Research protocol

Accelerated repetitive transcranial magnetic stimulation for chronic musculoskeletal pain control: a crossover parallel group study protocol

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ABSTRACT | BACKGROUND: Chronic musculoskeletal pain is a prevalent condition associated with significant disability and high healthcare costs. Repetitive Transcranial Magnetic Stimulation (rTMS) has shown promise in pain management, but traditional protocols require daily sessions, posing logistical challenges. Accelerated Theta Burst Stimulation (TBS) offers a more practical alternative by delivering multiple stimulations in a single day. However, its use in chronic pain has not been investigated. **OBJECTIVE:** This study aims to evaluate the efficacy and safety of an accelerated TBS protocol in reducing pain in individuals with chronic musculoskeletal pain. It also explores neurophysiological mechanisms underlying treatment effects using electroencephalography (EEG). **METHODS:** A randomized, double-blind, two-phase crossover trial will be conducted with 25 chronic musculoskeletal pain adults. Participants will undergo both active and sham TBS protocols with a minimum one-week washout between phases. Each active session will consist of four 3-minute stimulations targeting the dorsolateral prefrontal cortex (DLPFC) with 600 pulses per session. The primary outcome is pain reduction, and secondary outcomes include changes in EEG oscillations and pressure pain thresholds. Safety will be monitored through reports of adverse effects. **RESULTS:** This protocol aims to generate preliminary evidence on the feasibility and efficacy of accelerated TBS for chronic musculoskeletal pain. It is expected that active TBS will result in significant pain reduction and modulation of EEG activity, including increased alpha power and reduced theta activity post-treatment. **CONCLUSION:** This study represents a novel application of accelerated TBS in chronic musculoskeletal pain management. The findings will also contribute to understanding the neuroplastic mechanisms involved in pain modulation through non-invasive brain stimulation.

KEYWORDS: Transcranial Magnetic Stimulation. Theta Burst Stimulation. Chronic Pain.

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1. Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is widely used for the treatment of chronic pain[1,2], including chronic musculoskeletal pain, one of the main public health issues worldwide.[3,4] Individuals with chronic musculoskeletal pain of various etiologies, such as knee osteoarthritis, rheumatoid arthritis, foot pain, shoulder pain, temporomandibular disorder, and low back pain, were treated with noninvasive brain stimulation, resulting in a small to moderate effect size reduction in pain.[4-8] The rTMS treatment is painless and non-invasive, involving the placement of a coil on the patient's scalp, followed by the generation of electromagnetic pulses that will depolarize the neurons located beneath the coil.[9]

A limitation of rTMS treatment, both in clinical practice and research, is the need to perform stimulation on consecutive days. Typically, an average of five to ten consecutive days of treatment sessions are conducted, with one session per day. This overall intervention can be challenging to implement, as patients might face mobility issues related to their condition or difficulties accessing treatment centers. However, it is possible that other forms of rTMS administration, such as accelerated Theta Burst Stimulation (TBS), may be more suitable.[10,11] TBS technique, introduced a few years ago, has the advantage of being applied much more quickly than classical rTMS, as it uses higher frequencies (50Hz) modulated at low frequency (5Hz), with sessions lasting from two to three minutes, instead of the 30 to 40 minutes of a classical rTMS session.[12]

Furthermore, TBS can be applied as an accelerated protocol, with more than one intervention performed on the same day, thus reducing the need for the individual to attend the treatment center as frequently.[13,14] Accelerated TBS protocols have already been employed for certain mental health conditions and psychiatric disorders, particularly depression, a condition that has been extensively studied and has shown positive results.[15,16] Although the authors believe that an accelerated rTMS protocol could positively impact pain management, no studies were found applying this protocol in individuals with chronic pain. However, a recent study explored its use in experimental pain, showing positive results in reducing pain intensity, though these findings cannot be extrapolated to patients.[17]

The most commonly targeted area for accelerated TBS is the dorsolateral prefrontal cortex (DLPFC), and the stimulation of this area has been proven safe and effective for mental health issues.[11] DLPFC is also targeted for analgesic purposes, aiming to increase the excitability of this region.[18-20] High frequency stimulation of this superficial target leads to modulation of various cortical and subcortical regions involved in pain perception, as well as the emotional and cognitive components of pain.[19] Imaging and electrophysiology studies have demonstrated structural and functional changes following rTMS treatment in regions such as the prefrontal, cingulate, insular, and orbitofrontal cortices, as well as the thalamus and striatum.[20] Additionally, it has been suggested that rTMS activates the descending pain inhibition system in individuals with chronic pain and can regulate autonomic activity, which is occasionally dysfunctional in these volunteers.[21]

Another mechanism that may be involved in pain control through the use of rTMS is the reversal of intracortical disinhibition present in chronic pain.[22,23] The dysfunction of inhibitory circuitry in chronic pain is extensively studied.[24] However, there have been few studies that evaluated GABAergic function before and after rTMS treatment.[22,23,25-27] The inhibitory circuitry can be assessed through paired-pulse transcranial magnetic stimulation-evoked potentials in the primary motor cortex, recorded by surface electromyography in the target muscle (TMS-EMG).[28] Using this assessment technique, it has been demonstrated that the reduction in pain intensity after rTMS is associated with an increase in intracortical inhibition.[23] The disadvantage of TMS-EMG is that its assessment is limited to the motor cortex.[29] Therefore, assessments using electroencephalography (EEG) can aid in building knowledge about the phenomenon of intracortical disinhibition in other brain regions.[30]

EEG data demonstrate a characteristic pattern in volunteers with chronic pain, including an increase in power density in the theta frequency band and a decrease in the response of evoked potentials.[31] The increase in power density in the theta band has been associated with a mechanism known as thalamocortical dysrhythmia, where the lack of effective modulation from the cortex to the thalamus leads to lower electroencephalographic frequencies becoming predominant in the brains of individuals

with a range of neuropsychiatric dysfunctions, including chronic pain.[32-35] Studies of connectivity using EEG also demonstrate abnormalities in different pain conditions. Nickel et al. (2020) showed abnormal connectivity in the alpha and beta bands in the sensorimotor cortex of individuals subjected to experimental acute pain[36] and Dinh et al. (2019) in gamma band connectivity in individuals with chronic pain.[37] Both these findings and the possible presence of thalamocortical dysrhythmia point to a dysfunction in the activity of GABAergic interneurons[38,39], which appears to be a key factor in the central mechanisms associated with chronic pain.[40] There are still a few studies that assess changes in power density and connectivity with EEG before and after rTMS, which would be essential to better understand the plastic changes resulting from pain and the mechanisms of neuromodulation. Despite the need for further research, there is an association between increased alpha power density and decreased pain intensity after rTMS.[41-43]

In this regard, this project aims to address two important gaps in the management of chronic pain: 1) assess the safety and effectiveness of an accelerated TBS protocol in controlling pain in individuals with chronic musculoskeletal pain; 2) conduct neurophysiological measures to understand the neuroplastic mechanisms associated with the accelerated TBS protocol in the treatment of individuals with chronic musculoskeletal pain.

2. Hypothesis

It is hypothesized that TBS treatment in individuals with chronic musculoskeletal pain will be effective in pain control. Through EEG assessment, individuals with chronic pain are expected to exhibit increased theta activity at baseline, and after treatment, there will be an increase in alpha density associated with a decrease in pain intensity. This post-treatment alteration will be present in central and frontal regions.

3. Objectives

3.1 Primary objective

To assess the efficacy and safety of an accelerated TBS protocol in controlling pain in individuals with chronic musculoskeletal pain.

3.2 Secondary objective

To conduct an exploratory study of different EEG oscillations before and after TBS treatment.

3.3 Specific objectives

a) To verify if there is a correlation between time since pain, distribution, and intensity of pain with EEG oscillation and connectivity measures assessed through EEG. b) To investigate whether pain control through TBS is accompanied by changes in brain oscillation and connectivity measures assessed through EEG. c) To evaluate the effectiveness of an accelerated TBS protocol on pressure pain threshold. d) To identify biomarkers for responders and non-responders to the accelerated TBS protocol proposed in this study.

4. Materials and methods

This is a phase-one, randomized, double-blind clinical trial with a two-stage crossover design, registered at REBEC on 19/09/2024 (RBR-4mzhbd3) under UTN U1111-1306-2836. Individuals with chronic musculoskeletal pain will be personally invited by the authors. The study will take place at the Instituto Multidisciplinar de Reabilitação e Saúde (IMRS) at the Universidade Federal da Bahia (UFBA).

4.1 Ethical considerations

This study was approved by the Research Ethics Committee of the Universidade Federal da Bahia (CAAE: 59546822.5.0000.5531). All participants will be fully informed about the study objectives, procedures, potential risks, and benefits prior to participation.

Each participant will sign a detailed Informed Consent Form (ICF), clearly outlining the study steps, potential discomforts (such as fatigue or emotional distress from questionnaires, minor discomfort from EEG or TMS), and their right to withdraw consent at any time without affecting their medical care or treatment.

Confidentiality will be strictly maintained. Data collected will be anonymized, securely stored, and used exclusively for academic and scientific purposes, following Brazilian regulations (Resolution Nº 466/12, National Health Council[44]). Data will be archived by the principal investigator for five years after the completion of the study, after which it will be destroyed. Participants will be provided with contact details for the Ethics Committee at the Universidade Federal da Bahia should they have any ethical concerns or complaints regarding their participation.

Participants will be informed about all potential adverse effects and the steps that will be taken to manage any possible medical emergencies, including specialized medical referral if necessary. They will also have the option to authorize or deny the use of their data for future research, with clear communication preferences indicated within the consent form.

4.2 Subjects

A total of 25 adult participants (age > 18 years) with chronic musculoskeletal pain, diagnosed by a specialist physician for at least three months, and with a pain intensity greater than 4/10 on the numerical rating scale (NRS) will be included. Participants may have pain from various etiologies and distributions, including low back pain, neck pain, epicondylitis, knee pain, shoulder pain, hip pain, and hand pain. Exclusion criteria include: 1) Contraindications for TMS use - presence of metal in the skull or implanted devices, history of epilepsy, pregnancy, brain trauma or surgery, intracranial hypertension, and complications related to exposure to magnetic fields (TMS or magnetic resonance imaging). 2) History of substance abuse; 3) Inability to comprehend the assessment tools used even after extensive explanation. Participants will be excluded if they have: 1) A Diagnosis of fibromyalgia and migraine; 2) More than 20% of EEG channels requiring rejection due to artifacts; 3) Change in their pharmacological or non-pharmacological treatment regimen during the study. The use of drugs that may interfere with cortical electrical activity (anticonvulsants, antidepressants, and antipsychotics) will be controlled and should remain unchanged throughout the study; 4) Fail to attend or undergo treatment interventions for more than 50% of the total scheduled sessions. In cases of exclusion based on reasons 2 and 3, individual data will be treated using Intention to Treat Analysis (ITT).

The sample size was defined based on previous neuromodulation studies for chronic pain. Early-phase clinical trials involving rTMS and TBS commonly use sample sizes ranging between 20 and 30 participants per group to preliminarily evaluate safety and efficacy. Therefore, a total of 25 participants were chosen considering established guidelines for neuromodulation studies1, ensuring adequate statistical power even considering possible losses during follow-up.

4.3 Intervention

Initially, individuals will be recruited, and questions related to inclusion and exclusion criteria will be asked. Individuals who agree to participate will be allocated to two different treatment groups randomly (using www.randomizer.org). The individual responsible for randomization will have no other role in the study. To ensure allocation concealment, information regarding the group that participants will be assigned to will be placed inside a brown envelope. Each envelope will only be opened on the first treatment day, in the presence of the participant and the therapist responsible for TBS. Both the participants and the evaluators of clinical and physical measures will be blinded to the type of TBS, whether active or sham.

The Intervention group will undergo active accelerated TBS first, which consists of four stimulations on the same day with a 10-minute interval between stimulations. Each TBS stimulation consists of pulse trains applied at 50Hz and modulated at 5Hz in time. A total of 600 pulses will be applied at an intensity of 80% of the resting motor threshold (RMT) over the left DLPFC. For this purpose, a cooled figure-eight coil (Neuro-MS, Russia) will be used, and each application will last for a total of three minutes. The Sham group will undergo Sham accelerated TBS first. For Sham TBS simulation, the coil will be positioned on the individual's head in the same target as in the Intervention Group, but no stimulation will be applied. To maintain the treatment illusion, the coil will be placed upright on the volunteer's head, without contact with the region of the coil that

provides the stimulus; nevertheless, the individual will hear the sound of TBS for three minutes. In total, four three-minute sham stimulations will be performed with a 10-minute interval between them. The washout period will be at least one week and a maximum of two weeks. All research participants will undergo both active and sham treatment conditions in different orders.

4.4 Assessment: clinical measures

The evaluation will be conducted by the same professional in all stages, who will be trained and blinded to the group to which the participant was assigned. Initially, socio-demographic and clinical data will be collected from participants through a semi-structured questionnaire prepared by the authors, including identification and contact information, ethnicity, marital status, education, occupation, family income, government benefits, and health status. The scales and questionnaires used in this study adhere to the recommendations of the IMMPACT, in which pain specialists recommend which outcomes and tools should be present in clinical trials involving individuals with pain. The assessment battery will consist of:

1) Evaluation of pain intensity using the Numerical Rating Scale (NRS).[45] The NRS is a validated and widely used assessment tool. The participant is verbally asked to choose a number from zero to ten. The chosen number represents a "score" that reflects the individual's pain intensity, with zero representing "no pain" and ten representing the "worst imaginable pain." The NRS will be assessed before and after each TBS stimulation, meaning there will be five measurements per treatment day, regardless of the type of stimulation, whether active or sham. A follow-up measurement will be conducted 24 and 48 hours after each intervention day through telephone contact, using the NRS. Pain intensity will be the primary outcome of the study.

2) The assessment of pain distribution, intensity, and impact will be conducted using the Brief Pain Inventory (BPI).[46] This is a self-administered questionnaire consisting of nine items related to pain intensity and location, effectiveness of therapies used for pain, and the impact of pain on the individual's life (general activities, mood, ability to walk, work, relationships, sleep, and ability to enjoy life).[46]

3) Pain quality will be assessed using the short form of the McGill Pain Questionnaire (SF-McGill).[47] Proposed by Melzack in 1975, the McGill Pain Questionnaire is a tool designed to quantitatively assess the affective, motivational, and evaluative components of pain. In this study, the Brazilian version of the questionnaire will be used[47], consisting of 78 words organized into 4 groups and 20 subgroups. Each group is related to a component of pain. The sensory group comprises subgroups 1 to 10, the affective group contains subgroups 11 to 15, subgroup 16 belongs to the evaluative category, and the miscellaneous group encompasses subgroups 17 to 20 volunteers will be instructed to indicate zero or one word from each subgroup that most accurately describes their pain. The measurements will be obtained from the pain rating index and the number of chosen words.

4) Type of pain, classified as nociceptive, neuropathic, or mixed, will be assessed using the Brazilian versions of neuropathic pain questionnaires, including the Douleur Neuropathique 4 (DN4) to exclude the presence of neuropathic pain.[48]

5) The assessment of central sensitization will be performed using the Central Sensitization Inventory (CSI).[49] The questionnaire consists of two parts. The first part (Part A) comprises 25 questions on a five-point scale (0-never, 1-rarely, 2-sometimes, 3-often, 4-always), where the scores are cumulative and range from 0 to 100. The cutoff point for the questionnaire is 40 points, and higher scores indicate more severe symptoms.[50,51] Part B consists of additional information regarding previous medical diagnoses.

6) Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale (HAD).[52] The scale consists of 14 items, which are divided into seven questions for assessing anxiety and seven questions for assessing depression. The total score ranges from 0 to 21 for each section. A score less than eight indicates the absence of anxiety and/or depression, a score of 8 to 10 suggests the possibility of a disorder, and a score greater than 10 indicates it is highly likely that anxiety and/or depression are present.

7) The safety of TBS treatment in individuals with pain will be assessed through a questionnaire containing the main adverse effects reported in the literature. The questionnaire will be administered at the end of the active or SHAM treatment protocols. Additionally, any spontaneous statements from research participants will be recorded.

8) To assess volunteer satisfaction or their perception of improvement after treatment, the Brazilian version of the Patient Global Impression of Change (PGIC) scale will be used.[53]

The BPI, HAD, SF-McGill, and CSI will be administered immediately before both active and sham interventions to categorize participants and evaluate potential carry-over effects from the first intervention. The adverse effects questionnaire and PGIC will be administered at the end of each treatment protocol, alongside the blinding assessment.

4.5 Neurophysiological measurement

Quantitative EEG data will be acquired using a 64-channel cap following the 10/20 international system. The data will be recorded at a 1000 Hz sampling rate and referenced to the Cz electrode. Impedances will be kept below 50 kΩ. Participants will remain seated in a relaxed posture with eyes closed for five minutes during each recording session. The environment will be illuminated and noise-free. Data will be extracted, preprocessed, and analyzed using the EEGLab software and MATLAB, estimating power in the alpha, beta, delta, and theta bands, as well as connectivity data. The EEG assessment will be conducted at two different time points, both in the active and SHAM conditions, immediately before and after the treatment protocol.

For EEG data preprocessing, the signals will be offline band-pass filtered between 0.5 and 45Hz. The data will be segmented into 2-second epochs. EEG artifacts with amplitudes below -750μV and above 750μV will be rejected using a semi-automatic protocol. EEG data with more than 33% of rejected epochs will be excluded from the analysis. After the artifact rejection protocol, all EEG data will be adjusted to have the same number of epochs. Power density will be calculated by performing the Fast Fourier Transform on each epoch and electrode for each participant. The average power densities will be grouped into frequency bands: delta (1.2-3.5Hz), theta (4–7Hz), alpha (8–12Hz), beta1 (13–20Hz), beta2 (20-30Hz), gamma1 (30-48Hz), gamma2 (52-70Hz). Regions of interest for analysis will be defined by averaging power densities across electrode groups: frontal, central, parietal, temporal, and occipital. After obtaining absolute power densities, relative power density will be calculated by dividing the value of each electrode in each frequency band by its total value in the power spectrum.

Functional connectivity will be assessed using the Phase Lag Index (PLI), which reduces volume-conduction artifacts and measures the consistency of phase differences between electrode pairs across trials. This metric will be applied to all pairs of electrodes across each frequency band. We will also calculate Small-World Parameters (SWP) to assess the efficiency of brain networks. These metrics include: Clustering coefficient (measures local connectivity); Global efficiency (reflects the ease of information flow across the network); Characteristic path length (indicates network integration). The Standardized Low-Resolution Brain Electromagnetic Tomography (sLORETA) method will be used to estimate the sources of EEG activity. This technique will help identify the brain regions most involved in treatment effects and neuroplastic changes.

4.6 Physical assessment

The pressure pain threshold (PPT) will be evaluated using a pressure algometer.[54] The evaluator will apply increasing pressure with the algometer, perpendicular to the skin, on the area identified by the volunteer as the site of worst pain. The volunteer will be instructed to say "stop" when the sensation of pressure becomes painful.[55] At that point, the pressure value will be recorded, and the test will be concluded. The PPT will be measured immediately before treatment, between the second and third active rTMS or sham stimulation, and immediately after the completion of the treatment protocol, resulting in three PPT measurements per treatment day for a total of six measurements.

4.7 Data analysis

Continuous descriptive data will be summarized using means and standard deviations (for normally distributed data) or medians and interquartile ranges (for non-normally distributed data). Normality will be assessed using the Shapiro-Wilk test.

Categorical variables will be reported as frequencies and percentages. Group comparisons will be performed using analysis of variance (ANOVA), followed by post-hoc tests with Bonferroni correction to control for multiple comparisons. When assumptions for parametric tests are not met, non-parametric alternatives (such as the Kruskal-Wallis test) will be applied. Correlations between clinical outcomes (e.g., pain intensity) and EEG measures will be tested using Pearson's or Spearman's correlation coefficients, depending on data distribution. Statistical significance will be set at $p < 0.05$.

Given the crossover design, it is critical to control for carry-over effects between the active and sham conditions. A washout period of at least one week (maximum of two weeks) will be implemented to minimize residual effects, following evidence from previous studies showing that neuromodulation effects typically dissipate within this period. To detect potential carry-over effects, baseline values (e.g., NRS scores and EEG data) will be compared across the two phases. If significant differences are found between the baselines of the first and second phases, a carry-over effect will be suspected. In such cases, ANOVA with the treatment order as a covariate will be employed to adjust the analysis. Additionally, exploratory subgroup analyses will compare participants starting with sham versus active treatment. If interaction effects between treatment order and outcomes are detected, further post-hoc analyses will be conducted to isolate the source of the effect. All statistical analyses will be performed using SPSS version 20.0.

5. Results

Accelerated TBS is expected to significantly reduce pain intensity, demonstrating superior effectiveness compared to SHAM stimulation. Additionally, it is anticipated that the analgesic effects of active stimulation will be cumulative across sessions performed on the same day. EEG data are expected to show increased alpha power density and decreased theta activity following active stimulation. Finally, an increase in pressure pain thresholds is also anticipated after the active intervention.

6. Discussion

This is an innovative study, as, to our knowledge, no published articles have explored accelerated rTMS protocols in individuals with chronic pain, nor TBS in musculoskeletal chronic pain - only in experimental pain.[17,56] In depression studies, accelerated rTMS protocols achieved outcomes comparable to traditional protocols but in a much shorter time.[57] The accelerated TBS protocol has the potential to bring significant clinical impact to the management of chronic pain by offering a more efficient and less burdensome alternative to conventional treatments. Chronic pain management typically requires repeated interventions and extended visits to specialized centers, creating logistical challenges for many patients, particularly those with limited mobility or restricted access to healthcare services.

If proven effective, the reduction in the number of treatment days achieved with the accelerated protocol would alleviate the burden on healthcare systems and improve patient adherence and quality of life. Compared to traditional rTMS protocols, which involve daily sessions for one to two weeks, performing multiple sessions in a single day presents a more practical approach for patients and healthcare providers.[57] From an economic standpoint, the accelerated protocol has the potential to lower the costs associated with chronic pain management, which often involves long-term medication use and non-pharmacological treatments.[58,59] The introduction of this protocol could also expand the clinical applicability of neuromodulation, making it a more viable option in public health settings and facilities managing large patient volumes. Individuals with chronic pain also frequently suffer from comorbidities such as anxiety and depression, increasing the complexity and cost of care.[60] The use of TBS targeting the dorsolateral prefrontal cortex (DLPFC) may not only relieve pain but also alleviate emotional symptoms.[61] Although the current study focuses on a single day of treatment, its results could provide preliminary evidence to support future studies with longer treatment durations, multiple sessions per day, and long-term follow-up, aligning more closely with protocols used in depression research.[57]

The proposed protocol includes four sessions of TBS, delivering 600 pulses per session. According to the most accepted definition of accelerated protocols, more than one rTMS session per day should be performed on the same target, with a dose exceeding that of the classical treatment.[11] Classical intermittent TBS delivers 600 pulses, with extended or prolonged protocols reaching up to 1800 pulses.[12,62] In this study, participants will receive a total of 2400 pulses across four sessions, exceeding even the pulse count of extended protocols. Although no minimum number of rTMS sessions has been established for treating chronic musculoskeletal pain, at least four sessions have been suggested for neuropathic pain.[63] The DLPFC target was chosen because it is the most studied in accelerated rTMS protocols and has been proven safe in individuals with mental health disorders.[11,63,64] However, the analgesic effect may be smaller than if the primary motor cortex had been targeted.[2]

Nevertheless, the researchers are also interested in contributing to the understanding of the DLPFC's role in treating chronic pain, especially through the EEG measures. Alterations in power density are well described in the chronic pain literature, as increases in theta and beta activity, and a reduction in alpha power.[65] Connectivity analyses offer crucial insights into neuroplastic changes induced by pain, revealing heightened connectivity within the pain network, especially in the prefrontal cortex, insula, and anterior cingulate cortex, through coherence and phase-based measures.[66] Additionally, studies on Small-World Network properties in chronic pain populations report reduced modularity and longer path lengths, reflecting a less efficient network organization, which may contribute to the persistence and resistance to treatment.[67] However, research in this area remains limited. These metrics could also help predict which participants are most likely to benefit from the intervention, identifying neurophysiological biomarkers and open new avenues for research on personalized treatment approaches.[68,69] This would optimize clinical practice by avoiding prolonged therapies for non-responders, enhancing the efficiency of care.

The main limitations of this study are likely related to the sample size and short follow-up period. Although no sample size calculation was performed, we followed the guideline that neuromodulation clinical trials with 25 participants per arm are considered Class I studies.[1] Regarding the short follow-up, while it is sufficient for a phase-one study, the results cannot be extrapolated to longer follow-up periods.

7. Conclusion

In conclusion, this study represents an initial step toward applying accelerated protocols in individuals with chronic pain and will provide valuable insights into the neuroplastic changes associated with pain and the mechanisms involved in its treatment. Assessing the feasibility and safety of this technique is essential to guide future large-scale clinical trials.

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Authors contributions

The authors declared that they have made substantial contributions to the work in terms of the conception or design of the research; the acquisition, analysis or interpretation of data for the work; and the writing or critical review for relevant intellectual content. All authors approved the final version to be published and agreed to take public responsability for all aspects of the study.

Competing interests

No financial, legal, or political conflicts involving third parties (government, private companies, and foundations, etc.) were declared for any aspect of the submitted work (including but not limited to grants and funding, advisory board participation, study design, manuscript preparation, statistical analysis, etc.).

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