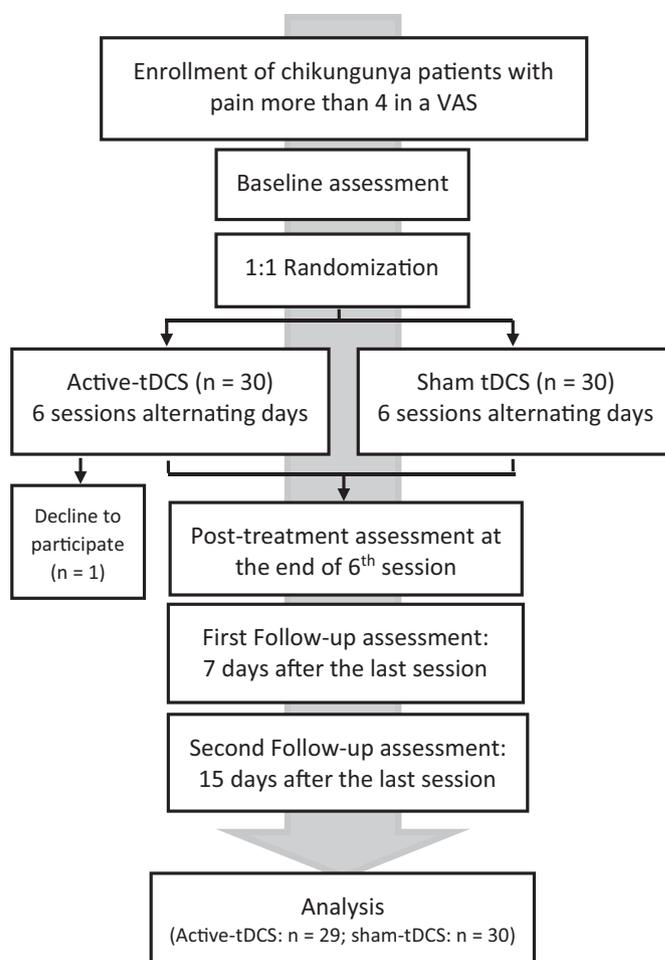
Possible mechanisms of action of M1-SO montage on pain involve: 1) M1 network with brain structures decreasing thalamic hyperactivity induced by chronic pain; 2) neurochemical mediation of neurotransmitters and central receptors involved in the inhibitory control of pain [18,19]; and/or 3) diffuse current flow leading to broad stimulation of pain-related cortical and subcortical structures [15]. Several studies demonstrated the tDCS effects on chronic pain conditions [20,21], more specifically in fibromyalgia [22], migraine [23], nonspecific low back pain [24], and knee osteoarthritis [25]. We previously reported pain reduction in symptomatic individuals with CHIKV after five consecutive sessions of M1-SO tDCS [26].

Multiple daily sessions of tDCS are typically used clinically to maximize the size and duration of the effect. However one of the barriers for individuals with chronic diseases is the difficulty to access specialized services, which hinders treatment adherence [27]. A previous study assessed the impact of the absence of up to two consecutive sessions of tDCS on the clinical efficacy of ten sessions for major depression and found similar results to consecutive sessions [28]. Previous studies in healthy individuals suggested that stimulation on alternate days might produce cumulative (lasting) effects [29]. Moreover, there are few reports on the effects of tDCS applied on nonconsecutive days. Therefore, the present study evaluated the effects of nonconsecutive tDCS session on pain and functional capacity in individuals with chronic CHIKV arthralgia.

## Material and methods

### Study design

A randomized, double-blinded clinical trial was conducted in the city of Natal, Brazil, in 2018. The sample was recruited at the Onofre Lopes University Hospital. The inclusion criteria were female patients, aged between 28 and 70 years, who had received a chikungunya diagnosis over three months prior, as evidenced by laboratory or clinical exams, and a minimum of CHIKV related pain score of 4 on the Visual Analogue Scale (VAS). The flowchart illustrating the process of the study is shown in Fig. 1. These criteria were based on previous studies that demonstrated that the evolution of the chronicity of joint symptoms is more commonly observed in women and in this age group [30,31]. The participants who withdrew from treatment or who did not comply with the study schedule were included as intention to treat [32]. Individuals with epilepsy, metallic implants at the stimulation sites, and history of alcohol abuse, as well as breastfeeding and pregnant women were not included in this study. The sample was randomly divided into two groups using the software randomization.com: active



**Fig. 1.** Flowchart of the progress through the phases of randomized double-blinded clinical trial of two groups.

group (active-tDCS) and sham group (sham-tDCS). To ensure concealment of allocation, opaque and sealed envelopes with sequential numbering were used. Only one independent researcher had access to the list of participants.

### Sample size

A pilot test was performed with 17 participants, and the results were used to calculate the sample size of the study, considering the estimated difference between groups and the respective standard deviations [33]. VAS was selected as the primary outcome with a difference of 1.70 between groups, and a standard deviation of 1.40 for the active-tDCS and 2.00 for the sham-tDCS. Based on these data and adopting a significance level of 95% and a statistical power of 80%, the ideal number of participants for each group was 24, for a total of 48 participants. To circumvent the selection bias and account for losses to follow-up and systematic errors, the sample was increased by 20%; therefore, 30 participants were included in each group with one missing in active-tDCS group for a total of 59 participants in the study. Participants were recruited through social media and television outreach and screened by the researchers according to the eligibility criteria established for this research.

### Variables

Pain was selected as the primary outcome and assessed by VAS, graded on a scale of 11 points (0–10), where 0 indicates the absence

of pain and 10 the worst possible pain [34]. This variable was evaluated before and after six tDCS sessions, and at follow-up consultations on the 7th and 15th days after the last session.

Functional capacity was evaluated as a secondary outcome by the Health Assessment Questionnaire (HAQ), which assesses the ability to perform daily activities that require the use of body joints, such as dressing and feeding oneself, taking the bus, and climbing stairs, among others. This score establishes three levels of disability: mild (0–1), moderate (>1–2), and severe (>2–3) [35]. The Brief Pain Inventory (BPI), which assesses pain severity and interference with daily living, based on a recall of pain, was also used [36]. Both assessment instruments were applied before and after the six sessions.

#### Data collection

A general evaluation form recorded sociodemographic and clinical information, such as time of CHIKV infection, medications used for treatment, and impacts on activities of daily living. The VAS, HAQ, and BPI instruments were applied before and after the intervention protocol. All the collections took place at the Onofre Lopes University Hospital, in the city of Natal, Brazil. For the patients who were absent, an intention-to-treat method was adopted in which the data of the participants who did not continue treatment were tabulated, repeating the last values obtained [32].

#### Intervention protocol

The participants underwent six sessions of tDCS on alternate days, corresponding to two weeks of treatment. The active-tDCS group received stimulation with an anode placed in the region of the M1 and the cathode over the contralateral supraorbital region according to the international 10/20 EEG system (C3/Fp2 montage). It was used 35 cm<sup>2</sup> surface electrodes (5 × 7 cm) covered by a sponge soaked in 0.9% sodium chloride (NaCl) saline solution. Active tDCS was performed on six alternate days of a constant current of 2 mA for 20 min. The same protocol was applied in the sham-tDCS, but a gradual current ramp-up and ramp-down of 30 s was used [37]. Direct current stimulation was administered using a continuous electric stimulator, with three batteries (9 V) connected in parallel with a maximum energy output of 10 mA and controlled by a professional digital multimeter (DT832, WeiHua Electronic Co., Ltd, China) with a standard error of ±1.5%. Participants were blinded to which group they belonged to during the research protocol.

#### High-resolution computational model

Current flow was simulated using finite element methods (FEM) models of two magnetic resonance imaging (MRI) derived female heads using our previously established [38,39] and validated [40–42] workflow. Briefly, FEM models were created to analyze the cortical electric field generated during tDCS. High-resolution MRIs were segmented into seven tissue/material masks of varying conductivities through a combination of automated and manual tools. Computer generated models of electrodes, gel, and/or sponge pads were incorporated into the segmentation. Simulation was 2 mA with a 5 × 7 cm electrode with anode positioned vertically over 10–20, location C3, and cathode positioned on the contralateral-supraorbital, over 10–20, location Fp2. (Fig. 2).

#### Data analysis

Analyses were performed using the SPSS software (V.19.0, Chicago, USA) and Graph Pad Prism 5. Descriptive statistics were initially performed. Results were expressed in absolute and relative

values; the mean was used as a measure of central tendency and the standard deviation (SD) as a measure of dispersion. Analytic statistics were performed based on the repeated measurements mixed-model analysis of variance (ANOVA), which compared the effects of the variables within the same group and over time (intragroup comparison) and between the groups (intergroup comparison), in addition to the simultaneous interaction of both factors. Initially, the theoretical assumptions for the application of ANOVA were assessed by analyzing data distribution through the Kolmogorov-Smirnov test. T-test for independent samples and the Levene test were performed to assess the equality of variances and homogeneity of the groups, and a chi-squared test was used for the categorical variables. The sphericity of the set of variables was assessed by the Mauchly test and, when it was violated, the Greenhouse-Geisser correction was used. To determine the difference between different times or within the groups, the Bonferroni post hoc test was used; the values of the differences were considered significant when  $p < 0.05$ .

The cumulative proportion of responders [43] was analyzed, with a cut-off point of 30% change in the VAS score, which, according to the literature, is considered clinically relevant for studies on chronic pain [44]. The number needed to treat (NNT) was calculated using these values. The NNT is the mean number of patients who need to receive a specific intervention for one of them to benefit from the desired outcome in one compared with the control [45]. According to the Brazilian National Health Surveillance Agency (ANVISA), this information is of significant relevance to clinical effectiveness and should be included in clinical trials. For the variables functional capacity, interference of pain, and severity of pain, the effect size was calculated using Cohen's "d" index, considering the difference between means and standard deviation; the results were classified as insignificant ( $d < 0.19$ ), small (0.2–0.49), moderate (0.5–0.79), and high (0.8–1.29) [46].

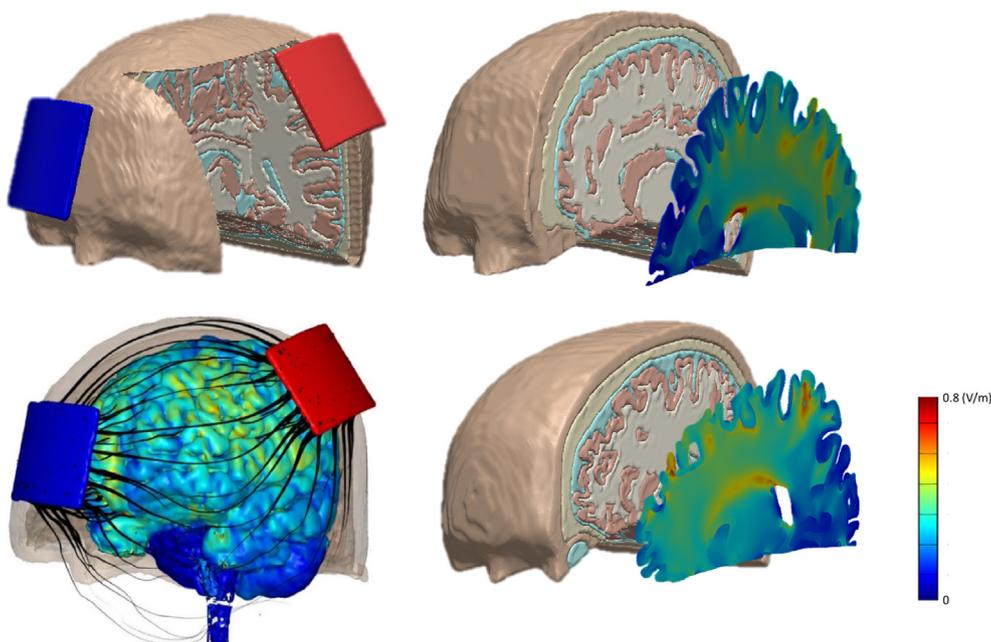
#### Ethical aspects

The experimental procedures were developed in accordance with the guidelines of Resolution 466/12 of the National Health Council and conducted according to the Declaration of Helsinki, which addresses ethics in research with human beings. This study was approved by the local ethics committee (number 2932953) and registered in the Brazilian Clinical Trials Registry (ReBeC) under registration number: RBR-5FH5R4. All subjects were volunteers and signed an informed consent form and were made aware of the objectives and procedures of the study, as well as of the risks and benefits.

#### Results

A total of 58 women participated in the study, with a mean age of  $52.85 \pm 10.76$  years. Only one participant from the sham-tDCS withdrew from the study and was analyzed as intention to treat. The time of CHIKV infection was  $21.54 \pm 3.53$  months. There were no differences in sociodemographic and pain variables between groups at baseline, but functional capacity and pain interference variables showed differences between groups, as shown in Table 1 (Table 1).

Accordingly, mixed ANOVA showed a significant interaction between the group and time on pain evaluated using VAS  $F(3.171) = 14.303$ ;  $p = 0.0001$ , partial  $\eta^2[2] = 0.20$ . There were significant main effects of time  $F(3.171) = 60.128$ ,  $p = 0.0001$ , partial  $\eta^2[2] = 0.51$  and group  $F(3.57) = 7.902$ ,  $p = 0.007$ , partial  $\eta^2[2] = 0.12$ . A simple main effect for group and time was performed for testing differences in VAS between groups at each category of the within-subjects factor using three separate one-way ANOVAs with



**Fig. 2.** Computational current flow model of M1-SO tDCS montage. Electric field intensity is shown in the cortical surface, cross section (False Color, Electric Field) and flux line. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Bonferroni adjustment. No significant simple main effect difference in VAS between groups at the baseline was found ( $p = 0.09$ ). However, significant difference between groups was found in day 6 ( $p = 0.001$ ; mean difference: 1.98), 1st follow-up ( $p = 0.0001$ ; mean difference: 2.39) and 2nd follow-up ( $p = 0.0001$ ; mean difference: 1,32) (Fig. 3).

**Table 1**  
Sample characterization with absolute and relative values, as well as the mean and standard deviation.

Variables	Active-tDCS	Sham-tDCS	p value
	Mean ± SD	Mean ± SD	
Age	50,83 ± 10,38	54,80 ± 10,94	0,158*
Time with CHIKV	20,97 ± 4,25	22,10 ± 2,60	0,225*
Drugs for pain	4,76 ± 1,62	4,43 ± 1,61	0,442*
VAS baseline	6,86 ± 1,66	6,07 ± 1,91	0,094*
HAQ baseline	1,61 ± 0,42	1,14 ± 0,47	0,001*
BPI sev baseline	6,0 ± 1,37	5,64 ± 1,77	0,390*
BPI interf baseline	7,11 ± 1,47	5,63 ± 2,14	0,003*
Ethnicity	n (%)	n (%)	
White	14 (48%)	14 (47%)	0,121**
Black	1 (3,4%)	6 (20%)	
Mixed-race	14 (48%)	10 (33%)	
Total	29	30	
Education			
Elementary school	6 (20%)	5 (16%)	0,703**
Secondary school	17 (60%)	16 (54%)	
College	6 (20%)	9 (30%)	
Total	29	30	
Comorbidity			
Yes	16 (55%)	20 (67%)	0,365**
No	13 (45%)	10 (33%)	
Total	29	30	
Rheumatic disease			
Yes	12 (41%)	11 (37%)	0,711**
No	17 (59%)	19 (63%)	
Total	29	30	

Legend of Table 1: SD = Standard Deviation. VAS = Visual Analogic Scale. HAQ = Health Assessment Questionnaire. BPI = Brief Pain Inventory. \* p-value: t-test for independent samples. \*\* p-value: chi-squared test.

Analysis of the cumulative proportion of responders showed that 79.31% of the participants in the active-tDCS had an improvement in VAS score greater than 30% compared with the sham-tDCS. These data were used to calculate the NNT, which in this study was 2, meaning that two patients needed to be treated with this technique for one more to benefit from the desired effect.

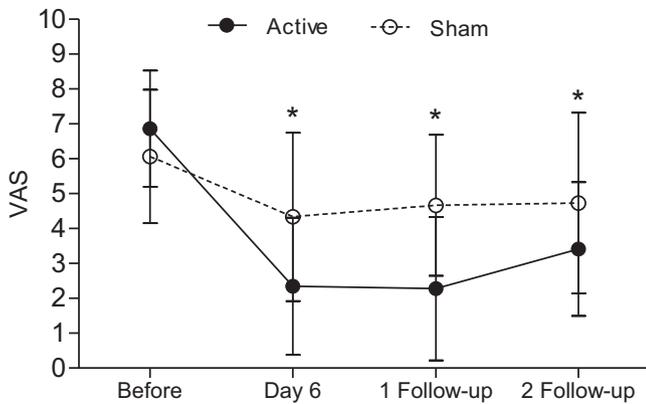
A significant interaction between time and group was found for functional capacity  $F(1,57) = 36.549$ ;  $p = 0.0001$ , partial  $\eta^2 = 0.39$ . Similarly, there was significant main effect of time,  $F(1,57) = 133.085$ ,  $p = 0.001$ , partial  $\eta^2 = 0.7$  but not for group  $F(1,57) = 2.797$ ,  $p = 0.1$ , partial  $\eta^2 = 0.04$  (Fig. 4). Impact of pain interference showed a significant interaction group and time,  $F(1,57) = 25.598$ ,  $p = 0.0001$ , partial  $\eta^2 = 0.31$ . Similarly, for pain severity  $F(1,57) = 16.513$ ,  $p = 0.0001$ , partial  $\eta^2 = 0.22$  (Fig. 5). No significant effect was observed for group ( $p = 0.96$ ;  $p = 0.06$  respectively).

When the effect size between the active-tDCS and sham-tDCS was analyzed, no significant effect was observed for functional capacity ( $d = 0.11$ ), moderate for interference of pain ( $d = 0.60$ ), and high for pain severity ( $d = 0.96$ ).

### Discussion

The objective of the study was to evaluate the effect of six nonconsecutive sessions of tDCS on chronic pain of women with CHIKV chronic arthralgia. It showed a significant reduction of pain after stimulation in a short and long-term follow-up. This result suggests that tDCS could be a relevant strategy with cost-effective approach to relief persistent pain in chronic CHIKV patients. However, no change in functional capacity has been found.

Silva-Filho et al. [26] showed significant clinical pain improvement after five consecutive sessions of M1-SO tDCS in individuals with chronic chikungunya arthralgia. The authors did not find an effect on functional capacity. In the present study, we assessed a modified dosing protocol, with alternate sessions of tDCS. A reduction in pain intensity was observed after six sessions only for



**Fig. 3.** Pain reduction was observed in short and long-term only in active-tDCS (n = 29) when compared with sham-Group (n = 30). Mixed ANOVA showed a significant interaction between the group and time (p < 0.0001) with a group effect (p < 0.05) over time. \*Significant difference between groups in day 6 (p = 0.001; mean difference: 1.98), 1st (7 days after last tDCS session) follow-up (p = 0.0001; mean difference: 2.39) and 2nd (15 days after last tDCS session) follow-up (p = 0.0001; mean difference: 1.32) Pairwise comparisons with Bonferroni adjustment.

active-tDCS and persisted until 15th day post-treatment, meaning a long-term effect.

A study that used tDCS over 12 consecutive days in individuals with chronic low back pain combined with peripheral transcutaneous electrical stimulation showed an improvement in pain level and a higher percentage of responders in the stimulated group [47]. This was also observed in the present study.

A review [21] on the effects of tDCS on chronic pain in diverse clinical conditions found a decrease of 17% in pain intensity in the stimulated group compared with the control and placebo groups, which was considered a minimal difference. Although a reduction in pain was observed in both groups over time, in the present protocol, in the active-tDCS pain level was reduced more than 50% even 15 days after the intervention, reaching the lowest level reported by the participants. These outcomes are consistent with other pain studies [20,48] that showed the efficacy of tDCS in reducing the VAS score in patients with fibromyalgia. Other studies [49,50] that performed the stimulation consecutively demonstrated pain improvement up to three months later.

Although most studies on tDCS stimulation are applied on consecutive days, the number of sessions and the application method used in the present study sought to accommodate the practicality of rehabilitation programs. A previous study assessed the impact of the absence of up to two consecutive sessions of tDCS

on the clinical efficacy of ten treatment sessions for major depression and found results similar to those that performed all sessions consecutively. A 60% absence rate was observed in at least one tDCS session. This same study highlighted the difficulty in carrying out long-term treatments with neuromodulation, continuously, due to time, cost and patient access, suggesting the analysis of other models of application of tDCS [28]. In the present study, there was only one withdrawal, and no absence of participants in the application of tDCS on alternate days. There is no consensus on the minimum number of sessions required for tDCS for some health conditions, and the time interval between sessions [51]. Such factors hypothesize that a tDCS protocol with sessions on alternate days can present satisfactory results, with a lower dropout rate, therefore greater adherence. Nonconsecutive days of tDCS could be an alternative strategy for long-term treatment of debilitating diseases.

Functional capacity did not show significant differences between groups, as observed by Silva-Filho et al. (2018) [26]. The difference found in the baseline for functional capacity and interference of pain with daily life may have interfered with the final result, considering that both had remarkably reduced scores after the intervention, although without statistical significance. Moreover, this fact may be explained by the characteristics of the research participants, who already had functional capacity limitation, but did not receive a stimulus other than tDCS to change these aspects of the functionality. Ahn et al. (2017) [25] evaluated the efficacy of tDCS with regard to safety, mobility, and clinical pain in subjects with knee osteoarthritis; these authors observed a significant reduction in the numerical pain scale after five daily sessions applied over three weeks but did not observe changes in mobility, although there were moderate clinical effects for some variables, similar to what occurred in the present study.

Musculoskeletal pain caused by CHIK is related to neuropathic and nociceptive peripheral mechanisms, which can progress to central sensitization [52,53]. It was suggested that M1-SO montage activates several circuits present in the pre-central gyrus responsible for connecting structures involved in the sensory and emotional component of pain processing [13]. This hypothesis justifies the potential to reduce pain through the inhibitory control of the descending pathways [18,54].

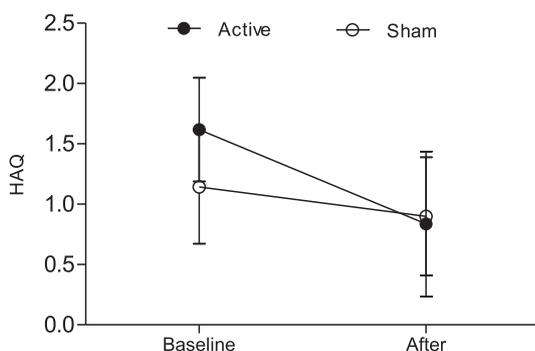
Despite the large number of studies on tDCS, its neurophysiological foundations are not yet fully clarified, especially the optimal dosimetry of stimulation. The time of application and repetition of the alternate sessions used in this study yielded significant results. Also, tDCS sessions on alternate days provided good adherence to the protocol. Thus, further studies should focus on the number of tDCS sessions and the association with other resources, such as simultaneous physical exercise.

**Conclusions**

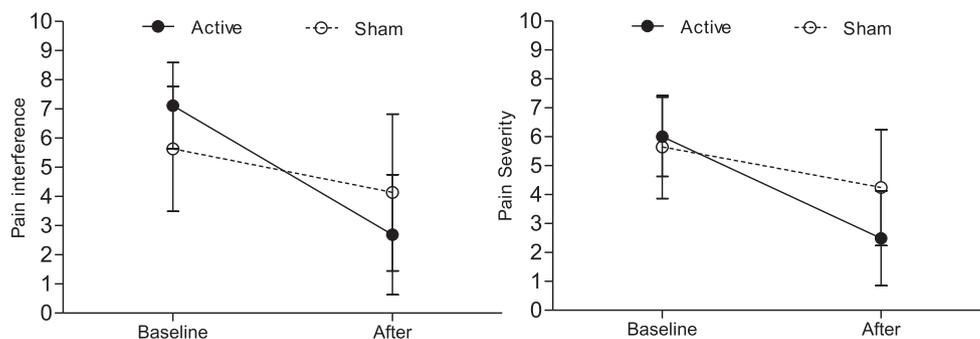
Six nonconsecutive sessions of anodal tDCS over M1 were effective in reducing pain in short and long-term in women with chronic CHIKV arthralgia. Alternate session is an available approach to support treatment adherence and reduction of treatment withdrawal. Future intervention including additional stimulation sessions and combination tDCS with other therapeutic resources such as physical exercise could be a rational strategy to decrease pain and improve functional capacity in chronic CHIKV arthralgia.

**REBEC platform under registration number: RBR-5FH5R4**

This study protocol was approved by the Committee for Ethics and Research at the Federal University of Rio Grande do Norte, with registration number 2932953. All research procedures were



**Fig. 4.** Mixed ANOVA showed an interaction between time and group for functional capacity (p = 0.0001), with main effect of time (p = 0.001) but not for group (p = 0.1).



**Fig. 5.** BPI domains. Pain interference ( $p = 0.0001$ ) and pain severity ( $p = 0.0001$ ) showed a significant interaction between group and time (ANOVA). But no significant effect was observed for group ( $p = 0.96$ ;  $p = 0.06$  respectively).

followed in accordance with the Helsinki Declaration of 1975. All persons gave informed consent prior to their inclusion in the study. No animals were used in this study.

### CRedit author contribution statement

**C.G. De Souza:** Conceptualization, Conception and design of the study, submitted the project to the ethics committee, recruited the participants, evaluated it before and after the stimulation and wrote the manuscript, Final approval of the manuscript. **R. Pegado:** Writing – original draft, conception and design of the study, submitted the national platform of clinical trials REBEC, data analysis, interpretation and writing of the manuscript, Final approval of the manuscript. **J.F. Costa:** Writing – review & editing, recruited participants, assessed before and after stimulation and wrote the manuscript and critically reviewed the article. **E. Morya:** Final approval of the manuscript. **G. Unal:** Writing – review & editing, Formal analysis, cooperated in the analysis and interpretation of data, critical review and analysis of the high definition computational model, Final approval of the manuscript. **M. Bikson:** Writing – review & editing, Formal analysis, cooperated in the analysis and interpretation of data, critical review and analysis of the high definition computational model, Final approval of the manuscript. **A.H. Okano:** Conceptualization, Formal analysis, Conception and design of the study, analysis and interpretation of data, Final approval of the manuscript.

### Declaration of competing interest

The City University of New York (CUNY) has IP on neuro-stimulation system and methods with author MB as inventor. MB has equity in Soterix Medical. MB serves on Boston Scientific and GlaxoSmithKline Inc. advisory boards.

### Acknowledgements

This study was partially funded by grants to MB from NIH (NIH-NIMH 1R01MH111896, NIH-NINDS 1R01NS101362, NIH-NCI U54CA137788/U54CA132378, R03 NS054783), New York State Department of Health (NYS DOH, DOH01-C31291GG), CEPID/BRAINN - The Brazilian Institute of Neuroscience and Neuro-technology (FAPESP - Process: 13/07559–3) to AHO, AFB and EM, Brazilian Ministry of Education to AHO, AFB, CGS, EM and RP, Santos Dumont Institute to EM, and Federal University of Rio Grande do Norte to RP e CGS.

### References

- [1] Kolawole OM, Seriki AA, Irekeola AA, Ogah JI. Diseases. The neglect and fast spread of some arboviruses: a note for healthcare providers in Nigeria 2018;6(4):e99. <https://doi.org/10.3390/diseases6040099>.
- [2] Madariaga M, Ticona E, Resurreccion C. Chikungunya: bending over the Americas and the rest of the world. *Braz J Infect Dis* 2016;20(1):91–8. <https://doi.org/10.1016/j.bjid.2015.10.004>.
- [3] Marques CDL, Duarte ALBP, Ranzonlin A, Dantas AT, Cavalcanti NG, Gonçalves RSG, Rocha Junior LF, Valadares LDA, Melo AKG, Freire EAM, Teixeira R, Bezerra Neto FA, Medeiros MMC, Carvalho JF, Santos MSF, Océa RALC, Levy RA, De Andrade CAF, Pinheiro GRC, Abreu MM, Verztman JF, Merenlender S, Ribeiro SLE, Costa IP, Pileggi G, Trevisani VFM, Lopes MIB, Brito C, Figueiredo E, Queiroga F, Feitosa T, Tenório AS, Siqueira GR, Paiva R, Vasconcelos Jts, Christopoulos G. Recomendações da Sociedade Brasileira de Reumatologia para diagnóstico e tratamento da febre chikungunya. Parte 1 – diagnóstico e situações especiais. *Rev Bras Reumatol* 2017;57(2):421–37. <https://doi.org/10.1016/j.rbre.2017.05.006>.
- [4] De Andrade DC, Jean S, Clavelou P, Dallel R, Bouhassira D. Chronic pain associated with the Chikungunya fever: long lasting burden of an acute illness. *BMC Infect Dis* 2010;10(31):1–6. <https://doi.org/10.1186/1471-2334-10-31>.
- [5] Sam IC, Kümmerer BM, Chan YF, Roques P, Drosten C, AbuBakar S. Updates on chikungunya epidemiology, clinical disease, and diagnostics. *Vector Borne Zoonotic Dis* 2015;15(4):223–30. <https://doi.org/10.1089/vbz.2014.1680>.
- [6] Marques CDL, Duarte ALBP, Ranzonlin A, Dantas AT, Cavalcanti NG, Gonçalves RSG, Rocha Junior LF, Valadares LDA, Melo AKG, Freire EAM, Teixeira R, Bezerra Neto FA, Medeiros MMC, Carvalho JF, Santos MSF, Océa RALC, Levy RA, De Andrade CAF, Pinheiro GRC, Abreu MM, Verztman JF, Merenlender S, Ribeiro SLE, Costa IP, Pileggi G, Trevisani VFM, Lopes MIB, Brito C, Figueiredo E, Queiroga F, Feitosa T, Tenório AS, Siqueira GR, Paiva R, Vasconcelos Jts, Christopoulos G. Recomendações da Sociedade Brasileira de Reumatologia para diagnóstico e tratamento da febre chikungunya. Parte 2 – Tratamento. *rev bras reumatol.* 2017;57(2):438–51. <https://doi.org/10.1016/j.rbr.2017.05.005>.
- [7] Marimoutou C, Ferraro J, Javelle E, Deparis X, Simon F. Chikungunya infection: self-reported rheumatic morbidity and impaired quality of life persist 6 years later. *Clin Microbiol Infect* 2015;21(7):688–93. <https://doi.org/10.1016/j.cmi.2015.02.024>.
- [8] Perocheau D, Laroche F, Perrot S. Relieving pain in rheumatology patients: repetitive transcranial magnetic stimulation (rTMS), a developing approach. *Joint Bone Spine* 2014;81(1):22–6. <https://doi.org/10.1016/j.jbspin.2013.04.015>.
- [9] Fregni F, Pasqual-leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. *Nat Clin Pract Neurol* 2007;3(7):383–93. <https://doi.org/10.1038/ncpneuro0530>.
- [10] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, Cohen LG, Fregni F, Herrmann CS, Kappenman ES, Knotkova H, Liebetanz D, Miniussi C, Miranda PC, Paulus W, Priori A, Reato D, Stagg C, Wenderoth N, Nitsche MA. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol* 2016 February;127(2):1031–48. <https://doi.org/10.1016/j.clinph.2015.11.012>.
- [11] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000;527(3):633–9. <https://doi.org/10.1111/j.1469-7793.2000.t011-1-00633.x>.
- [12] Jackson MP, Rahman A, Lafon B, Kronberg G, Ling D, Parra LC, Bikson M. Animal models of transcranial direct current stimulation: methods and mechanisms. *Clin Neurophysiol* 2016 Nov;127(11):3425–54. <https://doi.org/10.1016/j.clinph.2016.08.016>.
- [13] Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring

- electrode versus conventional rectangular pad. *Brain Stimul* 2009 Oct;2(4):201–7. 2007.e1.
- [14] Nitsche MA, Liebetanz D, Antal A, Lang N, Tergau F, Paulus W. Modulation of cortical excitability by weak direct current stimulation- technical, safety and functional aspects. *Suppl Clin neurophysiol* 2003;56:255–76. [https://doi.org/10.1016/S1567-424X\(09\)70230-2](https://doi.org/10.1016/S1567-424X(09)70230-2).
- [15] Da silva AF, Mendonca ME, Zaghi S, Lopes M, Dossantos MF, Spierings EL, Bajwa Z, Datta A, Bikson M, Fregni F. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. *Headache* 2012 Sep;52(8):1283–95. <https://doi.org/10.1111/j.1526-4610.2012.02141.x>. Epub 2012 Apr 18.
- [16] Morya E, Monte-Silva K, Bikson M, et al. Beyond the target area: an integrative view of tDCS-induced motor cortex modulation in patients and athletes. *J NeuroEngineering Rehabil* 2019;16:141. <https://doi.org/10.1186/s12984-019-0581-1>.
- [17] Baptista AF, Fernandes AMBL, Sá KN, et al. Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC2-NIN-CP). *PAIN Rep* January/February 2019;4(1):e692. <https://doi.org/10.1097/PR9.0000000000000692>.
- [18] Lefaucheur JP, Hatem S, Nineb A, Ménard-Lefaucheur I, Wendling S, Keravel Y. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *Neurology* 2006;67(11):1998–2004. <https://doi.org/10.1212/01.wnl.0000247138.85330.88>.
- [19] Nguyen JP, Nizard J, Keravel Y, Lefaucheur JP. Invasive brain stimulation for the treatment of neuropathic pain. *Nat Rev Neurol* 2011;7:699–709. <https://doi.org/10.1038/nrneurol.2011.138>.
- [20] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P, Mylius V, Nitsche MA, Padberg F, Palm U, Poulet E, Priori A, Rossi S, Schecklmann M, Vanneste S, Ziemann U, Garcia-Larrea L, Paulus W. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017;128(1):56–92. <https://doi.org/10.1016/j.clinph.2016.10.087>.
- [21] O'Connell NE, Martson L, Spencer S, De Souza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2018;3:1–216. <https://doi.org/10.1002/14651858.CD008208>.
- [22] Fregni F, Gimenes R, Valle AC, Ferreira MJ, Rocha RR, Natalle L, Bravo R, Rigonatti SP, Freedman SD, Nitsche MA, Pascual-Leone A, Boggio PS. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. *Arthritis Rheum* 2006 Dec;54(12):3988–98.
- [23] Andrade SM, de Brito Aranha REL, de Oliveira EA, de Mendonça CTPL, Martins WKN, Alves NT, Fernández-Calvo B. Transcranial direct current stimulation over the primary motor vs prefrontal cortex in refractory chronic migraine: a pilot randomized controlled trial. *J Neurol Sci* 2017 Jul 15;378:225–32. <https://doi.org/10.1016/j.jns.2017.05.007>. Epub 2017 May 3.
- [24] Hazime FA, de Freitas DG, Monteiro RL, Maretto RL, Carvalho NA, Hasue RH, João SM. Analgesic efficacy of cerebral and peripheral electrical stimulation in chronic nonspecific low back pain: a randomized, double-blind, factorial clinical trial. *BMC Musculoskel Disord* 2015 Jan 31;16:7. <https://doi.org/10.1186/s12891-015-0461-1>.
- [25] Ahn H, Woods AJ, Kunik ME, Bhattacharjee A, Chen Z, Choi E, Fillingim RB. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: an experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study. *Brain Stimul* 2017 Sep - Oct;10(5):902–9. <https://doi.org/10.1016/j.brs.2017.05.007>. Epub 2017 May 19.
- [26] Silva-Filho E, Okano AH, Morya E, Albuquerque J, Cacho E, Unal G, Bikson M, Pegado R. Neuromodulation treats Chikungunya arthralgia: a randomized controlled trial. *Sci Rep* 2018 Oct 30;8(1):16010. <https://doi.org/10.1038/s41598-018-34514-4>.
- [27] Castillo-Saavedra L, Gebodh N, Bikson M, Diaz-Cruz C, Brandao R, Coutinho L, Truong D, Datta A, ShaniHershkovich R, Weiss M, Laufer I, Reches A, Peremen Z, Geva A, Parra LC, Fregni F. Clinically effective treatment of fibromyalgia pain with HighDefinition transcranial direct current stimulation: phase II. Open-label dose optimization. *J Pain* 2016 January;17(1):14–26. <https://doi.org/10.1016/j.jpain.2015.09.009>.
- [28] Zanao TA, Moffa AH, Shiozawa P, Lotufo PA, Benseñor IM, Brunoni AR. Impact of two or less missing treatment sessions on TDCS clinical efficacy: results from a factorial, randomized, controlled trial in major depression. *Neuro-modulation* 2014;17(8):737–42. <https://doi.org/10.1111/ner.12167>.
- [29] Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, Ferrucci R, Priori A, Boggio PS, Fregni F. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul* 2012 Jul;5(3):175–95. <https://doi.org/10.1016/j.brs.2011.03.002>. Epub 2011 Apr 1.
- [30] Thiberville SD, Boisson V, Gaudart J, Simon F, Flahault A, de Lamballerie E. Chikungunya fever: a clinical and virological investigation of outpatients on Reunion Island South-West Indian Ocean. *PLoS Neglected Trop Dis* 2013;7:e2004.
- [31] Rodriguez-Morales AJ, Gil-Restrepo AF, Ramirez-Jaramillo V, Montoya-Arias CP, Acevedo-Mendoza WF, Bedoya-Arias JE, et al. Post-chikungunya chronic inflammatory rheumatism: results from a retrospective follow-up study of 283 adult and child cases in La Virginia. *Risaralda*. F1000 Res. 2016;5:360.
- [32] McCoy CE. Understanding the intention-to-treat principle in randomized controlled trials. *West J Emerg Med* 2017;18(6):1075–8.
- [33] Harris DR, Lemeshow S, Lwanga SK, Chin J, Duchesneau R. Evaluation of a standardized survey design proposed for use in epidemiological research on AIDS. *Int J Epidemiol* 1991 Dec;20(4):1048–56.
- [34] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain Questionnaire (MPQ), short-form McGill pain Questionnaire (SF-mpq), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res* 2011 Nov;63(Suppl 11):S240–52. <https://doi.org/10.1002/acr.20543>.
- [35] Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983 Dec 15-21;306(5944):686–8.
- [36] Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain* 1983 Oct;17(2):197–210.
- [37] Luedtke K, May A, Jürgens TP. No effect of a single session of transcranial direct current stimulation on experimentally induced pain in patients with chronic low back pain—an exploratory study. *PLoS One* 2012;7(11):e48857. <https://doi.org/10.1371/journal.pone.0048857>. Epub 2012 Nov 26.
- [38] Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. *Brain Stimul* 2009 Oct;2(4):201–7. 207.e1.
- [39] Datta A, Truong D, Minhas P, Parra LC, Bikson M. Inter-individual variation during transcranial direct current stimulation and normalization of dose using MRI-derived computational models. *Front Psychiatr* 2012 Oct 22;3:91. <https://doi.org/10.3389/fpsy.2012.00091>. eCollection 2012.
- [40] Datta AI, Zhou X, Su Y, Parra LC, Bikson M. Validation of finite element model of transcranial electrical stimulation using scalp potentials: implications for clinical dose. *J Neural Eng* 2013 Jun;10(3):036018. <https://doi.org/10.1088/1741-2560/10/3/036018>. Epub 2013 May 7.
- [41] Jog MV, Smith RX, Jann K, Dunn W, Lafon B, Truong D, Wu A, Parra L, Bikson M, Wang DJ. In-vivo imaging of magnetic fields induced by transcranial direct current stimulation (tDCS) in human brain using MRI. *Sci Rep* 2016 Oct 4;6:34385. <https://doi.org/10.1038/srep34385>.
- [42] Huang Y#1, Liu AA#2, Lafon B1, Friedman D2, Dayan M3, Wang X2, Bikson M1, Doyle WK2, Devinsky O2, Parra LC1. Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. *Elife* 2017 Feb 7;6. <https://doi.org/10.7554/eLife.18834>. pii: e18834.
- [43] Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present pain data over a range of cut-off points: making clinical trial data more understandable. *J Pain Symptom Manag* 2006 Apr;31(4):369–77.
- [44] Klein MM1, Treister R, Raji T, Pascual-Leone A, Park L, Nurmikko T, Lenz F, Lefaucheur JP, Lang M, Hallett M, Fox M, Cudkowicz M, Costello A, Carr DB, Ayache SS, Oaklander AL. Transcranial magnetic stimulation of the brain: guidelines for pain treatment research. *Pain* 2015 Sep;156(9):1601–14. <https://doi.org/10.1097/j.pain.0000000000000210>.
- [45] Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995 Feb 18;310(6977):452–4. Erratum in: *BMJ* 1995 Apr 22;310(6986):1056.
- [46] Grice JW1, Barrett PT. A note on Cohen's overlapping proportions of normal distributions. *Psychol Rep* 2014 Dec;115(3):741–7. <https://doi.org/10.2466/03.PR0.115c.2924>.
- [47] Hazime FA, Baptista AF, de Freitas DG, Monteiro RL, Maretto RL, Hasue RH, João SMA. Treating low back pain with combined cerebral and peripheral electrical stimulation: a randomized, double-blind, factorial clinical trial. *Eur J Pain* 2017 Aug;21(7):1132–43. <https://doi.org/10.1002/ejp.1037>. Epub 2017 Apr 25.
- [48] Jales Junior LH, Costa MDL, Jales Neto LH, Ribeiro JPM, Freitas WJSN, Teixeira MJ. Transcranial direct current stimulation in fibromyalgia: effects on pain and quality of life evaluated clinically and by brain perfusion scintigraphy. *Rev. dor* vol.16 no.1 São Paulo Jan./Mar. <https://doi.org/10.5935/1806-0013.20150008>.
- [49] Fregni F, Boggio PS, Lima MC, Ferreira MJ, Wagner T, Rigonatti SP, Castro AW, Souza DR, Riberto M, Freedman SD, Nitsche MA, Pascual-Leone A. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. *Pain* 2006 May;122(1–2):197–209. Epub 2006 Mar 27.
- [50] Lefaucheur JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, Nitsche M, Paulus W. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain Stimul* 2008 Oct;1(4):337–44. <https://doi.org/10.1016/j.brs.2008.07.003>. Epub 2008 Oct 7.
- [51] Thair H, Holloway AL, Newport R, Smith AD. Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Front Neurosci* 2017;11:641.
- [52] Schambra HM, Bikson M, Wager TD, DosSantos MF, DaSilva AF. It's all in your head: reinforcing the placebo response with tDCS. *Brain Stimul* 2014 Jul-Aug;7(4):623–4. <https://doi.org/10.1016/j.brs.2014.04.002>. Epub 2014 Apr 15.

- [53] Labadie K, Larcher T, Joubert C, Mannioui A, Delache B, Brochard P, Guigand L, Dubreil L, Lebon P, Verrier B, de Lamballerie X, Suhrbier A, Cherel Y, Le Grand R, Roques P. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J Clin Invest* 2010 Mar;120(3): 894–906. <https://doi.org/10.1172/JCI40104>. Epub 2010 Feb 22.
- [54] Nguyen JP, Nizard J, Keravel Y, Lefaucheur JP. Invasive brain stimulation for the treatment of neuropathic pain. *Nat Rev Neurol* 2011 Sep 20;7(12): 699–709. <https://doi.org/10.1038/nrneurol.2011.138>.