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Repetitive transcranial magnetic stimulation alone and in combination with motor control exercise for the treatment of individuals with chronic non-specific low back pain (ExTraStim trial): study protocol for a randomised controlled trial

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ABSTRACT

Introduction While multiple pharmacological and non-pharmacological interventions treating chronic non-specific low back pain (CLBP) are available, they have been shown to produce at best modest effects. Interventions such as repetitive transcranial magnetic stimulation (rTMS), a form of non-invasive brain stimulation, have exhibited promising results to alleviate chronic pain. However, evidence on the effectiveness of rTMS for CLBP is scarce due to limited rigorous clinical trials. Combining rTMS with motor control exercises (MCE) may help to address both central and nociceptive factors contributing to the persistence of LBP. The primary aim of this randomised controlled trial is to compare the effectiveness of a combination of rTMS and MCE to repeated rTMS sessions alone, sham rTMS and a combination of sham rTMS and MCE on pain intensity.

Methods and analysis One hundred and forty participants (35/group) with CLBP will be randomised into four groups (active rTMS+MCE, sham rTMS+MCE, active rTMS and sham rTMS) to receive 10 sessions of their allocated intervention. The primary outcome will be the pain intensity, assessed at baseline, 4, 8, 12 and 24 weeks. Secondary outcomes will include disability, fear of movement, quality of life and patient global rating of change.

Ethics and dissemination Ethics approval was obtained from the *Comité d'éthique de la recherche sectoriel en réadaptation et intégration sociale, CIUSS de la Capitale Nationale* in June 2019 (#2020–1844 – CER CIUSSS-CN). The results of the study will be submitted to a peer-reviewed journal and scientific meetings.

Trial registration number NCT04555278.

Strengths and limitations of this study

- This is the first powered randomised controlled trial investigating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) on chronic low back pain (CLBP).
- This study will provide both short-term and long-term effect of treatment using a 6-month follow-up.
- Participants and therapists providing the exercises will be blinded to the rTMS group allocation (active or sham).
- A limitation of this trial is the absence of blinding of the investigator providing the rTMS sessions.
- Given our recruitment strategies, our study sample may not fully represent the CLBP population treated in clinical practice.

BACKGROUND

Chronic low back pain (CLBP) produces an enormous individual, social and economic burden. CLBP is often associated with disability, fear of movement/injury[1] and with a decreased quality of life.[2] The prevalence of the disease is still rising[3] as interventions prescribed to alleviate CLBP (eg, medication, exercise and surgery) have been shown to produce at best modest effects.[4–6] Refractoriness to treatment could in part be explained by dysfunction of the pain modulation system within the central nervous system. Changes in the organisation or function of cerebral areas involved in pain modulation such as the dorsolateral prefrontal cortex, cingulate cortex and insula have been reported in people with CLBP (for a review, see ref 7). These regions are rich in opioid receptors[8] and contribute to the descending control of nociceptive inputs through projections to the brainstem (eg, periaqueductal grey matter). Alterations in these brain structures could contribute to reduced efficacy of descending pain inhibition and amplification of nociception in CLBP.[9 10]

Interventions with a capacity to activate the pain modulation system, such as non-invasive brain stimulations (NIBS), could contribute to alleviation of CLBP. Among NIBS techniques, transcranial magnetic stimulation (TMS) represents a non-painful approach that can depolarise neurons within the cortex under the stimulating coil.[11] In contrast to electrical stimulation, the area of stimulation is relatively small and allows targeting of relatively specific cortical areas.[11] Moreover, application of TMS in a repetitive manner (rTMS) at different frequencies can influence the corticospinal excitability and the networks' function of the targeted cortical areas.[12] Thus, because of all these advantages, rTMS has become one of the most studied interventions to influence brain function[13] with a particular focus on the primary motor cortex (M1).

Although the full scope of mechanisms through which rTMS modifies brain function is not yet clear, it is believed that rTMS can induce pain relief partly through the release of opioids,[14] via reciprocal corticothalamic connections[14–17] and by a potential remote action on anterior cingulate and insular cortices.[14] rTMS might have the capacity to influence neural networks involved in pain modulation and could induce pain relief in CLBP.

Repetitive TMS has been widely used in research environments to treat individuals with chronic pain who are refractory to conventional therapy.[18 19] Results of recent meta-analyses point towards a significant reduction of neuropathic pain (eg, pain associated with nerve injury or neurological lesion) using high-frequency rTMS.[18 19] Evidence for rTMS efficacy in alleviating non-neuropathic pain, including CLBP, is scarce as most clinical trials that have evaluated NIBS in CLBP have used transcranial direct current stimulation (tDCS, which is another type of NIBS) with the anode electrode positioned over M1. A recent meta-analysis from our group identified moderate quality evidence that tDCS does not lead to improved long-term pain and disability in CLBP (Patricio *et al. The effect of non-invasive brain stimulation to reduce non-specific low back pain: a systematic review and meta-analysis,* accepted in Clin J Pain), but two studies that evaluated the efficacy of rTMS for CLBP were found: a non-randomised clinical trial (n=10, cross-over design) reported a significant reduction in pain after one session of high-frequency rTMS compared with a sham stimulation.[20] A randomised controlled trial (RCT) (n=44 and n=12, respectively, for active and sham rTMS) reported that 13 sessions of rTMS induced a larger pain reduction than exercise therapy or transcutaneous electrical nerve stimulation applied to the back.[21] The latter study had high risk of bias (eg, open-label design, missing information about stimulation parameters and statistical analysis), and results should be interpreted with caution. Preliminary evidence of the effect of rTMS on CLBP appears promising, but high-quality clinical trials are needed to confirm these results.

Although early evidence suggests rTMS can induce pain relief, the effect attenuates with time and repeated sessions may be essential to produce long-lasting effects.[17 22] Combining NIBS with conservative CLBP treatments might be an effective intervention to enhance the treatment effect.[23] Exercise therapy is the most recommended conservative intervention for CLBP within clinical practice guidelines.[24] Within a wide range of exercise therapy, motor control exercises (MCE) have been extensively studied, with evidence of small to moderate effect size on pain at short, intermediate and long-term follow-up compared with minimal intervention.[25] This exercise approach aims to improve spine health by optimising spine loading. Since MCE is believed to address mechanical components of CLBP by minimising nociceptive inputs through a reduction in sensitisation related to poor movement patterns[26] and rTMS may impact on the efficacy of central pain modulation mechanisms, the combination has the potential to address the multifactorial nature of CLBP.

Objectives and hypothesis

Our primary objective is to compare the effectiveness of repeated sessions of active rTMS, sham rTMS, active rTMS+MCE and sham rTMS+MCE on pain intensity in patients with CLBP. Secondary objectives are to compare the effectiveness of these interventions on disability, fear of movement, quality of life and patient global rating of change. We hypothesise that the combination of rTMS and MCE will produce larger improvements for all outcomes at the end of the intervention period and at 6 months follow-up compared with each intervention used alone.

MATERIALS AND METHODS

Study design

This parallel group RCT with a pseudofactorial design (ie, no exercise instead of sham exercise) will include five evaluation sessions over 24 weeks (baseline, 4, 8, 12 and 24 weeks) and 10 sessions of treatment over 8 weeks (figure 1). All participants will take part in one session prior to the 10 sessions of treatment to determine rTMS parameters (see Interventions). During the baseline evaluation session, included participants will complete self-administered questionnaires on sociodemographic characteristics, comorbidities, pain intensity, disability and quality of life at baseline. Then, they will be randomly assigned to one of four intervention groups (active rTMS, active rTMS+MCE, sham rTMS and sham rTMS+MCE) and undergo the assigned intervention. Treatment will commence with a 1-week induction phase (ie, a phase with multiple sessions in a short period of time to enhance the effects of rTMS at the beginning of the treatment) as recommended for studies using rTMS as an analgesic therapy.[27] This will involve three sessions within a week. For the subsequent 7 weeks, participants will undertake a maintenance phase with one session

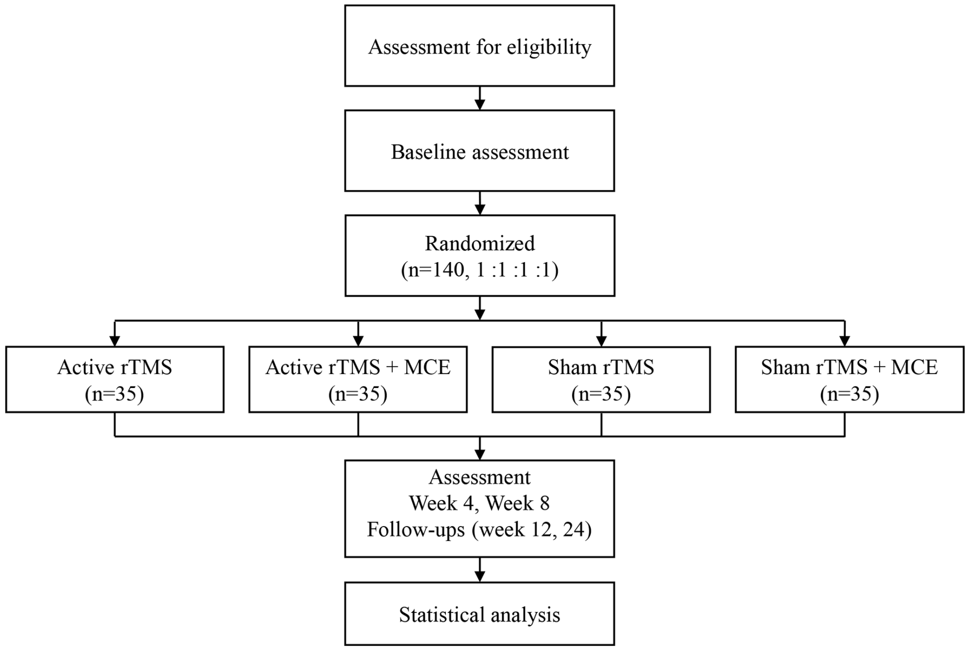

Figure 1 Flow chart of the study process. MCEs, motor control exercises; rTMS, repetitive transcranial magnetic stimulation.

per week. Study outcomes will be evaluated again at all subsequent follow-ups. The study will be conducted at the *Centre interdisciplinaire de recherche en réadaptation et en intégration sociale* (Cirris). This RCT is registered on ClinicalTrials.gov and will follow the CONSORT guideline.[28]

Participants

Four groups of 35 adults (≥18 years old) with CLBP (ie, pain in the low back area with or without leg pain below the knee limiting activities or daily routine that has been present for more than 3 months)[29] will be recruited. Potential participants will be reached through the mailing list of the *Université Laval*'s community, the Quebec Back Pain Consortium's database (patients who have accepted to be contacted for research project on low back pain), advertisement at primary care clinics and by referrals from physicians. Participants will be included if they report an average pain intensity of at least 3 out of 10 during the preceding week on a pain numerical rating scale (PNRS; anchored with 'no pain' at zero and 'worst pain imaginable' at 10) and at least 10 points on the Oswestry disability index (ODI). These criteria are based on the clinically important differences on PNRS (2 points)[30] and ODI (10 points)[31] and were chosen in order to include participants that are likely to benefit from the interventions as well as allowing the observation of clinically important differences following interventions. Participants will be excluded if they present with an identified cause of pain like neuropathic pain (if score ≥4 on the Douleur Neuropathique 4 questionnaire)[32] or a serious spinal pathology (eg, fracture, tumour and spinal infection), a history of back surgery or a major neurological, cardiovascular or psychiatric illness (eg, major psychosis and major depression) and if they currently use MCE to treat their LBP. Participants will also be excluded if they had previously experienced rTMS and if they present with any specific rTMS-related exclusion criteria such as previous seizure/convulsion, cochlear implant and pregnancy (for full list of contraindications for rTMS, see refs 33 34).

Randomisation/blinding

A randomisation list will be generated using a computer random number generator by an independent research assistant. Consecutive numbered sealed opaque envelopes will be used to guarantee concealment of allocation. Participants will be randomised 1:1:1:1 to receive either rTMS active or sham, with or without exercises, and stratified by sex and pain-related disability (score below or above 20 points on ODI). All outcomes will be assessed through an online procedure using Research Electronic Data Capture (REDCap), a secure web-based software designed to support data capture for research studies,[35] ensuring that no assessor could bias the data collection. The researcher who will analyse the data will be blinded to the allocation. The participants and physical therapists providing the exercises will be blinded on the allocation of rTMS. The effectiveness of blinding will be evaluated at the end of the 24-week follow-up. To evaluate its effectiveness, the participants and therapists providing the MCE will answer the following question: what rTMS intervention do you think the participant received?, with one of the following answers: (1) active rTMS, (2) sham rTMS or (3) don't know. If they answer 1 or 2, they will be requested to explain why they think they received this intervention. Participants will be asked to not describe their sensation during rTMS or their opinion of what group they are in during the MCE sessions to avoid unblinding the assessor and therapist. Emergency unblinding will occur only if severe side effects occur (eg, seizure) and if the participant's physician needs to know the group allocation for safety reasons. The emergency unblinding will be realised by a person not involved in the project. The actual allocation will not be disclosed to study personnel and will be disclosed to the patient only if deemed necessary.

Interventions

Evaluation session (rTMS parameters)

All participants will attend one session before the 10-session intervention to determine rTMS parameters (hotspot and motor threshold). A figure-of-8 coil and a biphasic Magstim Rapid 2 stimulator (The MagstimCo, Whitland, UK) will be used. Coil orientation and position will be guided throughout the experiment by a neuronavigation system (Brainsight, Rogue research, Montreal, Quebec, Canada). The hotspot and the resting motor threshold (RMT) of the first dorsal interosseous (FDI) muscle will be measured with electromyography electrodes placed over this muscle. The position of the hotspot will be saved by the neuronavigation system enabling a quick repositioning of the coil at each following session of treatment.

Repetitive transcranial magnetic stimulation

At each session, the hotspot and the RMT will be confirmed and/or adjusted. The intensity of rTMS will be set at 95% of the hand RMT. Previous studies of patients with CLBP[20] and fibromyalgia[17] have achieved significant reduction in clinical pain using these parameters (including stimulating hand M1 hotspot). For safety reasons, it is not possible to use the RMT of the back muscles because this requires very high intensity of stimulation at rest (100% of stimulator), which would result in very high rTMS intensity, that increases the risk of seizure.[33 36] Active rTMS will consist of 40 trains of 5s each at 10Hz (25s intertrain interval) applied over the primary motor cortex (M1) at the location that evokes the largest response of FDI cortical representation, for a total of 2000 stimulations over a period of 20min.[17] This aligns with current guidelines that recommend at least 1000 stimulations of high-frequency rTMS to produce pain relief[18] and remains within safety margin.[33]

Sham rTMS

A sham coil will be used to ensure the blinding of participants. This coil is the same as a regular rTMS coil but is equipped with a magnetic shield that blocks the magnetic field. It will provide auditory effects similar to the active coil.[37] At each session, the position of the participant's hotspot will be displayed by the neuronavigation system, and the sham coil will be placed over it. We believe that the use of the neuronavigation system will permit to enhance the credibility of the sham session (eg, precise positioning of the coil, use of state-of-the-art equipment and so on) and will help to blind participants allocated to sham rTMS. In addition, our paradigm has several advantages since it ensures that the placebo is: (1) inert (the shield stops all stimulations) and (2) structurally equivalent (ie, same number of sessions and duration of the session). We will also recruit participants that are naïve to rTMS (ie, they do not know the sensation of a true treatment). These specific characteristics of the sham design will improve blinding of the participants.[38]

Motor control exercise

The two groups combining active or sham rTMS to MCE (active rTMS+MCE and sham rTMS+MCE) will receive the same rehabilitation program that will consist of a 30min session of MCE following the rTMS intervention (three times during the induction week and then once a week for the following 7 weeks). An experienced physiotherapist will deliver the MCE according to the principles outlined by Hodges *et al*.[39] The first session will begin with an evaluation of the participant's abilities and deficiencies in posture, movement and muscle activation to design a tailored training program individually for each participant. Spinal alignment, muscle activity/stiffness and control, movement patterns, regions adjacent to the lumbar spine such the hip and pelvic floor, associated functions such as breathing pattern and symptoms will be considered in the clinical examination. Motor learning principles will be used to address sensorimotor function related to the participant's presentation on assessment, such as restoration of optimal trunk muscle coordination and control, encouraging pain-free posture and movement and progression to functional activities.[40–42] External feedback will be given by the physiotherapist at every stage of the rehabilitation, and participants will be encouraged to repeat their exercises as often as possible, with sufficient repetition and intensity to enhance experience-dependent plasticity[43] (eg, daily exercises with four series of 10 repetitions). External feedback will be reduced with improvement in the performance of the exercises. An emphasis on the quality of the contraction of deep muscles of the trunk (eg, transversus abdominis, lumbar multifidus), static and dynamic progression of spine and lumbopelvic orientation and movement and a functional re-education specific to participant goals will be made. Complexity will be added following the participant's progression with increasing the load, modifying the body position or adding dynamic movement. The exercises will be reported according to the Consensus on Exercise Reporting Template.[44] Participants will be encouraged to perform daily (~30min) three to five home exercises adapted to their condition and will complete an exercise log to evaluate adherence. Although not mandatory, participants will be invited to continue their exercises on their own after the 8-week intervention period.

Outcomes

Recommendations from an expert consensus on the best instrument measurements ('Core outcomes') for clinical trials in LBP will be followed to measure pain, disability and health-related quality of life domains.[45] Recommendations are based on the quality of psychometric properties of the instruments (eg, reliability and validity), ease of use and availability. Study outcome measures are presented in table 1 according to the SPIRIT guideline.[46]

Primary outcome

As pain is usually the main concern of people with CLBP,[47] our primary outcome will be the average pain intensity over the last week, assessed on a 11-point PNRS ranging from 0 to 10, anchored with 'no pain' at zero and 'worst pain imaginable' at 10. Pain assessment using the PNRS has been suggested as a core outcome for individuals with LBP.[48] This rating scale has an excellent reliability (intraclass correlation coefficient (ICC)=0.92)[49] and a clinically important difference (CID) of 2 points.[30]

Secondary outcomes

We will evaluate pain-related disability using the ODI V.2.1, which is a self-administered questionnaire based on the evaluation of pain elicited during the performance of 10 activities (eg, personal care, lifting, walking and sleeping).[50] ODI is valid, reliable and responsive to treatment for patients with CLBP[51] with an ICC of 0.84[52] and a CID of 10.[31]

Quality of life will be assessed using the SF-12, a generic quality-of-life questionnaire that consists of 12 questions evaluating eight mental and physical health domains (eg, physical functioning, general health, social functioning and mental health).[53] It is valid and reliable (Cronbach's alpha above the recommended level of 0.70)[54] in CLBP.[51]

Pain-related fear of movement will be evaluated by the Tampa scale for kinesiophobia (TSK). The original TSK is a 17-item questionnaire in which respondents have to indicate their agreement with the items on a 4-point Likert scale.[55] However, the scores on items 4, 8, 12 and 16 are reversed, and patients may encounter difficulties in interpreting these questions.[56] Thus, the 13-item version of the TSK (the reverse items are deleted) will be used, and it has shown an increased test–retest reliability (r=0.79) and internal consistency (Cronbach's alpha of 0.76)[56] compared with TSK-17. This questionnaire will allow to explore the effect of our interventions on a pain-related fear of movement.

The perception of the participants' improvement or deterioration after the intervention will be assessed using an 11-point global rating of change scale, ranging from −5 (very much worse) to 5 (completely recovered), with 0 for 'unchanged'.[57] This scale has a high test–retest reliability (ICC=0.90), an MDC of 0.45 points and a CID of 2 points.[57]

Sample size

Our sample was estimated using the CID for pain intensity (2 points)[30] and the standard deviation reported from a study that used a combination of transcranial direct current stimulation and exercise (3.0).[58] Considering an alpha of 0.05, a beta of 0.20 and 20% of dropout, a sample size of 140 participants (35 per group) was calculated using G*Power V.3.1.9 software.

Statistical analysis

Table 2 represents the pseudofactorial design (rTMS × MCE) used in our RCT. Generalised linear mixed models (GLMM) will be performed using terms for rTMS (active

Table 1 SPIRIT diagram of enrolment, interventions and assessments for the ExTraStim trial

	Enrolment	Baseline	First treatment	Post first treatment			
Timepoint	$-t_2$	$-t_1$	0	*w4*	*w8*	*w12*	*w24*
Enrolment							
Initial screening	×						
Eligibility assessment	×						
Informed consent	×						
Treatment allocation		×					
Interventions							
Active rTMS			◆———	———	———◆		
Sham rTMS			◆———	———	———◆		
Active rTMS+MCE			◆———	———	———◆		
Sham rTMS+MCE			◆———	———	———◆		
Assessments							
Baseline demographic information	×						
PNRS		×		×	×	×	×
ODI		×		×	×	×	×
SF-12		×			×	×	×
TSK		×			×	×	×
GRC					×		

0, starting day of the treatment; GRC, global rating of change; MCE, motor control exercises; ODI, Oswestry Disability Index; PNRS, pain numerical rating scale; rTMS, repetitive transcranial magnetic stimulation; SF-12, 12-Item Short Form Survey; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; t1, baseline evaluation; t2, first contact with participants; TSK, Tampa scale of kinesiophobia; w4–w24, weeks 4–26.

Table 2 Pseudofactorial design of the ExTraStim trial

		MCE	
		Yes	No
rTMS	Active	Group 1 n=35	Group 2 n=35
	Sham	Group 3 n=35	Group 4 n=35

MCE, motor control exercises; rTMS, repetitive transcranial magnetic stimulation.

vs sham), MCE (yes vs no), time (0, 4, 8, 12 and 24 weeks) and all interactions between terms with random effect for participants. GLMM will be apply on both primary (pain) and secondary (disability, quality of life and kinesiophobia) outcomes. The rTMS × MCE × time interactions will inform if there is a benefit to combine both treatments.

If a violation in assumptions allowing the use of GLMM occurs (eg, a change in the types of data distribution between the different time points), a non-parametric longitudinal data (nparLD) analysis will be performed as this procedure provides robust rank-based methods, even in case of an unknown distribution or atypical measurements and outliers.[59] Both GLMM and nparLD work well with missing data without any need to impute or reject participants. The significance threshold will be set at $p<0.05$. Participants will be asked to report any side effects that occurred during the study.

Patient and public involvement

A patient partner (Laurent Dupuis) reviewed the study design considering the perspective of a patient. Main results will be disseminated to study participants and to patient group (eg, *Association Québécoise de douleur chronique*).

Ethics and dissemination

All the data collected and study related information will be securely stored in password-protected files for numeric data and in locked file cabinets for hard copies. Only study investigators will have access to the data at the completion of the trial. This study has received ethics approval at the *Comité d'éthique de la recherche sectoriel en réadaptation et intégration sociale, CIUSS de la Capitale Nationale* in June 2019 (#2020–1844 – CER CIUSSS-CN). Any modification of the protocol will be submitted to the ethics committee for approval and to ClinicalTrials.org. A study investigator will send information sheets to potential participants. They will then be able to have an informed discussion with the investigator about the information provided in the information sheets. At the baseline visit, all participants will provide informed written consent prior to the beginning of the experiment, and they will be informed that they can withdraw at any moment during the study. Participants will also give written consent for the collection of data for ancillary studies (eg, MRI and sensory testing).

Results of the RCT will be published in a peer-reviewed journal, and deidentified data will be made available on a public repository at the time of publication. Results will also be disseminated through scientific meetings. The International Committee of Medical Journal Editors criteria for authorship will be followed, and no professional writer will be involved.

Participant withdrawal and adverse events

To minimise safety issues regarding rTMS intervention, we will follow safety guidelines and use a screening questionnaire.[33 34] In addition, a visual monitoring of 'proximal' motor evoked potentials in the trapezius muscle, which would indicate an intracortical spread of excitation, will be used.[33] Any potential adverse events reported by participants will be monitored at the end of the 8-week intervention (eg, nature of the event, duration and need to see a health professional). The decision to continue the study will depend on the nature of the incident and the participant desire. A participant will be able to withdraw from the study at any time and without justification. Previously collected data will be included in the analysis with the permission of the participant.

Timeline and feasibility

Recruitment started in September 2020 and is expected to be completed in September 2022. We expect to recruit at a rate of six participants per months, as a treatment facility entirely dedicated to this project is available. Also, the funding is secured by multiple grants from the Canadian Pain Society, Pfizer Inc and Eli Lilly and Company, and the Canadian Institutes of Health Research.

DISCUSSION

This is the first RCT to investigate both repeated rTMS sessions and the combination of rTMS and MCE for the treatment of patients with CLBP. The poor efficacy of surgery or drugs, and their significant risks of adverse effects, underpins a need for conservative non-pharmacological interventions. As the previous studies using rTMS for CLBP have shown promising results[20 21] and exercises are the most recommended intervention in international guidelines,[60] we believe their combination has the potential to produce a meaningful impact on pain and disability for patients with CLBP. This study has several strengths. First, it will provide robust evidence on the interest of rTMS alone or in association with MCE for the treatment of CLBP, up to a period of 6 months. The use of a sham rTMS coil and the control of blinding at the end of the study will efficiently control for the placebo effect of rTMS and allows to measure a true effect. Both participants and the physical therapists providing MCE will be blinded to the rTMS treatment. However, a limitation of this protocol might be the lack of blinding of the technician administering rTMS and the participants undergoing MCE due to the nature of the intervention. Nevertheless, as our main goal is to evaluate the contribution of rTMS (MCE have already been extensively studied),[25] an efficient blinding of rTMS is considered the priority. A further limitation could be that this trial will be conducted at one research centre, limiting the generalisability of the results, although the recruitment will be achieved through different processes as described previously.

This study provides the opportunity to determine the efficacy of these treatments/treatment combinations using a rigorous research protocol. rTMS is a non-invasive technique that is increasingly available for management of other conditions such as depression.[61] If we establish its effectiveness, this device could contribute to the care provided to people with CLBP and reduce its economic and social impact through greater pain relief and improvement of functional capacity.

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Contributors All authors conceived the idea of the study and developed the intervention. PP and HM-A wrote the article. PP, J-SR, LM, GL, MR and HM-A developed the design of the trial. All authors have read and approved the final manuscript.

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Disclaimer Study funders and sponsor had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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