


BMJ Open Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomised clinical trial

Abraão Sérvulo do Nascimento,¹ Antônio Felipe Lopes Cavalcante,² Thiago Anderson Brito De Araújo,³ João Danyell Dantas da Silva,¹ Edson Silva-Filho,¹ Alexandre Okano,⁴ Lucien Peroni Gualdi,¹ Rodrigo Pegado ^{2,5}

To cite: Nascimento ASdo, Cavalcante AFL, Araújo TABD, *et al.* Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomised clinical trial. *BMJ Open* 2022;**12**:e065387. doi:10.1136/bmjopen-2022-065387

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-065387>).

Received 02 June 2022
Accepted 23 September 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Professor Rodrigo Pegado;
rodrigopegado@gmail.com

ABSTRACT

Introduction The chikungunya virus infection is still an epidemic in Brazil with an incidence of 59.4 cases per 100 000 in the Northeast region. More than 60% of the patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years. Transcranial direct current stimulation (tDCS) appears promising as a novel neuromodulation approach for pain-related networks to alleviate pain in several pain syndromes. Our objective is to evaluate the effectiveness of tDCS (C3/Fp2 montage) on pain, muscle strength, functionality and quality of life in chronic arthralgia.

Methods and analysis This protocol is a single-centre, parallel-design, double-blind, randomised, sham-controlled trial. Forty participants will be randomised to either an active or sham tDCS. A total of 10 sessions will be administered over 2 weeks (one per weekday) using a monophasic continuous current with an intensity of 2 mA for 20 min. Participants will be evaluated at baseline, after the 10th session, 2 weeks and 4 weeks after intervention. Primary outcome: pain assessed using numeric rating scale and algometry. Secondary outcomes: muscle strength, functionality and quality of life. The effects of stimulation will be calculated using a mixed analysis of variance model.

Ethics and dissemination The study was approved by the ethics committee of the Faculty of Health Sciences of Trairí, Federal University of Rio Grande do Norte (No. 2.413.851) and registered on the Brazilian Registry of Clinical Trials. Study results will be disseminated through presentations at conferences and publications in peer-reviewed journals.

Trial registration number RBR-469yd6.

INTRODUCTION

In the last 8 years, Brazil has been a protagonist in infection caused by chikungunya virus (CHIKV) in America.¹ The spread of the disease in South America is critical and out of control, mainly in Brazil that represents 94% of confirmed chikungunya cases.^{2,3} Until 2021, the Brazilian Ministry of Health continues to

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The trial will be performed in an endemic area with lack of resources for chronic chikungunya arthralgia treatment.
- ⇒ This is a low cost, safe and mobile intervention that may be implemented in clinical practice for a neglected tropical disease.
- ⇒ The trial will include participants with chronic pain without any previous treatment for a cost-effectiveness evaluation and quantitative data collection.
- ⇒ The trial will not include laboratorial, image or electrophysiological data regarding brain modulation or maintenance of pain state after transcranial direct current stimulation protocol.

monitor the occurrence of chikungunya, and from December 2019 to April 2020, 17 636 chikungunya cases were recorded.¹ The re-emergence of chikungunya has become an increasing medical and economic problem in endemic areas.⁴ The acute phase (<7 days) of chikungunya fever is usually characterised by sudden high fever, polyarthritis, tenderness, headache, myalgia, maculopapular rash and vomiting.^{5,6}

Chikungunya fever presents as a chronic public health problem and could overtake the capacity of healthcare systems and rehabilitation centres because most cases are commonly followed by persistent chronic arthralgia lasting for years.⁷ Up to 50%–60% of chikungunya cases may progress to the chronic phase that begins when clinical symptoms persist for more than 3 months.^{8,9} No specific therapeutic agents can be used to treat and rehabilitate individuals with chronic chikungunya and persistent pain may lead to incapacitation and require long-term pharmacological treatment.¹⁰

Chronic pain is associated with development of adaptive neuroplasticity and functional reorganisation that could result in physical and behavioural impairment.¹¹ Pain has a multidimensional phenomenon that involve sensorial, emotional, motor and autonomic mechanisms associated with different brain areas connected in a large network named by Melzak as pain neuromatrix (PNM).¹² The activation of the primary (S1) and secondary (S2) somatosensory cortices, primary motor cortex (M1), dorsolateral prefrontal cortex (DLPFC), thalamus, insula and anterior cingulate cortex are involved in pain processing.¹² The M1 has been the primary target for the study of pain modulation and clinical intervention of chronic pain conditions including rheumatic diseases.¹³

The use of transcranial direct current stimulation (tDCS) on pain and other clinical outcomes have been published with significant improvement.^{14–17} Previous studies have supported the use of anodal tDCS over M1 (MI-SO montage) to reduce pain in osteoarthritis,¹⁸ post-stroke pain syndrome,¹⁷ back pain,¹⁸ fibromyalgia¹³ and recently chikungunya.^{14,15} In this context, tDCS promotes M1 activation, providing secondary modulatory effects on the PNM circuit that is associated with nociceptive modulation.¹⁹ The first study on CHIKV and neuromodulation suggested pain improvement after five consecutive sessions of tDCS.¹⁵ The second study evaluated six non-consecutive sessions of anodal tDCS on M1 and showed significant reduction on pain.¹⁴ These studies were the initial investigations of tDCS, but further work to optimise the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic chikungunya arthralgia.^{14,15} It is important to consider that the intensity, time of application and number of session have significant influence in neurophysiology and clinical responses including therapeutic efficacy.¹⁷ The number of sessions is associated with the time of duration of neuromodulation and 10 sessions could provide a long-term neuromodulation effect and produce a sustained effect on pain and other symptoms.¹⁸

Furthermore, tDCS could be a non-invasive, low-cost, safe and accessible treatment option to CHIKV-endemic areas.¹⁵ Herein, we present the methodology of a randomised double-blinded controlled study to evaluate the feasibility of a trial protocol for 10 consecutive sessions of tDCS in chronic chikungunya arthralgia. The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess pain threshold and tolerance, muscle strength, functionality and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.

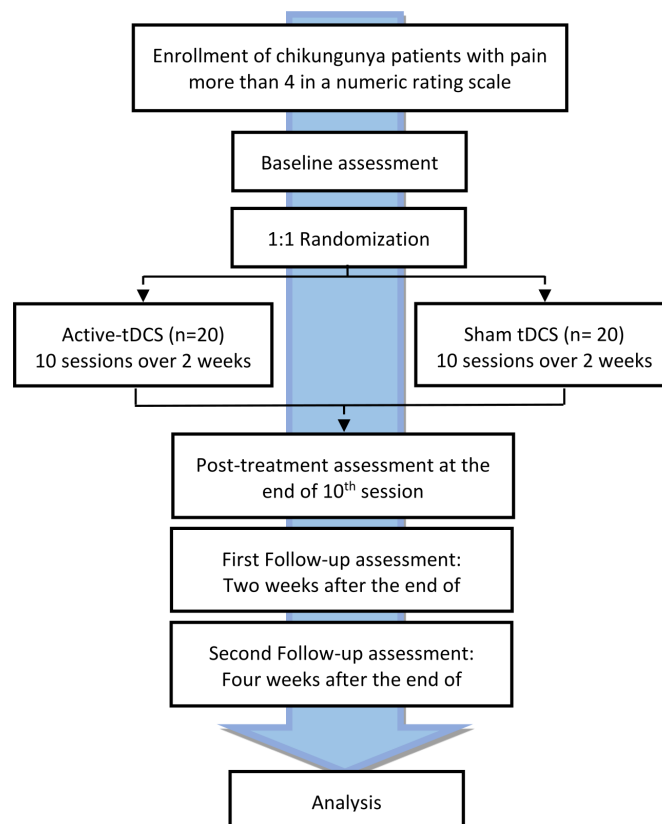


Figure 1 Flowchart summarising the trial. tDCS, transcranial direct current stimulation.

METHODS AND DESIGN

Study design

This is a protocol study of a single-centre, double-blind, parallel, sham-controlled, randomised clinical trial with two groups and a 1:1 allocation ratio. A total of 10 sessions of 20 min will be administered over a period of 2 weeks. Outcomes will be measured at baseline (1 week before intervention), immediately after day 10 of intervention and at 2 and 4 weeks after the end of the treatment as follow-up (figure 1). The Standard Protocol Items: Recommendations for International Trials statement 2013 and the Template for Intervention Description and Replication checklist²⁰ was followed to better describe the clinical trial.

This trial is registered on the Brazilian Registry of Clinical Trials (ReBEC). Participation is voluntary as determined by Resolution No. 466/12 of the National Health Council. Potentially eligible patients with chronic chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be informed about the methods of the study that include aims, allocation to sham or active group, evaluation procedures and timeline of intervention. All participants need to sign the Informed Consent Form (Supplementary File) before starting the study. The Informed Consent Form was submitted and approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (UFRN) (No. 2.413.851).

TIMEPOINT	Study Period						
	Enrolment	Allocation	Post-allocation			1 ^o Follow-up	2 ^o Follow-up
	Week 1	Week 2 Baseline	Intervention			Week 6	Week 8
			Week 3	Week 4	Last day of tDCS protocol		
ENROLMENT	X						
Eligibility screen	X						
Informed consent	X						
Sociodemographic characteristics	X						
Allocation		X					
INTERVENTIONS							
Active tDCS			◆————◆				
Sham tDCS			◆————◆				
ASSESSMENTS							
VAS		X			X	X	X
Pressure pain threshold		X			X	X	X
Pressure pain tolerance		X			X	X	X
BPI		X			X	X	X
Dynamometry		X			X	X	X
HAQ		X			X	X	X
SF-36							
Medication use		X			X	X	X
Adverse events					X	X	X
Success of blinding							X

Figure 2 Schedule of enrolment, interventions and assessments. VAS, Visual Analogue Scale; BPI, Brief Pain Inventory (Short Form); HAQ, The Health Assessment Questionnaire; SF-36, Short Form Health Survey; tDCS, transcranial direct current stimulation.

Participants and chikungunya diagnosis

Participants with previous serological confirmation of CHIKV infection²¹ based on immunoglobulin (Ig)G and IgM detected by direct ELISA/IgM/Euroimmun, according to the Central Laboratory (LACEN, Brazil) or on initial clinical symptoms (in the context of the epidemic) including at least fever and arthralgia who meet the eligibility criteria will be invited to participate in the study.²¹

Trial design

The study will start in August 2022 and is expected to be completed in August 2023. After the initial assessment, participants will be randomly allocated into two evaluator/participant blinded groups: active group and sham group.

Participants of both groups will undergo a 2-week protocol (five sessions per week) of active or sham tDCS. Sessions will be performed for 20 min by the same trained physical therapist. Two follow-ups will be performed after 2 and 4 weeks at the end of tDCS protocol by the same evaluator blinded for the allocation group. The schedule of enrolment, interventions and assessments is demonstrated in [figure 2](#).

All assessments and intervention procedures will be performed at the Physical Therapy Outpatient Clinic of Faculty of Healthy Science of Trairi, Federal University of Rio Grande do Norte, Santa Cruz, Brazil.

Four researchers will be involved in this clinical trial: one researcher for the evaluation procedures, one for the tDCS application, one for the randomisation of participants and one for statistical analysis. Before starting the trial, all researchers will be trained for evaluations and application of the tDCS.

Recruitment and eligibility criteria

Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities.

Eligibility criteria for participation in the study are: men and women aged ≥ 18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a Numeric Rating Scale (NRS); tolerate physical evaluation; satisfactory cognitive function to understand and sign the informed consent, study explanations and questionnaires. The exclusion criteria adopted are: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalisation, previous diagnosis of mental disorder and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Randomisation

Patients will be enrolled by the investigators and randomly allocated (1:1) to receive active tDCS or sham. Stratified randomisation will be performed using the order of entry into the study. To prevent imbalance between treatment groups, patients will be plotted according to gender (male and female) and age (under 20 years, 20–64 years and 65 years and older). Randomisation will be applied to each stratum using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone call. Allocation concealment will be performed using opaque envelopes. Participants will be blinded to group allocation throughout the trial.

Blinding

In this clinical trial, participants and evaluators will be blinded for allocation group. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be placed in the same position as in the active group, but the stimulator delivered 2 mA of current with the same ramp-up and ramp-down period of 30 s.^{15 22} Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS.²³ This is considered a valid methodology for clinical protocols with good effectiveness of blinding.^{14 15 23–25} The tDCS device does not allow a blinded model for the researchers involved in the interventions.

Intervention

The treatment will consist of 2 weeks of intervention divided into 10 sessions of 20 min each (one per weekday) using a monophasic continuous current with an intensity of 2 mA. The active and sham groups will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. All patients will be awake and seated in a comfortable chair with back and arm support during tDCS and sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room.

The tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supraorbital region (Fp2), according to international standards for electroencephalogram (EEG) 10–20 system. The electrodes will be placed into a 35 cm² sponge immersed in saline solution (154 mM sodium chloride, approximately 12 mL per sponge). For stimulation, current ramp-up and ramp-down with 30 s duration will be employed. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a stimulator MicroEstim Genius (NKL, Santa Catarina, Brazil). Device displays are identical in the active and sham groups.

For ethical reasons, no intervention will be performed in clinical care, and painkillers or other medications will

be prescribed as usual. If a participant will begin taking medications during the study period, this will be documented, but the participant will not be excluded from the analysis. At the end of the study, participants and outcome assessors will be asked about the treatment to ensure the success of blinding.

Outcomes

Primary outcomes

Participants will be assessed using a Visual Analogue Scale (VAS) for pain, which is a one-dimensional measure of pain intensity in adults, including those with chronic pain due to rheumatic disease.²⁶ The VAS is a continuous scale comprised of a horizontal line, usually 10 centimetres (100 mm) in length, anchored by two verbal descriptors (0 representing 'no pain' and 100 representing 'pain as bad as you can imagine').²⁶ The VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity.²⁶

Secondary outcomes

Algometry will be carried out to record pressure pain threshold (PPT_h) and pressure pain tolerance (PPT_o). Pain PPT_h and PPT_o will be assessed in eight different anatomical locations: trapezius, at the midpoint of the upper edge; lumbar spine, performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and thumb on the dorsal side of the hand. All points will be tested on the left and right sides of the body. Algometry will be performed perpendicular to the skin at 5–10 s intervals by the same qualified examiner. A pressure algometer will be used (MedDor, Minas Gerais, Brazil) through a 1 cm diameter rubber tip. PPT_h and PPT_o will be quantified in kg/cm². The examiner will position the rubber tip above the area to be examined and gradually increased the pressure by 1 kg/cm²/s.²⁷ The PPT_h will be measured when the patient says, 'I'm starting to feel pain'. To measure PPT_o, the patient will be asked to bear the maximum amount of pressure from the algometer and use the verbal affirmation 'stop'.

The Brief Pain Inventory (BPI) is one of the most used instruments to assess chronic pain in clinical trials.²⁸ The BPI (short form) will be used to assess the severity and effect of pain in daily living activities. It is a questionnaire that presents 15 items, including two multi-item scales to measure pain and its effect on functionality and well-being; the questionnaire is validated for the Brazilian population.²⁸ In the room allocated for evaluation, participants will be asked by the researcher about each item, and questionnaire will be filled according to the answers of the participants. All questions can be repeated if the participant does not understand. The BPI will be applied in all phases of evaluation and by the same researcher.

In the absence of a specific functional questionnaire for acute and long-term evaluation of rheumatic manifestations of chikungunya, the Health Assessment

Questionnaire (HAQ) will be used. HAQ is commonly used to assess rheumatoid arthritis and to evaluate patients with chikungunya.^{9 29} This is a validated tool to measure disability due to persistent arthralgia.³⁰ Rising, dressing, eating, walking, bathing, reaching, gripping and performing errands will be assessed on a scale that ranged from 0 to 3. The average of all scores will be considered to classify disability as: 0, no difficulty; 0–1, mild disability; 1–1.5, moderate disability; and >1.5, severe disability.

The grip strength will be evaluated by a hydraulic dynamometer Saehan model SH5001 (Saehan Corporation, Yangdeok-Dong, Masan, Korea), and the Bohannon protocol will be used.³¹ Participants will remain seated on a chair with the feet and trunk supported, shoulder adducted, elbow flexed at 90°, forearm in neutral position and wrist in 0–30° extension.³¹ Participants will be instructed to perform a maximum isometric contraction for 5s, and the peak force will be recorded. Three evaluations will be performed with an interval of 1 min. For statistical analysis, arithmetic mean of these three measurements will be obtained. If the examiner recognises some compensatory movement by the participant, a new measurement will be performed and recorded.³²

A short form health survey (SF-36) will be used to assess quality of life.³³ The questionnaire consists of a 36-item divided into eight domains: functional capacity, limitation by physical aspects, pain, general health, vitality, social and emotional aspects and mental health.³³ These domains have between 2 and 6 response options. For each scale, item scores are coded, summed and transformed, with final values (expressed as a percentage) ranging from 0 (worst health) to 100 (best health).

Adverse event monitoring and reporting

Serious adverse effect or irreversible injury following the use of conventional tDCS protocols in human trials (20 min, 2 mA and 10 sessions) has not been reported.²⁴ Adverse events will be carefully monitored throughout the study. The most commonly reported adverse events included itching and tingling under the electrode sites, which are reported in both active and sham conditions.^{24 34} Participants will receive care as appropriate for any harm that arises following study participation. After the study, results will be presented to the participants in the form of a lecture. If the positive effects of tDCS on the research outcomes are confirmed, tDCS will be offered and guaranteed to all participants in the sham group. In case of collateral events, or frequent serious adverse effect the principal investigator makes the final decision to stop the trial.

Adherence to treatment will be encouraged with regular messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's routine.

Sample size

The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by

Silva-Filho *et al.*¹⁵ The sample size was estimated using G-Power V.3.1.9.2 (RRID:SCR_013726) based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size and two groups. According to this methodology, the sample should include 32 participants. Considering a 20% of possibly loss, the number of participants will be increased by 25%, which corresponds to 8 participants. Thus, 40 participants will be recruited and allocated in the two groups, with 20 participants each.

Data collection and management

Sociodemographic and clinical data will be collected and recorded by trained and blinded research assistants in our research centre. A trained physical therapist will undertake a face-to-face interview to collect quantitative data (questionnaires and physical tests). Consistency checks by another researcher (physical therapist) will be performed to ensure data entry accuracy during data collection. Data will be collected using paper forms and entered electronically on to the trial database. To maintain confidentiality, each participant will be given a unique trial Participant Identification Number (PIN). PIN will be used for data entered onto the central database stored on the base of UFRN. After completion of the trial, the database will be retained on the servers of UFRN for ongoing analysis of outcomes. The principal investigator will be given access to the final trial data set.

All procedures will be conducted in accordance with the international ethical and scientific standard protocols, following the Good Clinical Practices guidelines with human participants. Participants will be free to refuse to participate or withdraw their consent, at any stage of the research, without any penalty and without prejudice to their care. In case of any problem during the trial, participants will have the right to free assistance that will be provided by the responsible researcher.

Although no serious adverse²⁴ events with a causal link with tDCS are expected, adverse events will be reported to the principal investigator. Serious adverse events²⁴ will be logged and reviewed by the trial researchers and Ethics Committee if necessary. No auditing is planned. If necessary, possible amendments to the research protocol will be reported to the Ethics Review Committee for approval.

Following completion of the trial, data sets used in this study will be available from the corresponding author on reasonable requests.

Patients and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The results of the study will be communicated to participants through a popular symposium.

Statistical analysis

The SPSS software V.19.0 (IBM, Armonk, New York, USA) will be used for statistical analyses. Clinical and sociodemographic characteristics will be described by means, medians and SD for continuous numeric parameters and



by frequency tables with 95% CIs for qualitative parameters. A χ^2 test or Fisher's exact χ^2 test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann-Whitney test will be used.

Shapiro-Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the assumption of sphericity is violated, the Greenhouse-Geisser correction will be applied. The effects of stimulation on VAS, PPT_h, PPT_o, BPI, dynamometry, HAQ and SF-36 will be calculated using a mixed analysis of variance (ANOVA) model. If necessary, the use of pain killers or other medication will be adjusted on ANOVA model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up and second follow-up), stimulation group (active and sham) and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons.

For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η^2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η^2 will be used to calculate the effect size, where $\eta^2=0.01$ will be considered small, $\eta^2=0.06$ moderate and $\eta^2=0.14$ large effect. Level significance will be set at p value less than 0.05.

DISCUSSION

Chikungunya is epidemic in Brazil, with significant incidence in the Northeast (the second-highest incidence with 59.4 cases per 100 000 population).³⁵ Most of patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years, but there are no specific therapeutic agents to treat and rehabilitate persons with chronic disease.³² Persistent pain can lead to incapacitation, requiring long-term pharmacological treatment.^{8 29} Advances in non-pharmacological options are necessary to promote pain relief without side effects and to restore functionality. Herein, we propose a trial protocol with tDCS (M1/Sp2 montage) to reduce pain and restore functionality in patients with chronic chikungunya. We will also clarify (1) whether the changes induced by anodal tDCS over M1 correlated with the patient's level of pain according to the clinical evaluation scales and (2) if there is a relationship between pain relief and functionality. Previously results would suggest that anodal tDCS over M1 may influence pain in chronic arthralgia caused by CHIKV.

It is urgent assess the clinical benefits and harms of interventions to prevent or treat persisting rheumatic disorders in patients with chikungunya.³⁶ Martí-Carvajal *et al* described that only five small trials with high risk of

bias were used in a systematic review of interventions for treating patients with chikungunya-related rheumatic and musculoskeletal disorders.⁸ The authors suggested the need for more high-quality randomised clinical trials to find significant clinical benefits for this population.⁸

The tDCS is a safe, effective and low-cost therapeutic approach to the treatment of chronic pain.^{16 17 31 37-40} Previous studies have suggested that M1 anodal stimulation (C3/Fp2 montage) stimulate neural circuits in this area with subsequently modulatory effect in deep brain areas evolved with pain balance. As a result, an important pain relief was found.¹⁷ Precentral gyrus are involved in sensory and emotional aspects of pain and anodal M1 stimulation could improve pain perception in different chronic pain states.¹⁷ Besides this montage, a protocol with an intensity of 2 mA, an electrode size of 35 cm² and more than 10 consecutive sessions is commonly recommended to treat chronic pain.¹⁶⁻¹⁹ Two studies have investigated the effect of tDCS on pain and functionality in chronic chikungunya arthralgia.^{14 15} In the first study, Silva-Filho *et al*¹⁵ conducted five sessions of anodal M1/Sp2 montage, and in the second study, De Souza *et al*¹⁴ applied six alternate sessions with the same tDCS parameters. These studies have suggested significant pain relief, but no significant difference in functional capacity was observed. Authors suggested that the number of sessions or brief period of intervention can be employed to improve functionality.^{14 15} With promising preliminary results with tDCS and chronic pain in chikungunya, investigating the long-term effect of tDCS and the most adequate dose for this population is necessary.

Clinical measures of this trial include the standard recommended outcomes, including pain intensity scales validated and universally accepted.⁴¹ Secondary outcomes will be used to add information about pain and its effects on activities of daily living, disability, decrease in medication use and participant satisfaction. Sociodemographic variables that can influence pain or functionality such as gender, age, income, educational level and ethnicity will be reported.⁴¹ Grip strength will be evaluated by a hydraulic dynamometer. This test was chosen because joint involvement in chronic chikungunya arthralgia is predominant in the wrists (66.3%), hands (72%), shoulders (70.1%) and elbows (40%).³² Chronic chikungunya arthralgia can promote articular imbalance with inflammation and degeneration of cartilage and bone.¹⁰ This process can last for years, and the continuous use of arthritic joints may improve the degenerative process. Furthermore, the loss of muscle strength and functional mobility could contribute to joint degeneration.¹⁰

This protocol has strengths: (1) a novel treatment option for pain will be used in patients with chronic chikungunya arthralgia and (2) the study will be conducted in an epidemic region with a significant number of patients. However, there are some limitations to the study methodology and execution. First, this study did not receive government funding for financial support. Second, recruitment is limited to patients with chronic

chikungunya (>3 months) and no patients with acute or subacute stage of the disease will be included. Third, no specific questionnaire is used to measure disability or effect of chikungunya on the quality of life or functionality. Thus, questionnaires for other rheumatic diseases and commonly used for chikungunya will be used.^{14 15 42} Finally, this is the third trial with tDCS (the first with 10 sessions) in chronic chikungunya arthralgia, and our results will not support definitive conclusions on the efficacy of this neuromodulatory method.

The results of the present study will provide important long-term treatment information about clinical management of tDCS in persisting rheumatic disorders caused by chikungunya. We believe that these results will interest the broad audience committed to improve the quality of life and functionality of patients and to better understand brain modulation on chikungunya arthralgia.

Author affiliations

¹Graduate Program in Rehabilitation Science, Federal University of Rio Grande do Norte, Santa Cruz, Brazil

²Graduate Program in Health Science, Federal University of Rio Grande do Norte, Natal, Brazil

³Graduate Program in Neuroengineering, Instituto Santos Dumont, Macaiba, Brazil

⁴Federal University of ABC Center of Mathematics Computing and Cognition, Santo Andre, Brazil

⁵Graduate Program in Physical Therapy, Federal University of Rio Grande do Norte, Natal, Brazil

Contributors ASdN and AFLC will perform initial and final evaluation, data entry in the database and informed consent of participants. TABDA will perform the transcranial direct current stimulation (tDCS) protocol and writing of the manuscript. JDDdS and ES-F will perform the tDCS protocol. AO will support the data analysis and writing of the manuscript. LPG and RP will perform data management and writing of the manuscript.

Funding This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Following completion of the trial, data sets used in this study will be available from the corresponding author on reasonable requests.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Rodrigo Pegado <http://orcid.org/0000-0002-7227-1075>

REFERENCES

- Souza JHM, Barros TÁcita B, Almeida PP, *et al.* Dynamics of transmission of urban arbovirus dengue, Zika and Chikungunya in southwestern region of Bahia, Brazil. *An Acad Bras Cienc* 2021;93:1–5.
- WHO, PAHO. Number of reported cases of Chikungunya fever in the Americas, by country or Territory 2013–2014 (to week noted) cumulative cases epidemiological week / EW 52, 2014. Available: http://www.paho.org/hq/index.php?option=com_topics
- Nunes MRT, Faria NR, de Vasconcelos JM, *et al.* Emergence and potential for spread of Chikungunya virus in Brazil. *BMC Med* 2015;13:102.
- Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med* 2015;372:1231–9.
- SantelliACFeS, da CLN, LiviaCarlaVinhafFruutuoso. Manejo Clínico Chikungunya Ministério da Saúde; 2017: 77.
- Kennedy Amaral Pereira J, Schoen RT. Management of Chikungunya arthritis. *Clin Rheumatol* 2017;36:2179–86.
- Pineda C, Muñoz-Louis R, Caballero-Urbe CV, *et al.* Chikungunya in the region of the Americas. A challenge for rheumatologists and health care systems. *Clin Rheumatol* 2016;35:2381–5.
- Marti-Carvajal A, Ramon-Pardo P, Javelle E, *et al.* Interventions for treating patients with Chikungunya virus infection-related rheumatic and musculoskeletal disorders: a systematic review. *PLoS One* 2017;12:1–15.
- van Aalst M, Nelen CM, Goorhuis A, *et al.* Long-Term sequelae of Chikungunya virus disease: a systematic review. *Travel Med Infect Dis* 2017;15:8–22.
- Javelle E, Ribera A, Degasne I, *et al.* Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in reunion island from 2006–2012. *PLoS Negl Trop Dis* 2015;9:1–18.
- Wu T-H, Tu C-H, Chao H-T, *et al.* Dynamic changes of functional pain connectome in women with primary dysmenorrhea. *Sci Rep* 2016;6:24543.
- Vaseghi B, Zoghi M, Jaberzadeh S. How does anodal transcranial direct current stimulation of the pain neuromatrix affect brain excitability and pain perception? a randomised, double-blind, sham-control study. *PLoS One* 2015;10:1–21.
- Mendonça ME, Simis M, Grecco LC, *et al.* 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.
- De Souza CG, Pegado R, Costa J, *et al.* Alternate sessions of transcranial direct current stimulation (tDCS) reduce chronic pain in women affected by Chikungunya. A randomized clinical trial. *Brain Stimul* 2021;14:541–8.
- Silva-Filho E, Okano AH, Morya E, *et al.* Neuromodulation treats Chikungunya arthralgia: a randomized controlled trial. *Sci Rep* 2018;8:1–10.
- Lefaucheur J-P. A comprehensive database of published tDCS clinical trials (2005–2016). *Neurophysiol Clin* 2016;46:319–98.
- Lefaucheur J-P, Antal A, Ayache SS, *et al.* Evidence-Based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017;128:56–92.
- 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* 2019;4:e692–20.
- 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 Neuroeng Rehabil* 2019;16:1–29.
- Yamato T, Maher C, Saragiotto B. The TIDieR checklist will benefit the physical therapy profession. *Physiother Pract Res* 2016;96.
- ACFES S, Da CLN. Livia Carla Vinhaf Fruutuoso. Manejo Clínico Chikungunya Ministério da Saúde; 2017: 77.
- Quintiliano A, Oehmen T, Kirsztajn GM, *et al.* Transcranial direct current stimulation in management of pain, mood, functionality, and quality of life in patients undergoing hemodialysis: a study protocol for a double-blind controlled randomized trial. *Trials* 2019;20:1–9.
- Fonteneau C, Mondino M, Arns M, *et al.* Sham tDCS: a hidden source of variability? Reflections for further blinded, controlled trials. *Brain Stimul* 2019;12:S76.
- Bikson M, Grossman P, Thomas C, *et al.* Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul* 2016;9:641–61.
- Dutra LRDV, Pegado R, Silva LK, *et al.* Modulating anxiety and functional capacity with anodal tDCS over the left dorsolateral prefrontal cortex in primary dysmenorrhea. *Int J Womens Health* 2020;12:243–51.
- Hawker GA, Mian S, Kendzerska T. Measures of adult pain: visual analog scale for pain (was 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;63 Suppl 11:240–52.
- 27 Freitas RPdeA, Spyrides MHC, Rosa JGdaSS, *et al.* Mapping the body distribution of pain perception in fibromyalgia. *Rev Neurocienc* 2014;22:227–33.
- 28 Ferreira KA, Teixeira MJ, Mendonza TR, *et al.* Validation of brief pain inventory to Brazilian patients with pain. *Support Care Cancer* 2011;19:505–11.
- 29 Marimoutou C, Ferraro J, Javelle E, *et al.* Chikungunya infection: self-reported rheumatic morbidity and impaired quality of life persist 6 years later. *Clin Microbiol Infect* 2015;21:688–93.
- 30 Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid arthritis: health assessment questionnaire (HAQ), modified health assessment questionnaire (MHAQ), multidimensional health assessment questionnaire (MDHAQ), health assessment. *Arthritis Care Res* 2011;63:S4–13.
- 31 Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. *Pain Pract* 2013;13:131–45.
- 32 Bouquillard E, Fianu A, Bangil M, *et al.* Rheumatic manifestations associated with Chikungunya virus infection: a study of 307 patients with 32-month follow-up (RHUMATOCHIK study). *Joint Bone Spine* 2018;85:207–10.
- 33 Laguardia J, Campos MR, Travassos C, *et al.* Brazilian normative data for the short form 36 questionnaire, version 2. *Rev Bras Epidemiol* 2013;16:889–97.
- 34 Brunoni AR, Amadera J, Berbel B, *et al.* A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011;14:1133–45.
- 35 Xavier J, Fonseca V, Bezerra JF, *et al.* Chikungunya virus ECSA lineage reintroduction in the northeasternmost region of Brazil. *Int J Infect Dis* 2021;105:120–3.
- 36 Marques CDL, Duarte ALBP, Ranzolin A, *et al.* Recommendations of the Brazilian Society of Rheumatology for the diagnosis and treatment of chikungunya fever. Part 2 - Treatment. *Rev Bras Reumatol Engl Ed* 2017;57 Suppl 2:438–51.
- 37 Luedtke K, Rushton A, Wright C, *et al.* Transcranial direct current stimulation for the reduction of clinical and experimentally induced pain: a systematic review and meta-analysis. *Clin J Pain* 2012;28:452–61.
- 38 Jensen MP, Day MA, Miró J. Neuromodulatory treatments for chronic pain: efficacy and mechanisms. *Nat Rev Neurol* 2014;10:167–78.
- 39 Fenton BW, Palmieri PA, Boggio P, *et al.* A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain. *Brain Stimul* 2009;2:103–7.
- 40 Zhu C-E, Yu B, Zhang W, *et al.* Effectiveness and safety of transcranial direct current stimulation in fibromyalgia: a systematic review and meta-analysis. *J Rehabil Med* 2017;49:2–9.
- 41 Klein MM, Treister R, Raj T, *et al.* Transcranial magnetic stimulation of the brain. *Pain* 2015;156:1601–14.
- 42 de Souza CG, da Costa JF, de Sousa Dantas D, *et al.* Evaluation of pain, functional capacity and kinesiophobia in women in the chronic stage of Chikungunya virus infection: a cross-sectional study in northeastern Brazil. *Acta Trop* 2019;199:104853.