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Repetitive Transcranial Magnetic Stimulation as An Adjunct to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

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rTMS and exercise for knee osteoarthritis

TITLE

Repetitive Transcranial Magnetic Stimulation as An Adjunct to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

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rTMS and exercise for knee osteoarthritis

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ABSTRACT

Objective: To examine the feasibility, safety and perceived patient response of a combined repetitive transcranial magnetic stimulation (rTMS) and quadriceps strengthening exercise intervention for knee osteoarthritis.

Methods: A two-arm, participant-, therapist- and assessor-blinded, randomised controlled trial with additional follow-up of pain and function at three months. Participants were randomised to receive active rTMS+exercise (AR+EX) or sham rTMS+exercise (SR+EX) twice weekly for six weeks whilst completing home exercises twice week. Primary outcomes included recruitment rate, treatment attendance, dropouts, willingness to undergo therapy (11-point numeric rating scale, 'not at all willing'=0 and 'very willing'=10), success of participant, therapist and outcome assessor blinding, adverse events and Global Perceived Effect Scale. Secondary outcomes were pain, function and measures of physiological mechanisms.

Results: Eighty-six people were screened, 31 (36%) were randomised, 28 (90%) completed the treatments and six (19%) dropouts at three-month follow-up. Both groups had high treatment attendance (98.4 and 100%). All participants scored at least 7 on the willingness to undergo therapy scale. Blinding was successful. No adverse events were reported. At the post-intervention assessment, 80% in the AR+EX group and 75% in the SR+EX group reported an improvement on the Global Perceived Effect Scale. Both groups demonstrated within-group improvements in pain at the post-intervention assessment but not at three-month follow-up. Function improved only in the AR+EX group at the post-intervention assessment.

Conclusion: Combined rTMS and quadriceps strengthening exercise intervention for knee osteoarthritis is feasible, safe and well-received. A full-scale trial is justified to assess the clinical benefits of this novel treatment.

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Registration: ACTRN12621001712897

Keywords: exercise, knee osteoarthritis, repetitive transcranial magnetic stimulation, randomised controlled trial.

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ARTICLE SUMMARY

Strengths and limitations of this study

- Randomised, assessor-, therapist- and participant-blind, sham-controlled study design
- Data on the feasibility, safety, analgesic effect and central mechanisms of the combined rTMS and exercise therapy in knee osteoarthritis
- This pilot study was not powered to determine treatment efficacy.

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INTRODUCTION

Knee osteoarthritis is a leading cause of global disease burden.(1) The main symptoms are pain and physical dysfunction that become persistent and debilitating as the disorder progresses.(2) Non-surgical, non-drug interventions have been recommended to reduce pain and improve function for knee osteoarthritis.(3) Strengthening exercise is the cornerstone of conservative treatment and is recommended as a first-line treatment in all international guidelines.(4, 5) Exercise yields analgesic effects via both peripheral (i.e., improving muscle strength/coordination and joint proprioceptive control that subsequently reduces nociceptive inputs from the affected knee) and central (i.e., activating endogenous opiodergic and pain control systems) mechanisms.(6, 7) However, the effects of exercise are at best, moderate for pain and function, and small for quality of life.(8) While knee osteoarthritis is a well-defined joint disorder, pain severity does not always correlate with radiographic findings.(9) This discordance has been attributed to maladaptive neuroplasticity of central pain processing pathways.(10) Novel treatments targeting the neurophysiological mechanisms underpinning osteoarthritic knee pain could bolster the effects of strengthening exercise and optimise outcomes.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, might boost the benefits of exercise for knee osteoarthritis. rTMS can induce neuroplasticity, either decreasing (inhibitory, low-frequency stimulation ≤1 Hz) or increasing (excitatory, high-frequency stimulation ≥5 Hz) cortical excitability.(11) Research suggests that rTMS alleviates pain via the activation of endogenous opioid pathways of brain regions involved in pain processing.(12) High-frequency rTMS applied over the primary motor cortex (M1) has demonstrated superiority to low-frequency rTMS in chronic pain populations.(13) Further, as increased M1 excitability is associated with motor learning,(14)

applying excitatory, high-frequency rTMS over M1 might increase the brain's responsiveness to the afferent inputs generated by subsequent treatments (i.e., exercise), a phenomenon known as 'priming'.(15)

Therefore, adding high-frequency rTMS over M1 to strengthening exercise could potentially improve outcomes beyond that which can be achieved with rTMS or exercise alone through two mechanisms: (i) simultaneously modulating peripheral (exercise) and central (rTMS and exercise) mechanisms underpinning knee osteoarthritis pain and/or; (ii) 'priming' the brain to increase its responsiveness to the corticomotor benefits of exercise (i.e., increased cortical excitability, enhanced voluntary muscle activation, strength gains, improved motor control).(16) Although a recent meta-analysis showed that a combined rTMS and exercise intervention yielded a moderate pain reduction (2 trials, n=38, standardised mean difference=-0.76) for chronic pain conditions in general,(17) the effect of this intervention specific to knee osteoarthritis remains unknown.

This study aimed to 1) examine the feasibility, safety and patient-perceived effect of a combined high-frequency rTMS and strengthening exercise intervention for knee osteoarthritis; 2) assess physiological mechanisms underlying the intervention; and 3) provide data to conduct a sample size calculation for a fully powered trial based on the results of pain and physical function outcomes.

METHODS AND ANALYSIS

Design

This was an assessor-, therapist- and participant-blinded, two-arm parallel group, pilot randomised controlled trial (RCT). The outcome measures were assessed at baseline and

upon treatment completion (six weeks post-randomisation). In addition, pain and function were also assessed three months post-intervention. The study was prospectively registered (ACTRN12621001712897) and approved by the University of New South Wales Human Research Ethics Committee (HC210954). The study protocol has been published.(18) All participants provided written informed consent. The study is reported using the Consolidated Standards of Reporting Trials statement extension for pilot trials (Supplementary Table S1).(19)

Participants

Participants were recruited from the community in Sydney, Australia. Inclusion criteria were: 1) people aged ≥50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria,(20) having at least one of the following: morning stiffness <30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth; 2) knee pain for ≥3 months and on most days in the past month; 3) average pain intensity ≥4 on an 11-point numeric rating scale (NRS) in the past week. Exclusion criteria were: 1) previous knee joint replacement or high tibial osteotomy on the affected side; 2) knee surgery or joint injection in the past six months; 3) planned surgery in the next nine months; 4) using oral corticosteroids currently or in the past four weeks; 5) confirmed diagnosis of systemic arthritis (i.e., rheumatoid arthritis); 6) previous knee fracture or malignancy; 7) other conditions affecting lower limb function; 8) participating in any knee strengthening exercise for knee osteoarthritis in the past six months; 9) loss of sensation of the affected lower limb; 10) neurological or psychiatric disorders; 11) use of neuroactive drugs; 12) contraindications to TMS (i.e., epilepsy, metal implant in the skull) using the TMS safety screening questionnaire(21); 13) resting motor threshold (rMT) >80% measured at the baseline assessment as this would lead to a high stimulating intensity for the rTMS intervention and

potential overheating of the coil. Participants were permitted to continue their usual medications during the trial.

Procedures

Potential participants completed an online screening questionnaire to determine eligibility. Eligible participants attended baseline assessment and were randomly allocated to the active rTMS+exercise (AR+EX) or sham rTMS+exercise (SR+EX) group. The assigned treatment was allocated through REDCap prior to the first treatment session, independently of the researchers involved with physiotherapy treatment and outcome assessment. Participants, treating physiotherapists and outcome assessors were blinded to group allocation. All participants received the same instructions and information about rTMS intervention. Participants received either active or sham rTMS immediately before 30 minutes of one-to-one supervised strengthening exercise twice weekly for six weeks (12 sessions). If bilateral symptoms were present, the most painful knee was assessed and treated. Six physiotherapists (at least 2 years' experience) delivered exercise therapies. All procedures were performed at Neuroscience Research Australia (NeuRA), Sydney, Australia.

Intervention

rTMS

The rTMS target is the motor hotspot, or the coil position inducing a maximal motor evoked potential (MEP) amplitude measured on electromyography (EMG) using a bipolar surface electrode (Ag-AgCl, Noraxon dual electrodes) on the first dorsal interosseous muscle ipsilateral to the treated knee using a Magstim Rapid^2 (Magstim Ltd., UK) and a 70 mm figure-of-eight coil (Supplementary Figure S1). Motor hotspots for the quadriceps muscles were not used as rTMS target as MEPs cannot be reliably elicited at rest,(22) and rTMS

targeting motor hotspot for the hand has non-somatotopic analgesic effect.(23) At each session, 3000 stimuli (10 Hz, 30 trains of 10 seconds, 20-second intertrain interval) were delivered at 90% of rMT (the minimum intensity at which five out of ten stimuli delivered to the hotspot, evoked a MEP >50 μV).(24) rMT was assessed at the beginning of each session. For sham rTMS, a sham coil that looks identical to a real coil but produces no magnetic pulse and only audible clicks was used to deliver the same stimulation protocol as active rTMS.

Exercise

Participants performed standardised quadriceps strengthening exercises (Supplementary Table S1) with demonstrated effectiveness for knee osteoarthritis using ankle cuff weights or resistance bands as appropriate.(6, 8) Each exercise was performed in 3 sets of 10 repetitions with a 30s rest between sets. The treating physiotherapists determined the starting level and when to progress the exercise based on participant's feedback and therapist's clinical judgement. Exercises were progressed as defined in the protocol.(18) Participants performed their supervised exercises at home at the same dosage using resistance bands twice per week. Home exercise diaries with instructions were provided for recording the number of sessions, type and number of exercises performed and adverse reactions and collected at the post-intervention assessment.

Outcome Measures

Primary Outcomes

Feasibility, safety and participant-perceived improvement to treatment were measured as: 1) the proportion of participants recruited from the total number screened; 2) the number of sessions attended by each participant; 3) the number of drop-outs in each group; 4) willingness of each participant to undergo therapy at baseline on an 11-point NRS with 'not

at all willing' at 0 and 'very willing' at 10; 5) success of participant/outcome assessor/therapist blinding; 6) the number of adverse events and the details of each event; 7) the Global Perceived Effect Scale, where each participant rated their perceived response to treatments on a 7-point Likert scale ranging from "completely recovered" to "vastly worsened".(25) The success of participant blinding was assessed at the completion of the intervention using a Yes/No response to the question 'Do you believe you received real brain stimulation?' and an 11-point NRS of the individual's confidence in that judgement. Participants were also be asked 'Why do you believe you received the real/sham brain stimulation?' and 'Was it divulged to you whether you were receiving real brain stimulation or not?' The success of outcome assessor and treating physiotherapist blinding was determined using a Yes/No response to the question 'Did you know which intervention group the participant was assigned to before completion of the follow-up laboratory assessment?' and 'If you answer "yes", how was it divulged to you?'.

Secondary Outcomes

Pain and function

Knee pain and function were assessed using: 1) an 11-point NRS (0='no pain', 10='worst pain imaginable') for average pain in the past week;(26) 2) the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (24 items [0-4 scale, 0='none', 4='extreme'], total score=96) (Likert version 3.1) and its pain subscale (5 items, total score=20) and physical function subscale (17 items, total score=68), with higher scores indicating worse pain and function;(27) 3) modified painDETECT (mPD-Q, 7 items, total score=38) to detect a neuropathic pain component (score ≥12) in people with knee osteoarthritis;(28) 4) the number of painful sites, measured by participants indicating the number of painful sites outside of the affected knee lasting >24 hours in the past week on a

four-sided body map (total score=35) with higher scores indicating more widespread hyperalgesia;(29) and 5) the Pain Catastrophising Scale (PCS, 13 items, total score=0-52) to assess participants' thoughts and feelings about pain in the domains of magnification, rumination and helplessness, with higher scores indicating higher severity.(30) The minimum clinically important change (MCIC) to be detected in knee osteoarthritis trials is 1 unit for pain(31) and 6 units for function.(32)

Physiological mechanism investigations

1) Corticomotor excitability was measured using TMS mapping.(18) Single-pulse TMS was delivered over M1, evoking MEPs recorded on EMG by bipolar surface electrodes over the rectus femoris (RF), vastus lateralis (VL) and vastus medialis oblique (VMO) muscles while participants were seated. EMG signals were amplified (x2000), filtered (20-1000 Hz) and sampled at 2k Hz. Active motor threshold (aMT) was determined on the hotspot for the RF while participants maintained a muscle contraction of 10% averaged root mean square (RMS) EMG of three, 3-s maximal muscle contractions of the RF. During TMS mapping, 126 single-pulse biphasic stimuli (120% of RF aMT, 18 trains of seven stimuli, 2-s interstimulus interval) were delivered pseudorandomly over a 6 x 7 cm (7 rows and 8 columns) grid using Magstim Rapid^2 (Magstim Ltd., UK) and a 70 mm figure-of-eight coil, while participants activated the RF to 10% of the averaged RMS EMG of three, 3-s maximal muscle contractions with feedback provided on a monitor. The coil was placed tangentially to the skull with the handle pointing laterally 90 degrees.(22) The Neural Navigator (Neurosoft, Russia) was used to track the positions of the TMS coil and participant's head and ensure stimuli were evenly distributed throughout the grid.

Maps for the RF, VL and VMO muscles were produced offline using a custom script in MATLAB 2023b (MathWorks Inc., USA) based on previously published methods.(22) RMS

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EMG amplitude of MEPs was extracted from a 26 to 46ms window after stimulation and background RMS EMG (55 to 5ms prior to stimulation) was subtracted. Surface maps within a transformed plane encompassing stimulation coordinates and their corresponding MEP amplitude were generated. The map was then divided into 2744 partitions (49 x 56), with each partition assigned an estimated MEP amplitude based on the nearest acquired MEP values using triangular linear interpolation. *Map volume*, a sum of the MEP amplitudes (μV) of all partitions with MEP amplitudes >10% of the maximum MEP amplitude, was used to index corticomotor excitability.

2) Maximum voluntary isometric contraction (MVIC) of the quadriceps muscles was measured when participants were seated with the hips and knees in 90 degrees flexion using a force transducer. Verbal encouragement was provided. Three attempts were recorded for each participant, and the highest value was used for analysis.

3) Pressure pain thresholds (PPTs) were assessed using a hand-held pressure algometer (Somedc, Hörby, Sweden, probe size 1cm^2) to quantify mechanical sensitivity. The probe (size 1 cm^2) was applied perpendicular to the skin (rate 40 kPa/s) until the participant first reported that the sensation of pressure had changed to pain. PPTs were measured at the side of the knee joint line of the most painful knee and ipsilateral thumbnail. Three measurements at each site were averaged for analysis. PPT assessment has good relative reliability (ICC=0.83, 95% confidence interval [CI] 0.72-0.90).(33)

4) Conditioned pain modulation (CPM) is a measure thought to reflect endogenous pain inhibition. The CPM response is quantified as a change in the threshold for a stimulus to become painful (test stimulus, TS) at one body site in the presence of pain during a second

noxious stimulus (conditioning stimulus, CS) at another body site. In a normal CPM response, painful stimuli at one body site reduces perceived pain intensity induced by noxious stimuli at another body site. PPTs at the upper trapezius muscle contralateral to the painful knee were used as the TS and the cold pressor test (CPT) in the ipsilateral hand was used as the CS. Three PPTs (TS_1) were measured before the CPT. For CPT, participants immersed the hand in cold water (4 ºC) for a maximum of two minutes.(34) Three PPTs (TS_2) were re-assessed when CPT-evoked pain reached 50 on a NRS (0-100). If the pain became unbearable, participants were permitted to remove their hand before completing the CPT and a pain rating was obtained immediately after participants removed their hand. The magnitude of CPM was determined as (1) absolute value: TS_2 minus TS_1; and (2) precent change: $[(TS_2\text{-}TS_1)/TS_1]x100$, where a positive value indicated normal descending pain inhibitory function.(35) CPM paradigm has shown good relative reliability (ICC>0.75).(36)

Statistical Analysis

Although a sample size calculation is not required in a pilot RCT, 15 to 20 participants per treatment arm is recommended.(18) We selected a sample size of total 30 participants based as we successfully completed a previous pilot RCT with a similar design.(16) As a pilot study has low power, between-group statistical comparisons were not conducted.(37) Participant demographics and primary outcome measures were analysed and reported descriptively (mean and standard deviation [SD] or percentages). A full-scale RCT would be deemed to be feasible if the following predefined criteria thresholds are met: 1) attendance rate >80%; 2) dropout rate <20%; 3) 80% of participants scored ≥7 on the 11-point willingness to undergo therapy scale at baseline.(18) For secondary outcome measures, within-group changes were calculated as follow-up minus baseline assessments (mean and 95% CI). Between-group differences (mean and 95% CI) were also calculated at post-intervention and three months.

Two-sided T-tests were used for within-group comparisons between baseline and follow-up measures and effect sizes (*Cohen's d*, 0.2 as small, 0.5 moderate and 0.8 large) were calculated. All analyses were conducted using R, version 4.03 (R Development Core Team, Vienna, Austria).(38)

RESULTS

Feasibility

Between June 2022 and August 2023, 86 people were screened for eligibility, 35 (41%) were eligible and attended baseline assessment. Three participants were excluded at baseline assessment, and one withdrew after baseline assessment due to a wrist fracture unrelated to the study (Figure 1). Thirty-one participants (36% of screened participants) were enrolled and entered randomisation (AR+EX group N=17; SR+EX group N=14). All participants (100%) scored ≥7 on the willingness to undergo therapy (Table 1). The dropout rate was 10% at post-intervention assessment. In the AR+EX group, one participant withdrew due to work commitments. In the SR+EX group, one participant withdrew due to a flare-up of knee pain after the first treatment and another due to traveling distance. The dropout rate was 19% at three months (AR+EX group: N=3; SR+EX group: N=3). The treatment attendance rate was 98.4% (11.8±0.54 sessions) in the AR+EX group and 100% in the SR+EX group. No participant reported that treatment allocation was revealed before completing the post-intervention assessment. Thirteen participants (81%) in the AR+EX group and three (25%) in the SR+EX group correctly guessed their treatment group. In the AR+EX group, 11 participants thought they received "real" rTMS because their symptoms improved, and for the other two participants, because of perceived "stimulation" sensations in the hand or knee during rTMS. The outcome assessor and physiotherapists reported the treatment group allocation was not divulged before the trial completion.

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Table 1. Baseline characteristics of participants (mean and standard deviation).

	Active rTMS + Exercise (N = 17)	Sham rTMS + Exercise (N = 14)
Age (year)	64.2 ± 7.6	67.1 ± 9.6
Sex (male/female)	5/12	5/9
Body mass index (kg/meter^2)	28.3 ± 6.4	27.7 ± 5.1
Previous arthroscopy	3	2
Side of worse pain (left/right)	9/8	5/9
Duration of knee pain (year)	6.7 ± 5.0	7.5 ± 5.0
Previous injection (yes)	6	4
Cortisone	2	4
Hyaluronic acid	1	0
Platelet-rich plasm	3	0
Willingness to undergo treatment (out of 10)	9.8 ± 0.7	9.4 ± 1.2
Expected treatment effect		
No improvement	1	0
Minimal improvement	0	1
Moderate improvement	10	9
Large improvement	6	4

Safety

No adverse event related to rTMS was reported. The AR+EX group reported mild side effects during rTMS: two episodes of transient feelings in a tooth filling and two episodes of transient sensation on the face. These side-effects did not impact rTMS and exercise treatment completion. One participant in the ST+EX group experienced an acute flare-up of knee pain after the first treatment, attributed to exercise, and subsequently withdrew from the study.

Participant-perceived improvement

Upon treatment completion, 13 (80%) participants in the AR+EX group and nine (75%) in the SR+EX group reported an improvement in their symptoms (Figure 2). One participant in each group reported worsened symptoms after treatment.

Pain and function

Average pain (11-point NRS) in the past week reduced after the six-week intervention in both groups (AR+EX group: $p<0.01$, $d=1.34$; SR+EX group: $p=0.03$, $d=1.07$) but did not change between baseline and three months ($p>0.11$) (Figure 3 and 4) (Table 2). WOMAC physical function subscale score improved after intervention in the AR+EX group ($p=0.02$, $d=1.02$) but not the SR+EX group ($p=0.23$). WOMAC physical function subscale score did not change between baseline and three months in either group ($p>0.12$).

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Table 2. Group data (mean and 95% confidence interval) for pain and functional outcomes.

	Baseline		Post-treatment		Difference between groups	3-month post-treatment		Difference between groups
	AR+EX	SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX
Pain (NRS, 0-10)	5.0 (6.1, 3.9)	4.4 (5.6, 3.2)	2.8 (3.8, 1.7)	2.6 (3.9, 1.3)	0.2 (1.9, -1.5)	3.7 (4.9, 2.5)	2.9 (4.3, 1.5)	0.8 (2.6, -1.0)
WOMAC								
Pain subscale	9.8 (11.7, 7.9)	8.0 (10.1, 5.9)	7.5 (9.4, 5.6)	7.4 (9.8, 5.0)	0.1 (3.0, -2.8)	7.5 (9.5, 5.5)	6.8 (9.2, 4.4)	0.7 (3.8, -2.4)
Physical function subscale	29.4 (35.9, 22.9)	25.6 (32.8, 18.4)	21.3 (28.0, 14.6)	20.2 (27.7, 12.7)	1.1 (11.2, -9.0)	23.2 (30.1, 16.3)	24.1 (32.3, 15.9)	-0.8 (-11.5, 9.9)
WOMAC total score	43.5 (52.4, 34.6)	37.3 (47.1, 27.5)	32.0 (41.1, 22.9)	30.1 (40.4, 19.8)	1.9 (15.6, -11.9)	34.1 (43.5, 24.7)	34 (45.1, 22.9)	0.1 (14.7, -14.4)
mPD-Q	12.7 (14.6, 10.8)	6.9 (9.0, 4.8)	9.5 (11.5, 7.5)	5.8 (8.1, 3.5)	3.7 (6.8, 0.6)	8.3 (10.5, 6.1)	4.6 (7.3, 1.9)	3.7 (7.2, 0.5)

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Number of painful sites	2.6 (-2.6, 7.7)	3.0 (10.3, -4.3)	4.1 (11.2, -2.9)	3.4 (13, -6.1)	0.7 (3.8, -2.4)	5 (12.8, 2.8)	4.3 (17.7, -9.0)	0.4 (3.9, -3.2)
PCS	29.3 (34.3, 24.3)	25 (30.4, 19.6)	20.7 (26.0, 30.3)	24.6 (30.3, 18.9)	-3.89 (-11.5, 3.71)	23.9 (29.1, 18.6)	21.9 (28.0, -15.8)	2 (10.1, -6.1)

Note: AR+EX = active rTMS and exercise; SR+EX = sham rTMS and exercise; WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index; mPD-Q = modified painDETECT questionnaire; PCS = Pain Catastrophising Scale.

WOMAC pain subscale score reduced at post-intervention (p=0.03, *d*=0.97) and at three-month follow-up (p=0.04, *d*=0.97) in the AR+EX group but did not change in the SR+EX group (p>0.83). mPD-Q score reduced at post-intervention (p=0.04, *d*=0.89) and at three-month follow-up (p<0.01, *d*=1.23) in the AR+EX group but did not change in the SR+EX group (p>0.74). The PCS score reduced at post-intervention (p<0.01, *d*=1.54) and at three-month follow-up (p=0.046, *d*=0.97) in the AR+EX group but did not change in the SR+EX group (p>0.98). The number of painful sites did not change within groups at any timepoints (p>0.18).

Physiological Mechanisms

Map volume for quadriceps muscles was unchanged after intervention in both groups (p>0.18), except for an increase in the VL muscle in the SR+EX group (0.99 mV, 95% CI -0.05 to 1.93, p=0.047, *d*=0.90) (Supplementary Table S3). MVIC was unchanged after intervention in both groups (p>0.18). PPTs were unchanged in both groups at the knee (p>0.30) and the thumb (p>0.34). Similarly, CPM was unchanged in both groups (p>0.45).

Sample Size Calculation

A study with 55 participants per arm would achieve 80% power considering a two-sided significance level of 0.05 and a correlation between pre- and post-measurements of 0.21 for pain. Accounting for a 20% dropout rate, a total of 138 participants would be required to detect the minimum clinically important between-group difference of 1.8 units for pain.(32)

DISCUSSION

This is the first study to evaluate the addition of rTMS to quadriceps strengthening exercise in knee osteoarthritis. The findings suggested the combined intervention is feasible, safe and

well-received to this population, and adding rTMS to quadriceps strengthening exercises might improve pain and function in knee osteoarthritis. Thus, our results support a definitive trial to examine the effects of this intervention on the symptoms in knee osteoarthritis.

Attendance was nearly 100% for treatments and 90% for the post-intervention assessment and all participants rated ≥7 on the willingness to undergo therapy. These findings met our predetermined criteria thresholds,(18) supporting the feasibility of a full-scale clinical trial. Although dropout rate at three-month follow-up was 19%, a full-scale trial with more resources could reduce the dropout rate. The proportion of participants thought they received active rTMS in both groups (AR+EX 81% vs SR+EX 75%) was similar. A recent study applying electrical stimulation synchronised to rTMS pulses on the head, mimicking scalp tapping sensation induced by active rTMS, for all participants, reported that 58% in the active rTMS and 44% in the sham rTMS groups thought they received active treatments.(39) Similar to that study, most our participants based their judgement on perceived analgesic effects. Future trials might consider this approach to strength participant blinding. Adverse reactions to rTMS during (e.g. seizure, syncope) and after (headache or pain at the stimulation site, hearing-related complaints) stimulation were reported previously, although occurring rarely (e.g. 0.1% for seizure).(40) No participant reported rTMS-related adverse reactions in this study. One participant in the SR+EX group reported an adverse reaction (flare-up of knee pain) attributed to exercise after the first treatment and discontinued the study. Our incidence rate of adverse reactions is lower than previous findings for the rTMS (i.e., 15% headaches)(13) or exercise therapy (23-30%)(41). Generally, we found no barriers to implementation of the interventions or outcome measures and the rTMS and exercise intervention appears to be safe and well tolerated.

Participants received 12 supervised exercise sessions recommended for knee osteoarthritis(42) over six weeks. Notably, recent meta-analyses found that at least three months of strengthening exercise are needed to improve pain and disability in this condition, regardless of exercise volume (i.e., frequency, intensity).(43) Future definitive trials may consider a three-month intervention duration. We did not identify any issue with the rTMS protocol. A recent RCT demonstrated that a 22-week rTMS intervention of the same rTMS parameters (15 sessions) had long-term analgesic effects on chronic neuropathic pain,(39) The authors suggested the efficacy could be attributed to the cumulative effects of rTMS sessions over time, further supporting a longer intervention duration in future trials.

Our results of pain outcomes suggest that AR+EX might induce larger and longer-lasting analgesic effects than SR+EX. At post-intervention assessment, the AR+EX group demonstrated improvements in pain (11-point NRS) and physical function (WOMAC physical functional subscale) exceeding the MCIC for these outcomes whereas the SR+EX group only improved in pain and this improvement was below the MCIC. Further, WOMAC pain subscale, mPD-Q and PCS scores at the post-intervention assessment and at three-month follow-up suggest that adding rTMS to quadriceps strengthening could lead to long-term benefits for osteoarthritic pain, neuropathic-like pain (measured by the mPD-Q) and pain catastrophisation (measured by the PCS) in knee osteoarthritis. To evaluate clinical efficacy of a combined rTMS and strengthening intervention on pain and physical function for knee osteoarthritis, full-scale trials may consider a sample size of 138, 12 treatment sessions over three months and assessing the primary outcomes of pain (11-point NRS) and physical function (WOMAC physical function subscale) at baseline and three months post-intervention.

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rTMS can induce long-lasting neuroplastic changes (i.e., decreasing or increasing cortical excitability) by modulating N-methyl-D-aspartate receptor activity, hypothesised as the underlying mechanism of analgesic effects.(44, 45) Despite improvements in pain and function, the AR+EX group (10-Hz M1-rTMS) did not display an increase in corticomotor excitability observed in previous research.(45) Another study also showed a pain reduction but no change in corticomotor excitability after10-Hz M1-rTMS (five consecutive days).(46) It is likely that analgesic effects of rTMS might be driven by neuroplastic effects at remote cortical regions connecting to M1, not M1 itself, unrelated to modulating corticomotor excitability and that were not measured here.(46) Future studies should evaluate rTMS-induced neuroplastic changes using other measures (i.e., altered brain oscillations on electroencephalography) and their relationship with pain outcomes.(47) Further, increased quadriceps strength, reduced pressure pain sensitivity and improved descending pain inhibition after quadriceps strengthening exercises (alone or with adjunct treatments) were reported in knee osteoarthritis.(16, 48) However, we found no changes in MVIC, PPTs and CPM in either group, regardless of observed within-group changes in pain and function. It is plausible that a longer intervention duration might be necessary to induce physiological changes similar to previous research. Alternatively, the interventions might act through other mechanisms such as placebo, pain catastrophisation or other pain-related psychological factors. As this is a feasibility study, future full-scale studies are needed to determine underlying physiological mechanisms of this novel intervention in knee osteoarthritis.

In conclusion, data from this pilot study support a definitive trial examining a combined rTMS and quadriceps strengthening exercise intervention for knee osteoarthritis. Despite no identified barriers to implementing this study methodology in future trials, a three-month intervention duration should be considered to yield long-term benefits. Based on our findings,

a fully powered clinical trial is justified to evaluate the clinical benefits of this novel treatment in knee osteoarthritis.

Patient and public involvement

We engaged a consumer representative from the Musculoskeletal Health Clinical Academic Group Consumer Community Council, Australian & New Zealand Musculoskeletal Clinical Trial Network and received feedback on the study including the proposed intervention and potential barriers to participant recruitment. The feedback from the consumer representative was used to guide the design of intervention and recruitment strategies.

AUTHOR'S CONTRIBUTION

WJC, SA, JMN and SMS were involved in the conception and design of the study. WJC, SA, JMN, NC, HF, RRNR, EO and SMS contributed to methodology of the study. WJC conducted recruitment, eligibility screening, and baseline and post-intervention assessment. AC and NC performed rTMS intervention. WJC performed the analysis and drafted the manuscript. All authors edited, reviewed and approved the final protocol.

ACKNOWLEDGEMENT

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COMPETING INTERESTS

None

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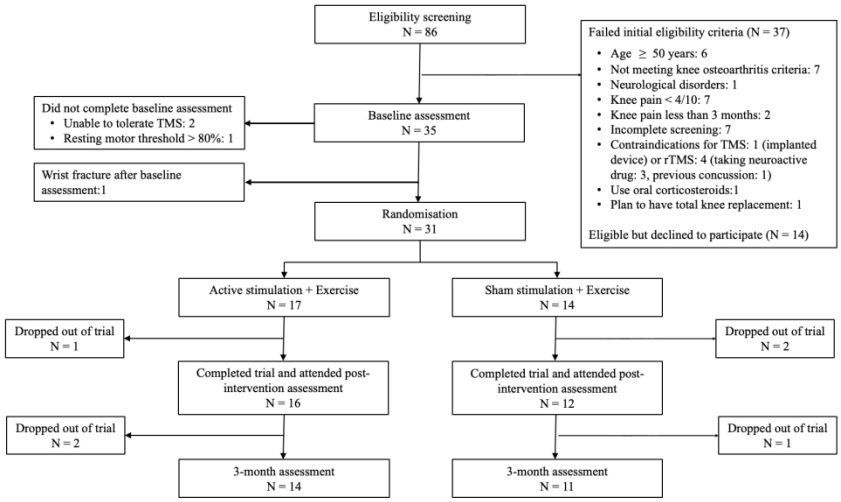
FIGURE LEGENDS

Figure 1. Flow of participants through the trial. *Note: rTMS - repetitive transcranial magnetic stimulation; TMS - transcranial magnetic stimulation*.

Figure 2. Percentage of participants reporting perceived change across categories from 'vastly worse' to 'completely recovered' after six-week interventions.

Figure 3. Pain and function (mean and 95% confidence interval) at baseline, post-intervention and three-month follow-up (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). *Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.*

Figure 4. Within-group changes in pain and function pre- and post-intervention (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). *Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.*



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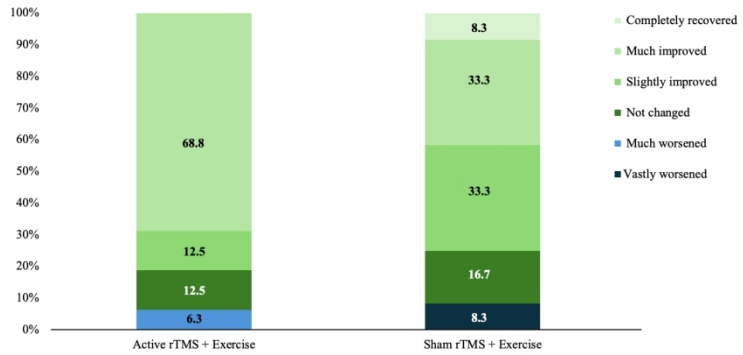

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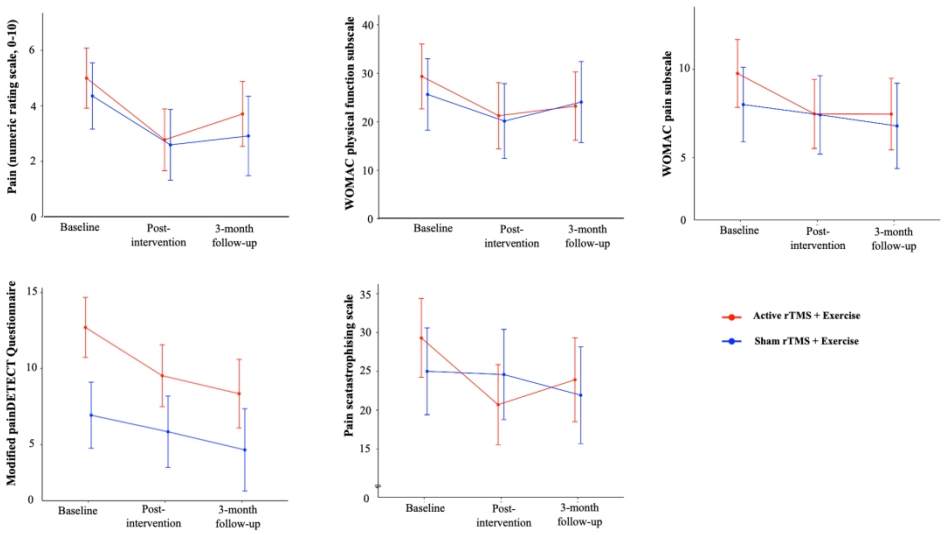

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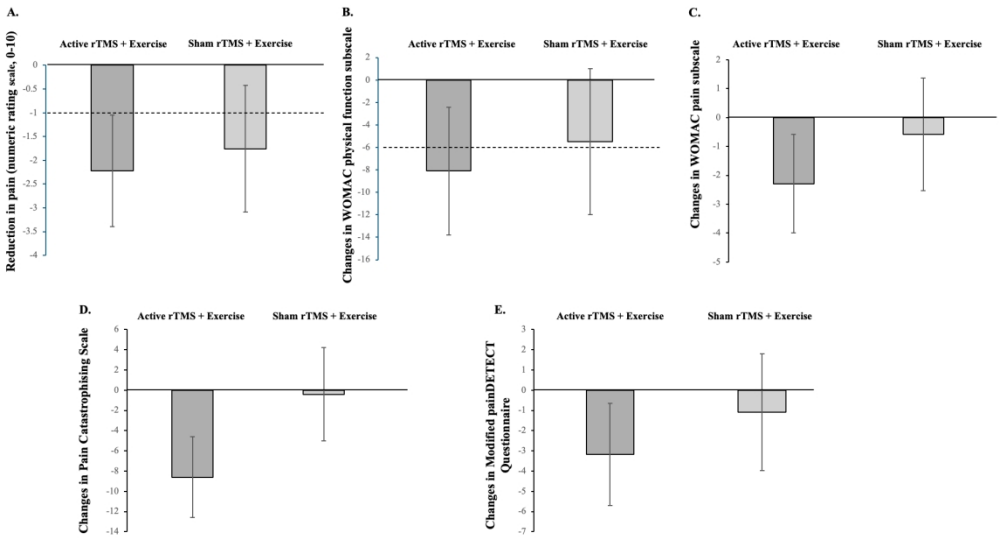

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SUPPLEMENTARY FILES

SUPPLEMENTARY Table S1. CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (specific guidance see CONSORT abstract extension for pilot trials)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial and reasons for randomised pilot trial	6-7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	9
	4c	How participants were identified and consented	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	10-14
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	14

Sample size	7a	Rationale for numbers in the pilot trial	14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	9-10
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	14-15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	15
	13b	For each group, losses and exclusions after randomisation, together with reasons	15
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	15-20
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	15-20
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	15-20
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17
	19a	If relevant, other important unintended consequences	NA

Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	20-24
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	20-24
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	20-24
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	20-24
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	8
Protocol	24	Where the pilot trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1
	26	Ethical approval or approval by research review committee, confirmed with reference number	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

SUPPLEMENTARY Table S2. Strengthening exercise program with progression and repetitions.

Exercise Description	Progression	Repetitions
1. Knee extensor strengthening Seated knee extensions with ankle weights. In a seated position, slowly straighten symptomatic knee until it is fully straight. Hold for 5 seconds and then lower slowly.	Ankle weights.	3 sets of 10. 30 second break period in between sets.
2. Hip abductor strengthening Level 1: Side lying hip abduction with ankle weights. Keep body still and knee straight and life affected leg up. Do not swing affected leg forward. Keep heel of foot higher than toes and behind hips while lifting straight upwards towards the ceiling. Hold for 5 seconds and then lower slowly.	Increase ankle weights or progress to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Standing hip abduction with thera elastic resistance band. Place looped thera elastic resistance band around both legs just above the ankle. Adequate tension on the elastic band and correct upright posture with shoulders and hips both facing forward is required prior to starting the exercise. The back of a chair or a wall can be used to provide support. Hold for 5 seconds and then lower slowly.	Increase thera elastic band resistance.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
3. Weight-bearing knee/hip extensor strengthening Level 1: Partial wall squats (option shown is to add thera elastic band around knees to incorporate the hip abductor muscles). Stand with one foot 30cm away from the wall with feet apart and turned inwards. With back straight and trunk and buttocks against a wall, slowly slide down the wall (as if to sit) to approximately 60° (less if painful) and then back up again while keeping contact with the wall at all times. Knees must go past the toes during the squat exercise. Hold position for 5 seconds.	Increase resistance by adding thera elastic resistance band or if already in use increase elastic band resistance strength. Progress further to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Sit-to-stand (option to add thera elastic band around knees to incorporate hip abductor muscles). Seated with back against a chair of standard height with firm seat, slowly stand up without using hands for support. Lean forward over toes so that the buttocks are lifted and hips go under the trunk. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.	Increase resistance by adding thera resistance elastic band. If already in use increase elastic band resistance strength. Progress further to level 3.	3 sets of 10. 30 second break period in between sets.
Level 3: Alternate split sit-to-stand Place the foot of the unaffected leg 10cm in front of the other foot.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly stand by leaning forward with back straight (nose in front of the toes) and squeeze buttock muscles. Most weight bearing must be on the symptomatic knee. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.		
Level 3+: Split partial wall squats Slowly slide down the wall (as if to sit) keeping the trunk and buttocks in contact with the wall. Knees must move over the toes. Most weight bearing must be on the symptomatic knee. Stop when symptomatic knee is bent to approximately 60° (less if painful) Hold for 5 seconds and then slowly slide back up keeping the trunk and buttocks in contact with the wall at all times.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.
4. Hamstring strengthening seated knee extensions Place a looped thera band elastic resistance band around the leg of a heavy table or chair. Seated in a chair, place the symptomatic leg in the looped thera elastic band with the knee slightly bent. Slowly pull the leg backwards into the elastic band until the knee is bent and a strong resistance is felt. Hold for 5 seconds.	Increase elastic band resistance.	3 sets of 10. 30 second break period in between sets.
5. Steps: a. Step ups: Place symptomatic leg onto the step. Slowly step up onto the step.	First increase the height of the step and second add weight.	3 sets of 10. 30-60 second break period in between sets.

Exercise Description	Progression	Repetitions
Touch foot of non-affected leg onto the step then place both feet back onto the starting position on the ground. b. Step downs: Start with both legs standing on top of the step. Bend the knee of the affected leg slowly to lower the non-affected leg towards the ground. Then straighten the affected knee slowly to return to the starting position. The knee of the affected leg must point forward during the movement.	Weight can be held across the chest with both hands or use two hand weights. First increase the height of the step and second add weight. Weight can be held across the chest with both hands or use two hand weights.	3 sets of 10. 30-60 second break period in between sets.

SUPPLEMENTARY TABLE S3. Group data (mean and 95% confidence interval) for physiological measures.

	Baseline		Post-treatment		Difference between groups
	AR+EX	SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX
Map volume					
Rectus femoris	0.6 (1.0, 0.1)	0.7 (1.2, 0.3)	0.9 (1.4, 0.5)	1.0 (1.5, 0.5)	-0.1 (-0.8, -0.6)
Vastus lateralis	0.8 (1.3, 0.2)	0.8 (1.4, 0.2)	1.1 (1.7, 0.5)	1.8 (2.7, 1.0)	-0.7 (-1.6, -0.3)
Vastus medialis oblique	1.1 (1.9, 0.3)	1.4 (2.3, 0.5)	1.3 (2.2, 0.4)	1.6 (2.7, 0.5)	-0.3 (-1.7, -1.1)
Pressure pain threshold					
Knee	662 (754.9, 569.1)	587 (689.3, 484.7)	686 (780.1, 591.9)	633 (739.2, 526.8)	53.3 (195.2, -88.6)
Thumb	379 (431.1, 326.9)	386 (443.4, 328.6)	393 (446.1, 339.9)	410 (470.0, 350.0)	-17.3 (62.9, -97.4)
Condition pain modulation	72.2 (108.9, -35.5)	97 (137.4, 56.6)	51.3 (90.5, 12.1)	90.5 (212.6, 46.6)	-39.2 (37.6, -98.2)
Maximum voluntary isometric contraction	298 (353.9, 242.1)	349 (408.8, 289.2)	331 (389.6, 272.4)	360 (420.8, 299.2)	-29.1 (55.4, -113.6)

Note: AR+EX = active rTMS and exercise; SR+EX = sham rTMS and exercise.

Supplementary Figure S1. Repetitive transcranial magnetic stimulation (rTMS) delivered to the primary motor cortex opposite to the most painful knee using a 70mm figure-of-eight coil (Magstim Ltd., UK).

Open access Protocol

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Feasibility and safety of combining repetitive transcranial magnetic stimulation and quadriceps strengthening exercise for chronic pain in knee osteoarthritis: a study protocol for a pilot randomised controlled trial

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ABSTRACT

Introduction Knee osteoarthritis is a leading cause of disability, resulting in pain and reduced quality of life. Exercise is the cornerstone of conservative management but effects are, at best, moderate. Early evidence suggests that repetitive transcranial magnetic stimulation (rTMS) applied over the primary motor cortex (M1) may improve the effect of exercise in knee osteoarthritis. This pilot study aims to (1) determine the feasibility, safety and participant-rated response to an intervention adding M1 rTMS to exercise in knee osteoarthritis; (2) elucidate physiological mechanisms in response to the intervention; (3) provide data to conduct a sample size calculation for a fully powered trial.

Methods and analysis This is a pilot randomised, assessor-blind, therapist-blind and participant-blind, sham-controlled trial. Thirty individuals with painful knee osteoarthritis will be recruited and randomly allocated to receive either: (1) active rTMS+exercise or (2) sham rTMS+exercise intervention. Participants will receive 15 min of either active or sham rTMS immediately prior to 30 min of supervised muscle strengthening exercise (2×/week, 6 weeks) and complete unsupervised home exercises. Outcome measures of feasibility, safety, pain, function and physiological mechanisms will be assessed before and/or after the intervention. Feasibility and safety will be analysed using descriptive analysis. Within-group and between-group comparisons of pain and function will be conducted to examine trends of efficacy.

Ethics and dissemination This study has been approved by the University of New South Wales Human Research Ethics Committee (HC210954). All participants will provide written informed consent. The study results will be submitted for peer-reviewed publication.

Trial registration number ACTRN12621001712897p.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised, assessor-blind, therapist-blind and participant-blind, sham-controlled study design.
⇒ Provide detailed methodology for collecting data on the feasibility, safety, analgesic effect and central mechanisms of combined repetitive transcranial magnetic stimulation and exercise therapy in knee osteoarthritis.
⇒ This proof-of-concept study is not powered to determine treatment efficacy.

INTRODUCTION

Knee osteoarthritis is a leading cause of global disease burden resulting in significant pain, and reduced quality of life.[1] It is estimated that 10% of people aged over 60 years experience knee osteoarthritis symptoms,[2] resulting in pain and impaired physical function.[3 4] Exercise is the cornerstone of conservative treatment for knee osteoarthritis and recommended by all international guidelines.[5] Although comparable to pharmacological treatments, the effects of exercise are at best, moderate, for pain and function, and small for quality of life.[5] To optimise patient outcomes, innovative treatments are needed to enhance the effects of exercise in knee osteoarthritis.

Knee osteoarthritis is a well-defined joint disorder, yet pain severity does not always correlate with structural changes observed on radiographs.[6–8] This discrepancy has been attributed to maladaptive changes of physiological mechanisms involved in central pain processing.[9] For example, ongoing nociceptive input from the affected joint and deficient endogenous pain inhibition are thought to increase neuronal excitability of central pain pathways (termed central sensitisation),[10] manifesting as pain hypersensitivity.[11] Furthermore, altered primary motor cortex

(M1) function has been implicated in the development of chronic pain as M1 plays an essential role in motor control and central pain processing.[12 13] For example, M1 organisational changes are associated with poor performance on knee movement tasks[14] and more severe pain is linked to reduced M1 intracortical excitability[15] in people with knee osteoarthritis. Additionally, quadriceps muscle weakness, a hallmark of knee osteoarthritis associated with pain and disability,[16] is associated with voluntary activation deficit, defined as a reduction in neural drive from the central nervous system to the muscles.[17] Reduced M1 excitability and voluntary activation deficit from M1, implicated in quadriceps muscle weakness,[18] may therefore contribute to pain and physical impairments in knee osteoarthritis. Thus, novel treatments simultaneously targeting these peripheral and central mechanisms could have a beneficial impact on pain and function in knee osteoarthritis.

Repetitive transcranial magnetic stimulation (rTMS), a safe, painless, non-invasive brain stimulation technique, has been used to alleviate chronic pain by inducing neuroplastic changes within M1. Neuroimaging evidence suggests that rTMS applied over M1 reduces pain by activating endogenous opioid systems of brain regions involved in pain processing.[19 20] rTMS modulates activity in both cortical and subcortical regions, either decreasing (inhibitory, low-frequency stimulation <1 Hz) or increasing (excitatory, high-frequency stimulation >5 Hz) cortical excitability.[21] High-frequency rTMS applied over M1 has been shown to produce superior analgesic effects to low-frequency rTMS in chronic pain populations.[22] Recent meta-analyses confirmed analgesic effects favouring high-frequency rTMS for short-term relief in chronic pain.[23] Although a case study reported positive effects on pain and function,[24] clinical trials of rTMS in knee osteoarthritis are absent.

Exercise is known to exert peripheral and central effects on pain. Peripherally, exercise improves muscle strength and coordination and proprioception to enhance control of the joint, therefore reducing nociceptive input from the affected knee.[25] Centrally, exercise activates opiodergic pathways and endogenous pain control.[26] Synergistic intervention simultaneously modulating peripheral (exercise), and central (rTMS and exercise) mechanisms of knee osteoarthritis could produce greater improvements in pain.[27] Thus, combining high-frequency rTMS over M1 and exercise has the potential to improve outcomes in knee osteoarthritis beyond what can be achieved with rTMS or exercise alone. Although pooled data from a recent meta-analysis in chronic pain showed a moderate reduction in pain severity favouring the combined rTMS and exercise intervention,[28] no study has investigated this intervention in knee osteoarthritis. A proof-of-concept study is needed to determine the feasibility, safety and participant-rated response to intervention and the effects of such an intervention on pain and central mechanisms.

The aims of this study are to (1) assess the feasibility, safety and perceived patient response to an intervention adding M1 rTMS to exercise in knee osteoarthritis; (2) elucidate physiological mechanisms in response to the intervention and (3) provide data to conduct a sample size calculation for a fully powered trial.

METHODS AND ANALYSIS

This protocol was prepared according to the Standard Protocol Items: Recommendations for Interventional Trials statement (online supplemental table S1).[29] The trial will be reported following the Consolidated Standards of Reporting Trials statement for non-pharmacological treatment,[30] the Template for Intervention Description and Replication checklist and guide[31] and Consensus on Exercise Reporting Template.[32] It has been prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621001712897p) (online supplemental table S2).

Trial design

We will conduct a pilot two-arm parallel-group design, assessor-blind, therapist-blind and participant-blind randomised controlled trial. The outcome measures will be assessed at baseline and on treatment completion (6 weeks postrandomisation). In addition, measures of pain and function will also be collected 3 months postintervention (figure 1).

Participants

Inclusion criteria for participants are: (1) individuals aged ≥50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria,[33] having at least one of the following items: stiffness <30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth; (2) knee pain for ≥3 months and on most days of the past month; (3) average pain intensity ≥4 on an 11-point Numeric Rating Scale (NRS) in the past week. Exclusion criteria are: (1) previous knee joint replacement or high tibial osteotomy on the affected side; (2) knee surgery or joint injection in the past 6 months; (3) planned surgery in the next 9 months; (4) using oral corticosteroids currently or in the past 4 weeks; (5) confirmed diagnosis of systemic arthritis (ie, rheumatoid arthritis); (6) previous knee fracture or malignancy; (7) other conditions affecting lower limb function; (8) taking part in any knee strengthening exercise in the past 6 months; (9) any loss of sensation of the affected lower limb; (10) neurological or psychiatric disorders; (11) use of neuroactive drugs; (12) contraindications to TMS (ie, epilepsy, metal implant in the skull) based on the TMS safety screening questionnaire.[34 35]

Recruitment

Participants in the community in Sydney, Australia will be recruited from local arthritis support groups, social media platforms and healthcare providers (medical practitioners, rheumatologists, orthopaedic surgeons and physiotherapists). Potential participants will first

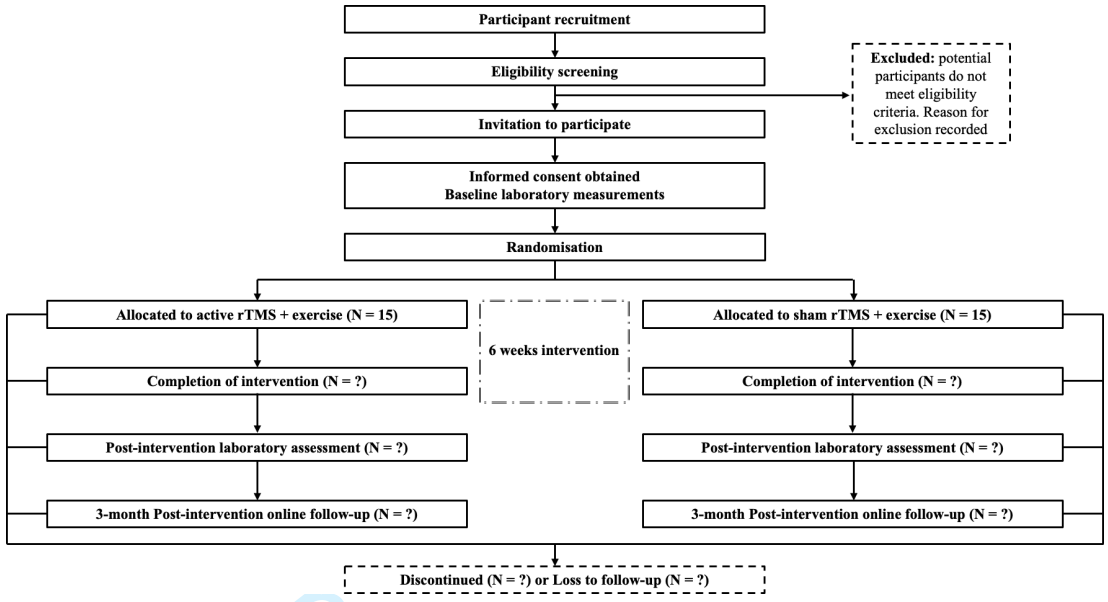

Figure 1 Study flow chart. rTMS, repetitive transcranial magnetic stimulation.

complete an eligibility screening questionnaire. Those who meet the eligibility criteria will be contacted by one of the researchers to confirm their willingness to participate in the study and to arrange the baseline assessment of outcomes. Participants will provide written informed consent to the outcome assessor on arrival for the baseline assessment.

Randomisation allocation concealment and blinding

Participants will be randomly allocated to either: (1) active rTMS+exercise or (2) sham rTMS+exercise, based on a 1:1 allocation ratio. The randomisation schedule will be generated by computer and a researcher not involved in recruitment, treatment provision or assessment. The randomisation schedule will be concealed in consecutively numbered, sealed opaque envelopes and given to the researcher who delivers rTMS intervention. Participants will be blinded to the type of rTMS they will receive and the study hypotheses. All participants will be given the same instructions and information about the rTMS intervention. Researchers conducting laboratory-based outcome assessment and physiotherapists providing exercise intervention will be blinded to group allocation. Unblinding will be allowed when an adverse or unexpected event occurs.

Outcome measurements

Measures of feasibility and safety

Feasibility and safety of the rTMS and exercise intervention will be assessed using the following measures: (1) the number of sessions attended by each participant (attendance rate >80% is considered feasible);[36] (2) the number of dropouts in each group (dropout rate <20% is considered feasible);[36] (3) the proportion of participants recruited from the total number screened; (4) willingness of each participant to undergo therapy at baseline on an 11-point NRS with 'not at all willing' at 0 and 'very willing' at 10 (80% of participants score 7 or more are considered feasible); (5) success of participant/outcome assessor/therapist blinding; (6) the number of adverse events and the details of each event.[27] Each adverse event will be considered separately. One or more serious adverse events will be considered unsafe. The success of participant blinding will be assessed at the completion of the intervention using a yes/no response to the question "Do you believe you received real brain stimulation?" and an 11-point NRS of the individual's confidence in that judgement. Participants will also be asked "Why do you believe you received the real/sham brain stimulation?" and "Was it divulged to you whether you were receiving real brain stimulation or not?"[27] Participant blinding will be considered successful if there is no difference between active rTMS+exercise and sham rTMS+exercise groups in the number of participants correctly guessing their treatment allocation at the completion of the follow-up laboratory assessment.[37] The success of blinding of the outcome assessor and treating physiotherapists will be determined at the completion of the follow-up assessment using a yes/no response to the question "Did you know which intervention group the participant was assigned to before completion of the follow-up laboratory assessment?" and "If you answer 'yes', how was it divulged to you?"[27] Blinding of the outcome assessor and treating physiotherapists will be considered successful if they answer 'no' to the first question.

Measures of pain and function

Knee pain and function will be assessed using: (1) an 11-point NRS for pain when walking in the past week;[38] (2) the Western Ontario and McMaster Universities Osteoarthritis Index (24 items, total score=96) (Likert V.3.1) and its pain subscale (7 items, total score=28) and physical function subscale (17 items, total score=68), a

valid, reliable and responsive instrument for knee osteoarthritis;[39] (3) the Global Perceived Effect Scale, where each participant will rate their perceived response to treatments on a 7-point Likert scale ranging from 'completely recovered' to 'vastly worsened';[40] (4) modified painDETECT questionnaire (7 items, total score=38), a simple, reliable and valid screening tool to detect a neuropathic pain component in patients with knee osteoarthritis;[41 42] (5) the number of painful sites, measured by participants indicating the number of painful sites outside of the affected knee lasting >24 hours in the past week on a four-sided body map (total score=35) with higher scores indicating more widespread hyperalgesia[43] and (6) the Pain Catastrophising Scale (13 items, total score=52), a reliable and valid, 13-item self-report instrument to assess patients' thoughts and feelings about pain in the domains of magnification, rumination and helplessness.[44]

To assess the long-term effects of the intervention, pain and function will also be assessed 3 months after the completion of intervention via an electronic version of these questionnaires.

Measures of physiological mechanisms

Measures of physiological mechanisms will be conducted in the same order for each participant.

1. M1 organisation and function will be measured using an established TMS mapping procedure.[45] Participants will be seated in a comfortable chair. Electromyography (EMG) of the quadriceps muscles will be recorded using bipolar surface electrodes (Ag-AgCl, Noraxon dual electrodes). The active electrode will be placed over the belly of the rectus femoris (RF), vastus lateralis (VL) and vastus medialis oblique (VMO) muscles and the ground electrode placed at the tibial shaft. EMG signals will be amplified (2000×) and filtered (20–1000 Hz), and digitally sampled at 2000 Hz using a Power 1902 Data Acquisition System and Spike2 software (CED, Cambridge, UK).

Single-pulse TMS delivered over M1 induces a magnetic field over the participant's scalp that evokes an electrical current in the underlying M1 tissue resulting in muscle activation recorded as motor evoked potentials (MEPs) using EMG. The scalp site evoking the largest MEP (termed the 'hotspot', the coil position inducing a maximal peak-to-peak MEP amplitude) for the RF muscle at a given TMS intensity will be identified.[46] The TMS motor threshold assessment tool will be used to determine the active motor threshold (aMT),[47] defined as the minimum intensity required to evoke a reliable MEP while participants maintained a muscle contraction of 10% averaged root mean square (RMS) EMG of three, 3 s maximal muscle contractions of the RF muscle.

During TMS mapping, 126 single-pulse biphasic stimuli (2 s interstimulus interval) will be delivered pseudorandomly to the scalp over a 6×7 cm (7 rows and 8 columns) grid oriented to the hotspot at 120% aMT of the RF muscle (Magstim Rapid^2/70 mm figure-of-eight coil; Magstim, UK). Participants will be asked to activate the RF muscle to 10% of their EMG recorded during a maximum voluntary contraction (determined as 10% of the highest RMS EMG for 1 s during three, 3 s maximal muscle contractions performed against manual resistance in sitting) with feedback provided on a monitor. The coil will be placed tangentially to the skull with the handle pointing laterally 90 degrees to induce a current in the lateral-to-medial direction. The Neural Navigator (Neurosoft, Russia) will be used to track the positions of the TMS coil and participant's head. To minimise muscle fatigue, stimuli will be delivered in trains of seven stimuli. The neuronavigational display is monitored to ensure adequate coverage of the grid and that adjacent positions not stimulated consecutively.

Maps for each of the RF, VL and VMO muscles will be produced offline using a custom MATLAB script (MathWorks, USA) according to previously published methods.[48 49] RMS amplitude of EMG traces of the MEPs will be extracted from a 20–50 ms window after stimulation and background RMS EMG (55–5 ms prior to stimulation) will be subtracted.[12 13] A surface map within a transformed plane encompassing stimulation coordinates and their corresponding MEP amplitude will be generated. The map will then be divided into 2744 partitions (49×56), with each partition assigned an estimated MEP amplitude based on the nearest acquired MEP values using triangular linear interpolation. Partitions with MEP amplitudes >10% of the maximum MEP amplitude will be considered as active.[48] Map volume is calculated as the sum of MEP amplitudes of all active partitions to index M1 corticomotor excitability.

2. Voluntary activation of the quadriceps muscles will be measured using a twitch interpolation technique when participants are seated with the hips and knees in 90 degrees flexion. A force increment will be recorded using a force transducer when an electrical stimulus delivered by a constant current stimulator (Digitimer, DS7AH) to the femoral nerve 1–2 s into the maximal muscle contraction (superimposed twitch), and again 3–4 s afterward when the muscles are at rest (control twitch). Voluntary activation (%)=[1−(superimposed twitch/control twitch)]×100.[50]
3. Pressure pain thresholds (PPTs) will be measured using a hand-held pressure algometer (Somedc, Hörby, Sweden, probe size 1 cm^2) to quantify mechanical sensitivity. The probe (size 1 cm^2) will be applied perpendicular to the skin (rate 40 kPa/s) until the participant first reports that the sensation of pressure has changed to pain. PPTs will be measured at the side of the knee joint line of the most painful knee and ipsilateral thumbnail. The average of three measurements at each site will be used in the analysis. PPT measures have been shown to be reliable in knee osteoarthritis (intraclass correlation coefficient (ICC)=0.83 (95% CI 0.72 to 0.90)).[51]
4. Conditioned pain modulation (CPM) is a well-established, reliable and safe measure of pain processing that is thought to reflect endogenous pain

inhibition. CPM is assessed as a change in the pain perceived in one body site (test stimulation) as a result of pain induced in another body site (conditioned stimulation). We will use PPT measured at the upper trapezius muscle contralateral to the painful knee as test stimulation[7] and pain is induced in the ipsilateral hand by cold pressor test (CPT) as conditioned stimulation. Three PPTs (test stimulation) will be measured before CPT (conditioned stimulation). For CPT, participants will immerse the hand in the cold water (4°C) for a maximum of 2 min.[52] Participants can remove their hand prior to the completion of CPT if the pain becomes unbearable and a pain rating on an NRS (0–100) will be obtained immediately after participants remove their hand. Three PPT measurements will then be repeated when pain score reaches 50 out of 100 after CPT. A reduction in PPT indicates deficient endogenous pain inhibition. CPM paradigm has shown good intrasession reliability (ICC >0.75).[53]

Intervention

Participants will be randomly allocated to either active rTMS+exercise or sham rTMS+exercise intervention groups. For participants with bilateral knee pain, the most painful knee or the right knee if both knees are equally painful, will be treated. All participants will receive a total of 12 treatment sessions (two sessions per week for 6 weeks). A systematic review recommended 12 supervised exercise sessions are needed to be effective for improving pain and disability in knee osteoarthritis.[54] Two qualified, registered physiotherapists with clinical experience in treating knee osteoarthritis will provide exercise therapy for all participants. A researcher trained in the use of rTMS will deliver active and sham rTMS to all participants according to their group allocation and will not be blinded to group allocation. Participants will be advised to continue with their usual medication during the study. Medications for their knee pain will be recorded at baseline and the follow-up laboratory assessment. Data for the frequency of use (in the past 6 months at baseline and during the 6-week intervention at follow-up) of pain medications will be collected. For each session, participants will receive active or sham rTMS (15 min) followed by supervised exercise (30 min).

Repetitive transcranial magnetic stimulation

For active rTMS, high-frequency rTMS will be applied to the motor hotspot of the first dorsal interosseous muscle ipsilateral to the treated knee using a Magstim Super Rapid^2 (Magstim) and a figure-of-eight air-cooled coil (70 mm). For each session, 3000 stimuli (10 Hz, 30 trains of 10 s, 20 s intertrain interval) will be delivered at 90% of resting motor threshold (rMT).[55] rMT is defined as the minimum intensity at which 5 out of 10 stimuli, delivered to the hotspot, evoked a peak-to-peak MEP of at least 50 µV.[46] To account for any between-session change in rMT, participants' rMT will be assessed at the beginning of each treatment session to determine the stimulation intensity.[56] For sham rTMS, a sham coil that looks identical to a real coil but produces only audible clicks and no magnetic pulse will be used to deliver the stimulation protocol identical to the one used for active rTMS. This is the most used sham rTMS protocol in controlled trials.[12 57 58]

Exercise

Immediately after the rTMS intervention, participants will receive one-to-one quadriceps strengthening exercise delivered by their treating physiotherapist. A standardised set of quadriceps strengthening exercises known to be effective in knee osteoarthritis will be performed using ankle cuff weights or resistance bands, and exercise intensity will be progressed by the physiotherapist as appropriate for each participant (online supplemental table S3).[5 25 59] A home exercise programme will also be developed and monitored by the physiotherapists for all participants to perform two times a week during intervention. Participants will complete an exercise diary and return to their treating physiotherapist weekly for compliance and adherence to their home exercise programme and for recording any adverse effects of home exercise (ie, whether pain was present, whether any exercises were difficult, the reason why exercises were unable to be completed if applicable).

Sample size and analysis

This is a pilot study designed to provide data to inform a full randomised controlled trial should the intervention appear feasible, safe and show trends of efficacy. Although a prospective sample size calculation is not required in a pilot randomised controlled trial, 15–20 participants per intervention group is recommended in pilot studies.[60 61] We have selected a sample size of 15 participants per group, or total 30 participants as this is achievable based on the successful completion of a previous pilot study with a similar design by our group.[27]

Measures of feasibility and safety will be analysed descriptively.[62] Within-group changes will be calculated as follow-up minus baseline (mean and SD). Two-sided t-tests will be used for within-group comparisons between baseline and follow-up measures and effect sizes will be calculated to indicate whether a full randomised controlled trial will be worthwhile. An effect size of 0.5 for pain and physical function outcomes is recommended for knee osteoarthritis clinical trials.[63] Due to the limitations of performing statistical comparisons with a small sample size and low power, statistical comparisons between groups will not be conducted.[64] Sample size calculation for a full randomised controlled trial will be based on the minimum clinically important difference (MCID) on outcome measures of pain and function.[64] The MCID in knee osteoarthritis studies is a change in pain of 1.8 unit (SD of 2.2) and a change in function of 6 units (SD of 9.7).[65] Power will be set at 80% to detect between-group differences, with an α of 0.05 and a dropout rate based on that of the pilot trial.

Patient and public involvement

We engaged a consumer representative form the Musculoskeletal Health Clinical Academic Group Consumer Community Council, Australian & New Zealand Musculoskeletal Clinical Trial Network and received feedback on the study including the proposed intervention and potential barriers to participant recruitment. The feedback from the consumer representative has been addressed and used to guide the design of intervention and recruitment strategies.

ETHICS, DATA SAFETY AND DISSEMINATION

This trial has been approved by the University of New South Wales Human Research Ethics Committee (HC210954), who may audit the study conduct during the study or after completion. Any deviation from protocol will require ethics amendment and be updated to the registry. This study will be terminated if any serious adverse event occurs. A serious adverse event is defined as any untoward medical occurrence or effect that results in death, or is life-threatening, requires hospitalisation, results in significant or persistent disability. There will not be a data monitoring committee due to the relatively short duration of this pilot study.

Participants' identifiers (ie, name, address, date of birth, sex, profession) will be removed from the data. Identifying information will be replaced with a unique anonymous identification number based on the recruitment order. Each participant will be assigned an anonymous identification number. This will be used in all further data recording and thus they will be de-identified. Paperwork that links anonymous identification number to participants' names will be stored in a locked room. All de-identified data that cannot be linked to an individual participant will be stored electronically with password protection. There is no perceived need to re-identify any electronic data. Only aggregate results will be reported; therefore, it will not be possible to identify individual participants in any information reported or published from this study. The data collected in hardcopy will be retained for 15 years after publication and electronic data will be stored for a minimum of 7 years.

Study results will be disseminated via presentations at scientific meetings and publications in a peer-reviewed journal. Publications and presentations related to this study will be authorised and reviewed by all study investigators.

Trial status

This trial will start recruiting in March 2022 and is expected to be completed by March 2023.

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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 and analysis' section for further details.

Patient consent for publication Not applicable.

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APPENDIX - Supplementary Tables

Table S1. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Check/details
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	✓ Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	✓ Page 7
	2b	All items from the World Health Organization Trial Registration Data Set	✓ Table 1
Protocol version	3	Date and version identifier	✓ Table 1
Funding	4	Sources and types of financial, material, and other support	✓ Page 18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	✓ Page 1, 18
	5b	Name and contact information for the trial sponsor	✓ Table 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	None

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	✓ Page 5-7
	6b	Explanation for choice of comparators	✓ Page 6
Objectives	7	Specific objectives or hypotheses	✓ Page 7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	✓ Page 7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	✓ Page 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	✓ Page 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	✓ Page 14-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	✓ Page 17

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	✓ Page 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	✓ Page 14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	✓ Page 9-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	✓ Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	✓ Page 16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	✓ Page 8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	✓ Page 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	✓ Page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓ Page 9

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓ Page 9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓ Page 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	✓ Page 9-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	✓ Page 9-14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	✓ Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	✓ Page 16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	✓ Page 16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	✓ Page 16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	✓ Page 17

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	✓ Page 17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	✓ Page 9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	✓ Page 17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	✓ Page 17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	✓ Page 17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	✓ Page 8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	✓ Page 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	✓ Page 18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	✓ Approved by ethics committee
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	✓ Page 18
	31b	Authorship eligibility guidelines and any intended use of professional writers	✓ Page 18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	✓ Page 17
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	✓ Approved by Ethics Committee
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

TABLE S2. WHO trial registration data set (v.1.1)

Item	Information
Primary registry and trial identifying number	Australian and New Zealand Clinical Trials Registry (ACTRN12621001712897p)
Date of registration in primary registry	14 December 2021
Universal Trial Number	U1111-1274-6922
Source of monetary or material support	Australian & New Zealand Musculoskeletal Clinical Trial Network Seed Granting Award
Primary Sponsor	Neuroscience Research Australia
Contact for public queries	Dr Wei-Ju Chang, Neuroscience Research Australia [w.chang@neura.edu.au]
Contact for scientific queries	Dr Wei-Ju Chang, Neuroscience Research Australia
Public title	Non-invasive brain stimulation and exercise for treating knee osteoarthritis
Scientific title	Feasibility and safety of combining repetitive transcranial magnetic stimulation and quadriceps strengthening exercise for chronic pain in knee osteoarthritis – A pilot randomised controlled trial
Country of recruitment	Australia
Health condition or problem studies	Knee osteoarthritis
Interventions	Active treatment: Combined repetitive transcranial magnetic stimulation and quadriceps muscle strengthening exercise

	Control treatment: Combined sham repetitive transcranial magnetic stimulation and quadriceps muscle strengthening exercise
Key eligibility criteria	Inclusion criteria: 1. People aged ≥ 50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria 2. Knee pain for at least 3 months and on most days of the past month. 3. Average pain intensity equal or greater than 4 on an 11-point numeric rating scale in the past week.
	Exclusion criteria: 1. Previous knee joint replacement or high tibial osteotomy. 2. Knee surgery or joint injection in past six months. 3. Planned surgery in the next nine months. 4. Current or past four weeks oral corticosteroids use. 5. Systemic arthritis. 6. Previous knee fracture or malignancy. 7. Other condition affecting lower limb function. 8. Participation in knee strengthening exercise in past six months. 9. Loss of sensation of the affected lower limb. 10. Neurological or psychiatric disorders. 11. Use of neuroactive drugs. 12. Contraindications to transcranial magnetic stimulation
Study type	Interventional
	Purpose of study: treatment
	Allocation: 1:1 randomised controlled trial: Intervention assignment: parallel; Masking: participant-/therapist-/assessor-blinded

Date of the first enrolment	March 2022
Sample size	30
Recruitment status	Recruiting
Primary outcomes	Feasibility and safety (measured as the number of session attended, the number of drop-outs, proportion of participants recruited, willingness of each participant to undergo therapy, success of blinding, adverse events)
Secondary outcomes	Pain and function: numeric rating scale, WOMAC, Global Perceived Effect Scale, modified painDETECT, number of painful site, pain catastrophising scale. Physiological mechanisms: primary motor cortex organisation and function, voluntary activation of the quadriceps muscles, pressure pain thresholds, conditioned pain modulation.
Ethical review	Status: approved, Date of approval: 31 January 2022; Committee: UNSW Human Research Ethics Committee A (HC210954)

TABLE S3: The muscle strengthening exercise program with exercise description, progression and repetitions.

Exercise Description	Progression	Repetitions
1. Knee extensor strengthening Seated knee extensions with ankle weights. In a seated position, slowly straighten symptomatic knee until it is fully straight. Hold for 5 seconds and then lower slowly.	Ankle weights.	3 sets of 10. 30 second break period in between sets.
2. Hip abductor strengthening Level 1: Side lying hip abduction with ankle weights. Keep body still and knee straight and life affected leg up. Do not swing affected leg forward. Keep heel of foot higher than toes and behind hips while lifting straight upwards towards the ceiling. Hold for 5 seconds and then lower slowly.	Increase ankle weights or progress to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Standing hip abduction with thera band/elastic resistance band. Place looped thera band/elastic resistance band around both legs just above the ankle. Adequate tension on the elastic band and correct upright posture with shoulders and hips both facing forward is required prior to starting the exercise. The back of a chair or a wall can be used to provide support. Hold for 5 seconds and then lower slowly.	Increase thera band/elastic band resistance.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
3. Weight-bearing knee/hip extensor strengthening Level 1: Partial wall squats (option shown is to add thera band/elastic band around knees to incorporate the hip abductor muscles). Stand with one foot 30cm away from the wall with feet apart and turned inwards. With back straight and trunk and buttocks against a wall, slowly slide down the wall (as if to sit) to approximately 60° (less if painful) and then back up again while keeping contact with the wall at all times. Knees must go past the toes during the squat exercise. Hold position for 5 seconds.	Increase resistance by adding thera band/elastic resistance band or if already in use increase elastic band resistance strength. Progress further to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Sit-to-stand (option to add thera band/elastic band around knees to incorporate hip abductor muscles). Seated with back against a chair of standard height with firm seat, slowly stand up without using hands for support. Lean forward over toes so that the buttocks are lifted and hips go under the trunk. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.	Increase resistance by adding thera band/resistance elastic band. If already in use increase elastic band resistance strength. Progress further to level 3.	3 sets of 10. 30 second break period in between sets.
Level 3: Alternate split sit-to-stand Place the foot of the unaffected leg 10cm in front of the other foot.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly stand by leaning forward with back straight (nose in front of the toes) and squeeze buttock muscles. Most weight bearing must be on the symptomatic knee. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.		
Level 3+: Split partial wall squats Slowly slide down the wall (as if to sit) keeping the trunk and buttocks in contact with the wall. Knees must move over the toes. Most weight bearing must be on the symptomatic knee. Stop when symptomatic knee is bent to approximately 60° (less if painful) Hold for 5 seconds and then slowly slide back up keeping the trunk and buttocks in contact with the wall at all times.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.
4. Hamstring strengthening seated knee extensions Place a looped thera band/elastic resistance band around the leg of a heavy table or chair. Seated in a chair, place the symptomatic leg in the looped thera band/elastic resistance band with the knee slightly bent. Slowly pull the leg backwards into the elastic band until the knee is bent and a strong resistance is felt. Hold for 5 seconds.	Increase elastic band resistance	3 sets of 10. 30 second break period in between sets.
5. Steps a. Step ups: Place symptomatic leg onto the step.	First increase the height of the step and second add weight.	3 sets of 10. 30-60 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly step up onto the step. Touch foot of non-affected leg onto the step then place both feet back onto the starting position on the ground.	Weight can be held across the chest with both hands or use two hand weights.	
b. Step downs: Start with both legs standing on top of the step. Bend the knee of the affected leg slowly to lower the non-affected leg towards the ground. Then straighten the affected knee slowly to return to the starting position. The knee of the affected leg must point forward during the movement.	First increase the height of the step and second add weight. Weight can be held across the chest with both hands or use two hand weights.	3 sets of 10 30-60 second break period in between sets.

BMJ Open

Repetitive Transcranial Magnetic Stimulation as An Adjunct to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

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Primary Subject Heading:	Rehabilitation medicine
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Keywords:	Exercise, Pain management < ANAESTHETICS, Chronic Pain, Clinical Trial, Feasibility Studies

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rTMS and exercise for knee osteoarthritis

TITLE

Repetitive Transcranial Magnetic Stimulation as An Adjunct to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

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rTMS and exercise for knee osteoarthritis

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ABSTRACT

Objective: To examine the feasibility, safety and perceived patient response of a combined repetitive transcranial magnetic stimulation (rTMS) and quadriceps strengthening exercise intervention for knee osteoarthritis.

Methods: A two-arm, participant-, therapist- and assessor-blinded, randomised controlled trial with additional follow-up of pain and function at three months. Participants were randomised to receive active rTMS+exercise (AR+EX) or sham rTMS+exercise (SR+EX) twice weekly for six weeks whilst completing home exercises twice week. Primary outcomes included recruitment rate, treatment attendance, dropouts, willingness to undergo therapy (11-point numeric rating scale, 'not at all willing'=0 and 'very willing'=10), success of participant, therapist and outcome assessor blinding, adverse events and Global Perceived Effect Scale. Secondary outcomes were pain, function and measures of physiological mechanisms.

Results: Eighty-six people were screened, 31 (36%) were randomised, 28 (90%) completed the treatments and three (10%) dropouts at three-month follow-up. Both groups had high treatment attendance (98.4 and 100%). All participants scored at least 7 on the willingness to undergo therapy scale. Blinding was successful. No adverse events were reported. At the post-intervention assessment, 80% in the AR+EX group and 75% in the SR+EX group reported an improvement on the Global Perceived Effect Scale. Both groups demonstrated within-group improvements in pain at the post-intervention assessment but not at three-month follow-up. Function improved only in the AR+EX group at the post-intervention assessment.

Conclusion: Combined rTMS and quadriceps strengthening exercise intervention for knee osteoarthritis is feasible, safe and well-received. A full-scale trial is justified to assess the clinical benefits of this novel treatment.

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Registration: ACTRN12621001712897

Keywords: exercise, knee osteoarthritis, repetitive transcranial magnetic stimulation, randomised controlled trial.

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ARTICLE SUMMARY

Strengths and limitations of this study

- Randomised, assessor-, therapist- and participant-blind, sham-controlled study design
- Data on the feasibility, safety, analgesic effect and central mechanisms of the combined rTMS and exercise therapy in knee osteoarthritis
- This pilot study was not powered to determine treatment efficacy.

rTMS and exercise for knee osteoarthritis

INTRODUCTION

Knee osteoarthritis is a leading cause of global disease burden. [1] The main symptoms are pain and physical dysfunction that become persistent and debilitating as the disorder progresses. [2] Non-surgical, non-drug interventions have been recommended to reduce pain and improve function for knee osteoarthritis. [3] Strengthening exercise is the cornerstone of conservative treatment and is recommended as a first-line treatment in all international guidelines. [4 5] Exercise yields analgesic effects via both peripheral (i.e., improving muscle strength/coordination and joint proprioceptive control that subsequently reduces nociceptive inputs from the affected knee) and central (i.e., activating endogenous opiodergic and pain control systems) mechanisms. [6 7] However, the effects of exercise are at best, moderate for pain and function, and small for quality of life. [8] While knee osteoarthritis is a well-defined joint disorder, pain severity does not always correlate with radiographic findings. [9] This discordance has been attributed to maladaptive neuroplasticity of central pain processing pathways. [10] Novel treatments targeting the neurophysiological mechanisms underpinning osteoarthritic knee pain could bolster the effects of strengthening exercise and optimise outcomes.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, might boost the benefits of exercise for knee osteoarthritis. rTMS can induce neuroplasticity, either decreasing (inhibitory, low-frequency stimulation ≤1 Hz) or increasing (excitatory, high-frequency stimulation ≥5 Hz) cortical excitability. [11] Research suggests that rTMS alleviates pain via the activation of endogenous opioid pathways of brain regions involved in pain processing. [12] High-frequency rTMS applied over the primary motor cortex (M1) has demonstrated superiority to low-frequency rTMS in chronic pain populations. [13] Further, as increased M1 excitability is associated with motor learning, [14] applying excitatory,

high-frequency rTMS over M1 might increase the brain's responsiveness to the afferent inputs generated by subsequent treatments (i.e., exercise), a phenomenon known as 'priming'. [15]

Therefore, adding high-frequency rTMS over M1 to strengthening exercise could potentially improve outcomes beyond that which can be achieved with rTMS or exercise alone through two mechanisms: (i) simultaneously modulating peripheral (exercise) and central (rTMS and exercise) mechanisms underpinning knee osteoarthritis pain and/or; (ii) 'priming' the brain to increase its responsiveness to the corticomotor benefits of exercise (i.e., increased cortical excitability, enhanced voluntary muscle activation, strength gains, improved motor control). [16] Although a recent meta-analysis showed that a combined rTMS and exercise intervention yielded a moderate pain reduction (2 trials, n=38, standardised mean difference=-0.76) for chronic pain conditions in general, [17] the effect of this intervention specific to knee osteoarthritis remains unknown. A rigorous and adequately powered randomised controlled trial (RCT) is needed to determine the efficacy of this combined intervention of rTMS and strengthening exercise for knee osteoarthritis. Before conducting a full-scale RCT, a pilot study is recommended to inform the feasibility of the processes essential to the success of a large RCT and the safety of the intervention. [18]

This study aimed to 1) examine the feasibility, safety and patient-perceived effect of a combined high-frequency rTMS and strengthening exercise intervention for knee osteoarthritis; 2) assess physiological mechanisms underlying the intervention; and 3) provide data to conduct a sample size calculation for a fully powered trial based on the results of pain and physical function outcomes.

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METHODS AND ANALYSIS

Design

This was an assessor-, therapist- and participant-blinded, two-arm parallel group, pilot RCT. The outcome measures were assessed at baseline and upon treatment completion (six weeks post-randomisation). In addition, pain and function were also assessed three months post-intervention. The study was prospectively registered (ACTRN12621001712897) and approved by the University of New South Wales Human Research Ethics Committee (HC210954). The study protocol has been published. [19] All participants provided written informed consent. The study is reported using the Consolidated Standards of Reporting Trials statement extension for pilot trials (Supplementary Table S1). [20]

Participants

Participants were recruited from the community in Sydney, Australia. Inclusion criteria were: 1) people aged ≥50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria, [21] having at least one of the following: morning stiffness <30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth; 2) knee pain for ≥3 months and on most days in the past month; 3) average pain intensity ≥4 on an 11-point numeric rating scale (NRS) in the past week. Exclusion criteria were: 1) previous knee joint replacement or high tibial osteotomy on the affected side; 2) knee surgery or joint injection in the past six months; 3) planned surgery in the next nine months; 4) using oral corticosteroids currently or in the past four weeks; 5) confirmed diagnosis of systemic arthritis (i.e., rheumatoid arthritis); 6) previous knee fracture or malignancy; 7) other conditions affecting lower limb function; 8) participating in any knee strengthening exercise for knee osteoarthritis in the past six months; 9) loss of sensation of the affected lower limb; 10) neurological or psychiatric disorders; 11) use of neuroactive drugs (e.g., tricyclic

antidepressant, Clozapine, Foscarnet); 12) contraindications to TMS (i.e., epilepsy, metal implant in the skull) using the TMS safety screening questionnaire[22]; 13) resting motor threshold (rMT) >80% measured at the baseline assessment as this would lead to a high stimulating intensity for the rTMS intervention and potential overheating of the coil. Participants were permitted to continue their usual medications during the trial.

Procedures

Potential participants completed an online screening questionnaire to determine eligibility. Eligible participants attended baseline assessment and were randomly allocated to the active rTMS+exercise (AR+EX) or sham rTMS+exercise (SR+EX) group. The assigned treatment was allocated through REDCap prior to the first treatment session, independently of the researchers involved with physiotherapy treatment and outcome assessment. Participants, treating physiotherapists and outcome assessors were blinded to group allocation. All participants received the same instructions and information about rTMS intervention. Participants received either active or sham rTMS immediately before 30 minutes of one-to-one supervised strengthening exercise twice weekly for six weeks (12 sessions). If bilateral symptoms were present, the most painful knee was assessed and treated. Six physiotherapists (at least 2 years' experience) delivered exercise therapies. All procedures were performed at Neuroscience Research Australia (NeuRA), Sydney, Australia.

Intervention

rTMS

The rTMS target is the motor hotspot, or the coil position inducing a maximal motor evoked potential (MEP) amplitude measured on electromyography (EMG) using a bipolar surface electrode (Ag-AgCl, Noraxon dual electrodes) on the first dorsal interosseous muscle

ipsilateral to the treated knee using a Magstim Rapid^2 (Magstim Ltd., UK) and a 70 mm figure-of-eight coil. Motor hotspots for the quadriceps muscles were not used as rTMS target as MEPs cannot be reliably elicited at rest, [23] and rTMS targeting motor hotspot for the hand has non-somatotopic analgesic effect. [24] At each session, 3000 stimuli (10 Hz, 30 trains of 10 seconds, 20-second intertrain interval) were delivered at 90% of rMT (the minimum intensity at which five out of ten stimuli delivered to the hotspot, evoked a MEP >50 μV). [25] rMT was assessed at the beginning of each session. For sham rTMS, a sham coil that looks identical to a real coil but produces no magnetic pulse and only audible clicks was used to deliver the same stimulation protocol as active rTMS.

Exercise

Participants performed standardised quadriceps strengthening exercises (Supplementary Table S2) with demonstrated effectiveness for knee osteoarthritis using ankle cuff weights or resistance bands as appropriate. [6 8] Each exercise was performed in 3 sets of 10 repetitions with a 30s rest between sets. The treating physiotherapists determined the starting level and when to progress the exercise based on participant's feedback and therapist's clinical judgement. Exercises were progressed as defined in the protocol. [19] Participants performed their supervised exercises at home at the same dosage using resistance bands twice per week. Home exercise diaries with instructions were provided for recording the number of sessions, type and number of exercises performed and adverse reactions and collected at the post-intervention assessment.

Outcome Measures

Primary Outcomes

Feasibility, safety and participant-perceived improvement to treatment were measured as: 1) the proportion of participants recruited from the total number screened; 2) the number of sessions attended by each participant; 3) the number of drop-outs in each group; 4) willingness of each participant to undergo therapy at baseline on an 11-point NRS with 'not at all willing' at 0 and 'very willing' at 10; 5) success of participant/outcome assessor/therapist blinding; 6) the number of adverse events and the details of each event; 7) the Global Perceived Effect Scale, where each participant rated their perceived response to treatments on a 7-point Likert scale ranging from "completely recovered" to "vastly worsened". [26] The success of participant blinding was assessed at the completion of the intervention using a Yes/No response to the question 'Do you believe you received real brain stimulation?' and an 11-point NRS of the individual's confidence in that judgement. Participants were also be asked 'Why do you believe you received the real/sham brain stimulation?' and 'Was it divulged to you whether you were receiving real brain stimulation or not?' The success of outcome assessor and treating physiotherapist blinding was determined using a Yes/No response to the question 'Did you know which intervention group the participant was assigned to before completion of the follow-up laboratory assessment?' and 'If you answer "yes", how was it divulged to you?'.

Secondary Outcomes

Pain and function

Knee pain and function were assessed using: 1) an 11-point NRS (0='no pain', 10='worst pain imaginable') for average pain in the past week; [27] 2) the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (24 items [0-4 scale, 0='none', 4='extreme'], total score=96) (Likert version 3.1) and its pain subscale (5 items, total score=20) and physical function subscale (17 items, total score=68), with higher scores indicating worse

pain and function; [28] 3) modified painDETECT (mPD-Q, 7 items, total score=38) to detect a neuropathic pain component (score ≥12) in people with knee osteoarthritis; [29] 4) the number of painful sites, measured by participants indicating the number of painful sites outside of the affected knee lasting >24 hours in the past week on a four-sided body map (total score=35) with higher scores indicating more widespread hyperalgesia; [30] and 5) the Pain Catastrophising Scale (PCS, 13 items, total score=0-52) to assess participants' thoughts and feelings about pain in the domains of magnification, rumination and helplessness, with higher scores indicating higher severity. [31] The minimum clinically important change (MCIC) to be detected in knee osteoarthritis trials is 1 unit for pain[32] and 6 units for function. [33]

Physiological mechanism investigations

1) Corticomotor excitability was measured using TMS mapping. [19] Single-pulse TMS was delivered over M1, evoking MEPs recorded on EMG by bipolar surface electrodes over the rectus femoris (RF), vastus lateralis (VL) and vastus medialis oblique (VMO) muscles while participants were seated. EMG signals were amplified (x2000), filtered (20-1000 Hz) and sampled at 2k Hz. Active motor threshold (aMT) was determined on the hotspot for the RF while participants maintained a muscle contraction of 10% averaged root mean square (RMS) EMG of three, 3-s maximal muscle contractions of the RF. During TMS mapping, 126 single-pulse biphasic stimuli (120% of RF aMT, 18 trains of seven stimuli, 2-s interstimulus interval) were delivered pseudorandomly over a 6 x 7 cm (7 rows and 8 columns) grid using Magstim Rapid^2 (Magstim Ltd., UK) and a 70 mm figure-of-eight coil, while participants activated the RF to 10% of the averaged RMS EMG of three, 3-s maximal muscle contractions with feedback provided on a monitor. The coil was placed tangentially to the skull with the handle pointing laterally 90 degrees. [23] The Neural Navigator (Neurosoft,

Russia) was used to track the positions of the TMS coil and participant's head and ensure stimuli were evenly distributed throughout the grid.

Maps for the RF, VL and VMO muscles were produced offline using a custom script in MATLAB 2023b (MathWorks Inc., USA) based on previously published methods.[23] RMS EMG amplitude of MEPs was extracted from a 26 to 46ms window after stimulation and background RMS EMG (55 to 5ms prior to stimulation) was subtracted. Surface maps within a transformed plane encompassing stimulation coordinates and their corresponding MEP amplitude were generated. The map was then divided into 2744 partitions (49 x 56), with each partition assigned an estimated MEP amplitude based on the nearest acquired MEP values using triangular linear interpolation. *Map volume*, a sum of the MEP amplitudes (μV) of all partitions with MEP amplitudes >10% of the maximum MEP amplitude, was used to index corticomotor excitability.

2) Maximum voluntary isometric contraction (MVIC) of the quadriceps muscles was measured when participants were seated with the hips and knees in 90 degrees flexion using a force transducer. Verbal encouragement was provided. Three attempts were recorded for each participant, and the highest value was used for analysis.

3) Pressure pain thresholds (PPTs) were assessed using a hand-held pressure algometer (Somedc, Hörby, Sweden, probe size 1cm^2) to quantify mechanical sensitivity. The probe (size 1 cm^2) was applied perpendicular to the skin (rate 40 kPa/s) until the participant first reported that the sensation of pressure had changed to pain. PPTs were measured at the side of the knee joint line of the most painful knee and ipsilateral thumbnail. Three measurements at each site were averaged for analysis. PPT assessment has good relative reliability (ICC=0.83, 95% confidence interval [CI] 0.72-0.90)[34]

4) Conditioned pain modulation (CPM) is a measure thought to reflect endogenous pain inhibition. The CPM response is quantified as a change in the threshold for a stimulus to become painful (test stimulus, TS) at one body site in the presence of pain during a second noxious stimulus (conditioning stimulus, CS) at another body site. In a normal CPM response, painful stimuli at one body site reduces perceived pain intensity induced by noxious stimuli at another body site. PPTs at the upper trapezius muscle contralateral to the painful knee were used as the TS and the cold pressor test (CPT) in the ipsilateral hand was used as the CS. Three PPTs (TS_1) were measured before the CPT. For CPT, participants immersed the hand in cold water (4 ºC) for a maximum of two minutes. [35] Three PPTs (TS_2) were re-assessed when CPT-evoked pain reached 50 on a NRS (0-100). If the pain became unbearable, participants were permitted to remove their hand before completing the CPT and a pain rating was obtained immediately after participants removed their hand. The magnitude of CPM was determined as (1) absolute value: TS_2 minus TS_1; and (2) precent change: $[(TS_2-TS_1)/TS_1]x100$, where a positive value indicated normal descending pain inhibitory function. [36] CPM paradigm has shown good relative reliability (ICC>0.75). [37]

Statistical Analysis

Although a sample size calculation is not required in a pilot RCT, 15 to 20 participants per treatment arm is recommended. [19] We selected a sample size of total 30 participants based as we successfully completed a previous pilot RCT with a similar design. [16] As a pilot study has low power, between-group statistical comparisons were not conducted. [38] Participant demographics and primary outcome measures were analysed and reported descriptively (mean and standard deviation [SD] or percentages). A full-scale RCT would be deemed to be feasible if the following predefined criteria thresholds are met: 1) attendance rate >80%; 2)

dropout rate <20%; 3) 80% of participants scored ≥7 on the 11-point willingness to undergo therapy scale at baseline. [19] For secondary outcome measures, within-group changes were calculated as follow-up minus baseline assessments (mean and 95% CI). Between-group differences (mean and 95% CI) were also calculated at post-intervention and three months. Two-sided T-tests were used for within-group comparisons between baseline and follow-up measures and effect sizes (*Cohen's d*, 0.2 as small, 0.5 moderate and 0.8 large) were calculated. All analyses were conducted using R, version 4.03 (R Development Core Team, Vienna, Austria). [39]

RESULTS

Feasibility

Between June 2022 and August 2023, 86 people were screened for eligibility, 35 (41%) were eligible and attended baseline assessment. Three participants were excluded at baseline assessment, and one withdrew after baseline assessment due to a wrist fracture unrelated to the study (Figure 1). Thirty-one participants (36% of screened participants) were enrolled and entered randomisation (AR+EX group N=17; SR+EX group N=14). All participants (100%) scored ≥7 on the willingness to undergo therapy (Table 1). The dropout rate was 10% at post-intervention assessment. In the AR+EX group, one participant withdrew due to work commitments. In the SR+EX group, one participant withdrew due to a flare-up of knee pain after the first treatment and another due to traveling distance. The dropout rate was 19% at three months (AR+EX group: N=3; SR+EX group: N=3). The treatment attendance rate was 98.4% (11.8±0.54 sessions) in the AR+EX group and 100% in the SR+EX group. No participant reported that treatment allocation was revealed before completing the post-intervention assessment. Thirteen participants (81%) in the AR+EX group and three (25%) in the SR+EX group correctly guessed their treatment group. In the AR+EX group, 11

participants thought they received "real" rTMS because their symptoms improved, and for the other two participants, because of perceived "stimulation" sensations in the hand or knee during rTMS. The outcome assessor and physiotherapists reported the treatment group allocation was not divulged before the trial completion.

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Table 1. Baseline characteristics of participants (mean and standard deviation).

	Active rTMS + Exercise (N = 17)	Sham rTMS + Exercise (N = 14)
Age (year)	64.2 ± 7.6	67.1 ± 9.6
Sex (male/female)	5/12	5/9
Body mass index (kg/meter^2)	28.3 ± 6.4	27.7 ± 5.1
Previous arthroscopy	3	2
Side of worse pain (left/right)	9/8	5/9
Duration of knee pain (year)	6.7 ± 5.0	7.5 ± 5.0
Previous injection (yes)	6	4
Cortisone	2	4
Hyaluronic acid	1	0
Platelet-rich plasm	3	0
Willingness to undergo treatment (out of 10)	9.8 ± 0.7	9.4 ± 1.2
Expected treatment effect		
No improvement	1	0
Minimal improvement	0	1
Moderate improvement	10	9
Large improvement	6	4

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Safety

No adverse event related to rTMS was reported. The AR+EX group reported mild side effects during rTMS: two episodes of transient feelings in a tooth filling and two episodes of transient sensation on the face. These side-effects did not impact rTMS and exercise treatment completion. One participant in the ST+EX group experienced an acute flare-up of knee pain after the first treatment and subsequently withdrew from the study. This acute episode of knee pain was attributed to strengthening exercise as it is unlikely that sham rTMS would yield negative effects on pain.

Participant-perceived improvement

Upon treatment completion, 13 (80%) participants in the AR+EX group and nine (75%) in the SR+EX group reported an improvement in their symptoms (Figure 2). One participant in each group reported worsened symptoms after treatment.

Pain and function

Average pain (11-point NRS) in the past week reduced after the six-week intervention in both groups (AR+EX group: $p<0.01$, $d=1.34$; SR+EX group: $p=0.03$, $d=1.07$) but did not change between baseline and three months ($p>0.11$) (Figure 3 and 4) (Table 2). WOMAC physical function subscale score improved after intervention in the AR+EX group ($p=0.02$, $d=1.02$) but not the SR+EX group ($p=0.23$). WOMAC physical function subscale score did not change between baseline and three months in either group ($p>0.12$).

Table 2. Group data (mean and 95% confidence interval) for pain and functional outcomes.

	Baseline		Post-treatment		Difference between groups	3-month post-treatment		Difference between groups
	AR+EX	SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX
Pain (NRS, 0-10)	5.0 (6.1, 3.9)	4.4 (5.6, 3.2)	2.8 (3.8, 1.7)	2.6 (3.9, 1.3)	0.2 (1.9, -1.5)	3.7 (4.9, 2.5)	2.9 (4.3, 1.5)	0.8 (2.6, -1.0)
WOMAC								
Pain subscale	9.8 (11.7, 7.9)	8.0 (10.1, 5.9)	7.5 (9.4, 5.6)	7.4 (9.8, 5.0)	0.1 (3.0, -2.8)	7.5 (9.5, 5.5)	6.8 (9.2, 4.4)	0.7 (3.8, -2.4)
Physical function subscale	29.4 (35.9, 22.9)	25.6 (32.8, 18.4)	21.3 (28.0, 14.6)	20.2 (27.7, 12.7)	1.1 (11.2, -9.0)	23.2 (30.1, 16.3)	24.1 (32.3, 15.9)	-0.8 (-11.5, 9.9)
WOMAC total score	43.5 (52.4, 34.6)	37.3 (47.1, 27.5)	32.0 (41.1, 22.9)	30.1 (40.4, 19.8)	1.9 (15.6, -11.9)	34.1 (43.5, 24.7)	34 (45.1, 22.9)	0.1 (14.7, -14.4)
mPD-Q	12.7 (14.6, 10.8)	6.9 (9.0, 4.8)	9.5 (11.5, 7.5)	5.8 (8.1, 3.5)	3.7 (6.8, 0.6)	8.3 (10.5, 6.1)	4.6 (7.3, 1.9)	3.7 (7.2, 0.5)

Number of painful sites	2.6 (-2.6, 7.7)	3.0 (10.3, -4.3)	4.1 (11.2, -2.9)	3.4 (13, -6.1)	0.7 (3.8, -2.4)	5 (12.8, 2.8)	4.3 (17.7, -9.0)	0.4 (3.9, -3.2)
PCS	29.3 (34.3, 24.3)	25 (30.4, 19.6)	20.7 (26.0, 30.3)	24.6 (30.3, 18.9)	-3.89 (-11.5, 3.71)	23.9 (29.2, 18.6)	21.9 (28.0, -15.8)	2 (10.1, -6.1)

Note: AR+EX = active rTMS and exercise; SR+EX = sham rTMS and exercise; WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index; mPD-Q = modified painDETECT questionnaire; PCS = Pain Catastrophising Scale.

WOMAC pain subscale score reduced at post-intervention (p=0.03, *d*=0.97) and at three-month follow-up (p=0.04, *d*=0.97) in the AR+EX group but did not change in the SR+EX group (p>0.83). mPD-Q score reduced at post-intervention (p=0.04, *d*=0.89) and at three-month follow-up (p<0.01, *d*=1.23) in the AR+EX group but did not change in the SR+EX group (p>0.74). The PCS score reduced at post-intervention (p<0.01, *d*=1.54) and at three-month follow-up (p=0.046, *d*=0.97) in the AR+EX group but did not change in the SR+EX group (p>0.98). The number of painful sites did not change within groups at any timepoints (p>0.18).

Physiological Mechanisms

Map volume for quadriceps muscles was unchanged after intervention in both groups (p>0.18), except for an increase in the VL muscle in the SR+EX group (0.99 mV, 95% CI -0.05 to 1.93, p=0.047, *d*=0.90) (Supplementary Table S3). MVIC was unchanged after intervention in both groups (p>0.18). PPTs were unchanged in both groups at the knee (p>0.30) and the thumb (p>0.34). Similarly, CPM was unchanged in both groups (p>0.45).

Sample Size Calculation

A study with 55 participants per arm would achieve 80% power considering a two-sided significance level of 0.05 and a correlation between pre- and post-measurements of 0.21 for pain. Accounting for a 20% dropout rate, a total of 138 participants would be required to detect the minimum clinically important between-group difference of 1.8 units for pain. [33]

DISCUSSION

This is the first study to evaluate the addition of rTMS to quadriceps strengthening exercise in knee osteoarthritis. The findings suggested the combined intervention is feasible, safe and

well-received to this population, and adding rTMS to quadriceps strengthening exercises might improve pain and function in knee osteoarthritis. Thus, our results support a definitive trial to examine the effects of this intervention on the symptoms in knee osteoarthritis.

Attendance was nearly 100% for treatments and 90% for the post-intervention assessment and all participants rated ≥7 on the willingness to undergo therapy. These findings met our predetermined criteria thresholds, [19] supporting the feasibility of a full-scale clinical trial. Although dropout rate at three-month follow-up was 19%, a full-scale trial with more resources could reduce the dropout rate. The proportion of participants thought they received active rTMS in both groups (AR+EX 81% vs SR+EX 75%) was similar. A recent study applying electrical stimulation synchronised to rTMS pulses on the head, mimicking scalp tapping sensation induced by active rTMS, for all participants, reported that 58% in the active rTMS and 44% in the sham rTMS groups thought they received active treatments. [40] Similar to that study, most our participants based their judgement on perceived analgesic effects. Future trials might consider this approach to strength participant blinding. Adverse reactions to rTMS during (e.g. seizure, syncope) and after (headache or pain at the stimulation site, hearing-related complaints) stimulation were reported previously, although occurring rarely (e.g. 0.1% for seizure). [41] No participant reported rTMS-related adverse reactions in this study. One participant in the SR+EX group reported an adverse reaction (flare-up of knee pain) attributed to exercise after the first treatment and discontinued the study. Our incidence rate of adverse reactions is lower than previous findings for the rTMS (i.e., 15% headaches) [13] or exercise therapy (23-30%)[42]. Generally, we found no barriers to implementation of the interventions or outcome measures and the rTMS and exercise intervention appears to be safe and well tolerated.

Participants received 12 supervised exercise sessions recommended for knee osteoarthritis[43] over six weeks. Notably, recent meta-analyses found that at least three months of strengthening exercise are needed to improve pain and disability in this condition, regardless of exercise volume (i.e., frequency, intensity). [44] Future definitive trials may consider a three-month intervention duration. We did not identify any issue with the rTMS protocol. A recent RCT demonstrated that a 22-week rTMS intervention of the same rTMS parameters (15 sessions) had long-term analgesic effects on chronic neuropathic pain, [40] The authors suggested the efficacy could be attributed to the cumulative effects of rTMS sessions over time, further supporting a longer intervention duration in future trials.

Our results of pain outcomes suggest that AR+EX might induce larger and longer-lasting analgesic effects than SR+EX. At post-intervention assessment, the AR+EX group demonstrated improvements in pain (11-point NRS) and physical function (WOMAC physical functional subscale) exceeding the MCIC for these outcomes whereas the SR+EX group only improved in pain and this improvement was below the MCIC. Further, WOMAC pain subscale, mPD-Q and PCS scores at the post-intervention assessment and at three-month follow-up suggest that adding rTMS to quadriceps strengthening could lead to long-term benefits for osteoarthritic pain, neuropathic-like pain (measured by the mPD-Q) and pain catastrophisation (measured by the PCS) in knee osteoarthritis. Notably, baseline mPD-Q score in the AR + EX group was higher than the SR + EX group (see Figure 3). Based on the cut-off points for mPD-Q, [29] the AR + EX group displayed a possible neuropathic pain profile (13-18) whereas the SR + EX group displayed a nociceptive pain profile (≤ 12). While a recent clinical trial has demonstrated the efficacy of rTMS in chronic neuropathic pain, [24] whether this combined intervention is more efficacious in people with a neuropathic component of osteoarthritic knee pain cannot be inferred in this polit study. To evaluate

clinical efficacy of a combined rTMS and strengthening intervention on pain and physical function for knee osteoarthritis, full-scale trials may consider a sample size of 138, 12 treatment sessions over three months and assessing the primary outcomes of pain (11-point NRS) and physical function (WOMAC physical function subscale) at baseline and three months post-intervention.

rTMS can induce long-lasting neuroplastic changes (i.e., decreasing or increasing cortical excitability) by modulating N-methyl-D-aspartate receptor activity, hypothesised as the underlying mechanism of analgesic effects. [45 46] Despite improvements in pain and function, the AR+EX group (10-Hz M1-rTMS) did not display an increase in corticomotor excitability observed in previous research. [46] Another study also showed a pain reduction but no change in corticomotor excitability after10-Hz M1-rTMS (five consecutive days). [47] It is likely that analgesic effects of rTMS might be driven by neuroplastic effects at remote cortical regions connecting to M1, not M1 itself, unrelated to modulating corticomotor excitability and that were not measured here. [47] Future studies should evaluate rTMS-induced neuroplastic changes using other measures (i.e., altered brain oscillations on electroencephalography) and their relationship with pain outcomes. [48] Further, increased quadriceps strength, reduced pressure pain sensitivity and improved descending pain inhibition after quadriceps strengthening exercises (alone or with adjunct treatments) were reported in knee osteoarthritis. [16 49] However, we found no changes in MVIC, PPTs and CPM in either group, regardless of observed within-group changes in pain and function. It is plausible that a longer intervention duration might be necessary to induce physiological changes similar to previous research. Alternatively, the interventions might act through other mechanisms such as placebo, pain catastrophisation or other pain-related psychological factors. As this is a

feasibility study, future full-scale studies are needed to determine underlying physiological mechanisms of this novel intervention in knee osteoarthritis.

Limitations

This study has some limitations. First, this pilot RCT was not powered to determine clinical efficacy, effects of the combined intervention of rTMS and strengthening exercise on pain and function in knee osteoarthritis cannot be inferred. Second, while self-reported WOMAC (physical function subscale) was used to assess function, objective outcome measures of physical function were not included in this study. The 2013 OARSI consensus recommends a set of performance-based tests for physical function in people with knee osteoarthritis. [50] According to this consensus, a minimal core set of three tests (i.e., 30-s chair-stand test, 40 m fast -paced walk test and stair-climb test) should be included as outcome measures to complement patient-reported measures in future large clinical trials.

In conclusion, data from this pilot study support a definitive trial examining a combined rTMS and quadriceps strengthening exercise intervention for knee osteoarthritis. Despite no identified barriers to implementing this study methodology in future trials, a three-month intervention duration should be considered to yield long-term benefits. Based on our findings, a fully powered clinical trial is justified to evaluate the clinical benefits of this novel treatment in knee osteoarthritis.

Patient and public involvement

We engaged a consumer representative from the Musculoskeletal Health Clinical Academic Group Consumer Community Council, Australian & New Zealand Musculoskeletal Clinical Trial Network and received feedback on the study including the proposed intervention and

potential barriers to participant recruitment. The feedback from the consumer representative was used to guide the design of intervention and recruitment strategies.

AUTHOR'S CONTRIBUTION

WJC, SA, JMN and SMS were involved in the conception and design of the study. WJC, SA, JMN, NC, HF, RRNR, EG, EO and SMS contributed to methodology of the study. WJC conducted recruitment, eligibility screening, and baseline and post-intervention assessment. AC and NC performed rTMS intervention. WJC performed the analysis and drafted the manuscript. All authors edited, reviewed and approved the final protocol. Guarantor - WJC

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COMPETING INTERESTS

None

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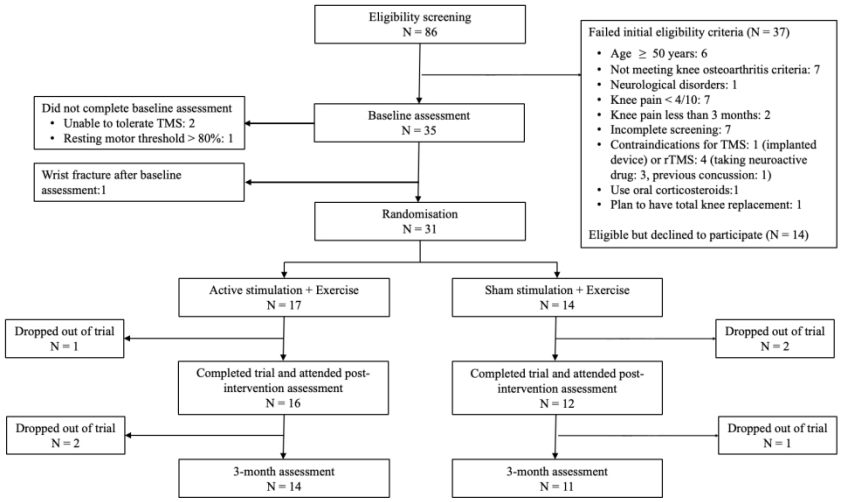
FIGURE LEGENDS

Figure 1. Flow of participants through the trial. *Note: rTMS - repetitive transcranial magnetic stimulation; TMS - transcranial magnetic stimulation*.

Figure 2. Percentage of participants reporting perceived change across categories from 'vastly worse' to 'completely recovered' after six-week interventions.

Figure 3. Pain and function (mean and 95% confidence interval) at baseline, post-intervention and three-month follow-up (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). *Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.*

Figure 4. Within-group changes in pain and function pre- and post-intervention (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). *Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.*



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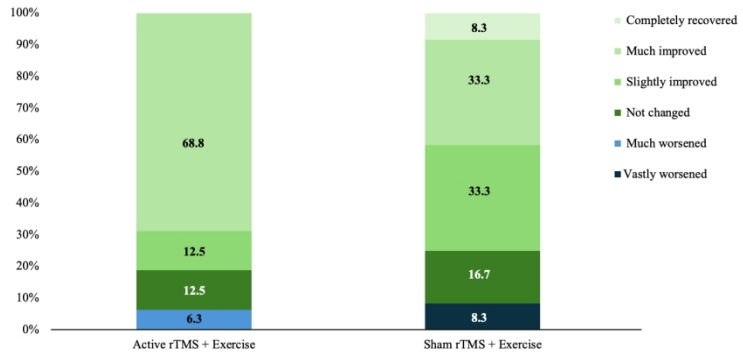

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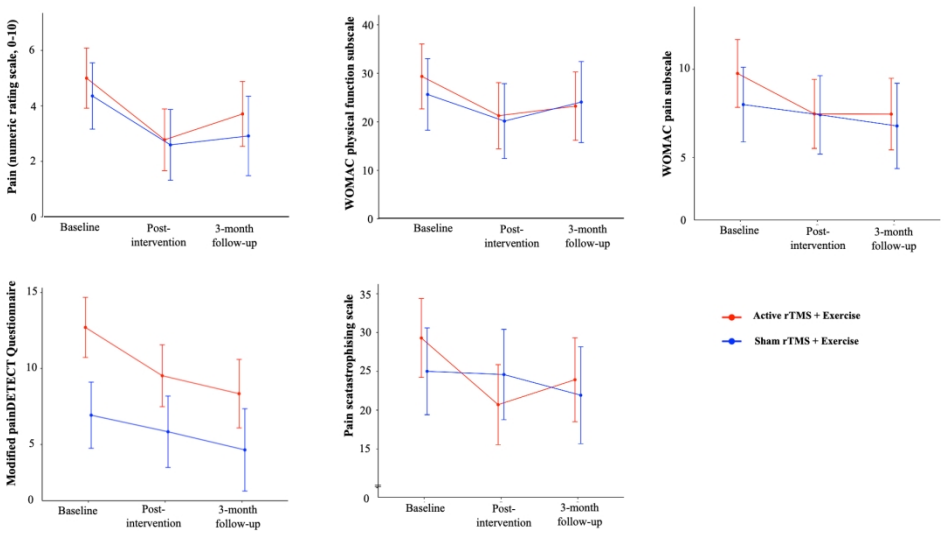

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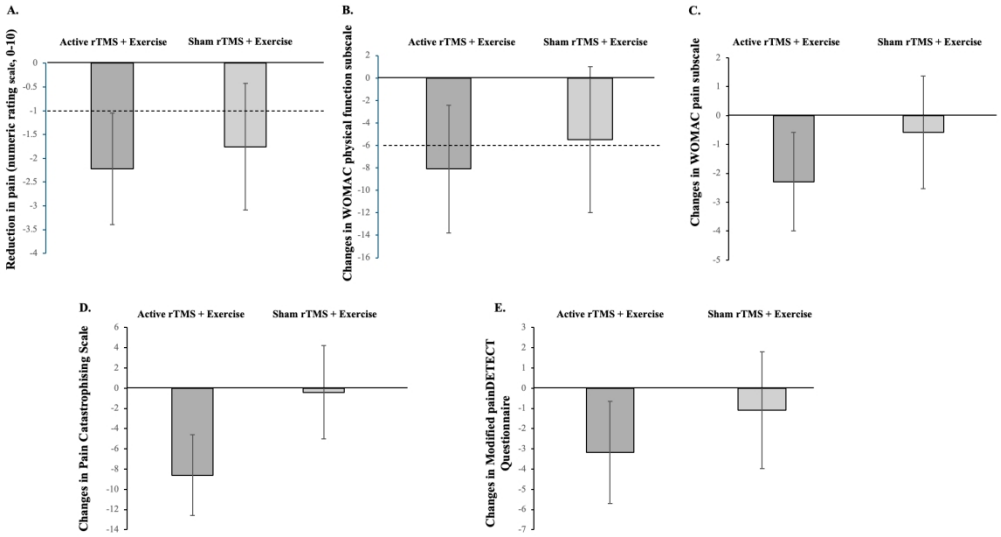

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SUPPLEMENTARY FILES

SUPPLEMENTARY Table S1. CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (specific guidance see CONSORT abstract extension for pilot trials)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial and reasons for randomised pilot trial	6-7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	9
	4c	How participants were identified and consented	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	10-14
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	14

Sample size	7a	Rationale for numbers in the pilot trial	14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	9-10
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	14-15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	15
	13b	For each group, losses and exclusions after randomisation, together with reasons	15
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	15-20
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	15-20
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	15-20
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17
	19a	If relevant, other important unintended consequences	NA

Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	20-24
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	20-24
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	20-24
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	20-24
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	8
Protocol	24	Where the pilot trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1
	26	Ethical approval or approval by research review committee, confirmed with reference number	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

SUPPLEMENTARY Table S2. Strengthening exercise program with progression and repetitions.

Exercise Description	Progression	Repetitions
1. Knee extensor strengthening Seated knee extensions with ankle weights. In a seated position, slowly straighten symptomatic knee until it is fully straight. Hold for 5 seconds and then lower slowly.	Ankle weights.	3 sets of 10. 30 second break period in between sets.
2. Hip abductor strengthening Level 1: Side lying hip abduction with ankle weights. Keep body still and knee straight and life affected leg up. Do not swing affected leg forward. Keep heel of foot higher than toes and behind hips while lifting straight upwards towards the ceiling. Hold for 5 seconds and then lower slowly.	Increase ankle weights or progress to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Standing hip abduction with thera elastic resistance band. Place looped thera elastic resistance band around both legs just above the ankle. Adequate tension on the elastic band and correct upright posture with shoulders and hips both facing forward is required prior to starting the exercise. The back of a chair or a wall can be used to provide support. Hold for 5 seconds and then lower slowly.	Increase thera elastic band resistance.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
3. Weight-bearing knee/hip extensor strengthening Level 1: Partial wall squats (option shown is to add thera elastic band around knees to incorporate the hip abductor muscles). Stand with one foot 30cm away from the wall with feet apart and turned inwards. With back straight and trunk and buttocks against a wall, slowly slide down the wall (as if to sit) to approximately 60° (less if painful) and then back up again while keeping contact with the wall at all times. Knees must go past the toes during the squat exercise. Hold position for 5 seconds.	Increase resistance by adding thera elastic resistance band or if already in use increase elastic band resistance strength. Progress further to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Sit-to-stand (option to add thera elastic band around knees to incorporate hip abductor muscles). Seated with back against a chair of standard height with firm seat, slowly stand up without using hands for support. Lean forward over toes so that the buttocks are lifted and hips go under the trunk. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.	Increase resistance by adding thera resistance elastic band. If already in use increase elastic band resistance strength. Progress further to level 3.	3 sets of 10. 30 second break period in between sets.
Level 3: Alternate split sit-to-stand Place the foot of the unaffected leg 10cm in front of the other foot.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly stand by leaning forward with back straight (nose in front of the toes) and squeeze buttock muscles. Most weight bearing must be on the symptomatic knee. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.		
Level 3+: Split partial wall squats Slowly slide down the wall (as if to sit) keeping the trunk and buttocks in contact with the wall. Knees must move over the toes. Most weight bearing must be on the symptomatic knee. Stop when symptomatic knee is bent to approximately 60° (less if painful) Hold for 5 seconds and then slowly slide back up keeping the trunk and buttocks in contact with the wall at all times.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.
4. Hamstring strengthening seated knee extensions Place a looped thera band elastic resistance band around the leg of a heavy table or chair. Seated in a chair, place the symptomatic leg in the looped thera elastic band with the knee slightly bent. Slowly pull the leg backwards into the elastic band until the knee is bent and a strong resistance is felt. Hold for 5 seconds.	Increase elastic band resistance.	3 sets of 10. 30 second break period in between sets.
5. Steps: a. Step ups: Place symptomatic leg onto the step. Slowly step up onto the step.	First increase the height of the step and second add weight.	3 sets of 10. 30-60 second break period in between sets.

Exercise Description	Progression	Repetitions
Touch foot of non-affected leg onto the step then place both feet back onto the starting position on the ground. b. Step downs: Start with both legs standing on top of the step. Bend the knee of the affected leg slowly to lower the non-affected leg towards the ground. Then straighten the affected knee slowly to return to the starting position. The knee of the affected leg must point forward during the movement.	Weight can be held across the chest with both hands or use two hand weights. First increase the height of the step and second add weight. Weight can be held across the chest with both hands or use two hand weights.	3 sets of 10. 30-60 second break period in between sets.

SUPPLEMENTARY TABLE S3. Group data (mean and 95% confidence interval) for physiological measures.

	Baseline		Post-treatment		Difference between groups
	AR+EX	SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX
Map volume					
Rectus femoris	0.6 (1.0, 0.1)	0.7 (1.2, 0.3)	0.9 (1.4, 0.5)	1.0 (1.5, 0.5)	-0.1 (-0.8, -0.6)
Vastus lateralis	0.8 (1.3, 0.2)	0.8 (1.4, 0.2)	1.1 (1.7, 0.5)	1.8 (2.7, 1.0)	-0.7 (-1.6, -0.3)
Vastus medialis oblique	1.1 (1.9, 0.3)	1.4 (2.3, 0.5)	1.3 (2.2, 0.4)	1.6 (2.7, 0.5)	-0.3 (-1.7, -1.1)
Pressure pain threshold					
Knee	662 (754.9, 569.1)	587 (689.3, 484.7)	686 (780.1, 591.9)	633 (739.2, 526.8)	53.3 (195.2, -88.6)
Thumb	379 (431.1, 326.9)	386 (443.4, 328.6)	393 (446.1, 339.9)	410 (470.0, 350.0)	-17.3 (62.9, -97.4)
Condition pain modulation	72.2 (108.9, -35.5)	97 (137.4, 56.6)	51.3 (90.5, 12.1)	90.5 (212.6, 46.6)	-39.2 (37.6, -98.2)
Maximum voluntary isometric contraction	298 (353.9, 242.1)	349 (408.8, 289.2)	331 (389.6, 272.4)	360 (420.8, 299.2)	-29.1 (55.4, -113.6)

Note: AR+EX = active rTMS and exercise; SR+EX = sham rTMS and exercise.

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rTMS and exercise for knee osteoarthritis

TITLE

Repetitive Transcranial Magnetic Stimulation as An Adjunct to Quadriceps Strengthening Exercise in Knee Osteoarthritis: A Pilot Randomised Controlled Trial

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rTMS and exercise for knee osteoarthritis

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ABSTRACT

Objective: To examine the feasibility, safety and perceived patient response of a combined repetitive transcranial magnetic stimulation (rTMS) and quadriceps strengthening exercise intervention for knee osteoarthritis.

Methods: A two-arm, participant-, therapist- and assessor-blinded, randomised controlled trial with additional follow-up of pain and function at three months. Participants were randomised to receive active rTMS+exercise (AR+EX) or sham rTMS+exercise (SR+EX) twice weekly for six weeks whilst completing home exercises twice week. Primary outcomes included recruitment rate, treatment attendance, dropouts, willingness to undergo therapy (11-point numeric rating scale, 'not at all willing'=0 and 'very willing'=10), success of participant, therapist and outcome assessor blinding, adverse events and Global Perceived Effect Scale. Secondary outcomes were pain, function and measures of physiological mechanisms.

Results: Eighty-six people were screened, 31 (36%) were randomised, 28 (90%) completed the treatments and three (10%) dropouts at three-month follow-up. Both groups had high treatment attendance (98.4 and 100%). All participants scored at least 7 on the willingness to undergo therapy scale. Blinding was successful. No adverse events were reported. At the post-intervention assessment, 80% in the AR+EX group and 75% in the SR+EX group reported an improvement on the Global Perceived Effect Scale. Both groups demonstrated within-group improvements in pain at the post-intervention assessment but not at three-month follow-up. Function improved only in the AR+EX group at the post-intervention assessment.

Conclusion: Combined rTMS and quadriceps strengthening exercise intervention for knee osteoarthritis is feasible, safe and well-received. A full-scale trial is justified to assess the clinical benefits of this novel treatment.

rTMS and exercise for knee osteoarthritis

Registration: ACTRN12621001712897

Keywords: exercise, knee osteoarthritis, repetitive transcranial magnetic stimulation, randomised controlled trial.

ARTICLE SUMMARY

Strengths and limitations of this study

- Randomised, assessor-, therapist- and participant-blind, sham-controlled study design
- Data on the feasibility, safety, analgesic effect and central mechanisms of the combined rTMS and exercise therapy in knee osteoarthritis
- This pilot study was not powered to determine treatment efficacy.

INTRODUCTION

Knee osteoarthritis is a leading cause of global disease burden. [1] The main symptoms are pain and physical dysfunction that become persistent and debilitating as the disorder progresses. [2] Non-surgical, non-drug interventions have been recommended to reduce pain and improve function for knee osteoarthritis. [3] Strengthening exercise is the cornerstone of conservative treatment and is recommended as a first-line treatment in all international guidelines. [4 5] Exercise yields analgesic effects via both peripheral (i.e., improving muscle strength/coordination and joint proprioceptive control that subsequently reduces nociceptive inputs from the affected knee) and central (i.e., activating endogenous opiodergic and pain control systems) mechanisms. [6 7] However, the effects of exercise are at best, moderate for pain and function, and small for quality of life. [8] While knee osteoarthritis is a well-defined joint disorder, pain severity does not always correlate with radiographic findings. [9] This discordance has been attributed to maladaptive neuroplasticity of central pain processing pathways. [10] Novel treatments targeting the neurophysiological mechanisms underpinning osteoarthritic knee pain could bolster the effects of strengthening exercise and optimise outcomes.

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique, might boost the benefits of exercise for knee osteoarthritis. rTMS can induce neuroplasticity, either decreasing (inhibitory, low-frequency stimulation ≤1 Hz) or increasing (excitatory, high-frequency stimulation ≥5 Hz) cortical excitability. [11] Research suggests that rTMS alleviates pain via the activation of endogenous opioid pathways of brain regions involved in pain processing. [12] High-frequency rTMS applied over the primary motor cortex (M1) has demonstrated superiority to low-frequency rTMS in chronic pain populations. [13] Further, as increased M1 excitability is associated with motor learning, [14] applying excitatory,

high-frequency rTMS over M1 might increase the brain's responsiveness to the afferent inputs generated by subsequent treatments (i.e., exercise), a phenomenon known as 'priming'. [15]

Therefore, adding high-frequency rTMS over M1 to strengthening exercise could potentially improve outcomes beyond that which can be achieved with rTMS or exercise alone through two mechanisms: (i) simultaneously modulating peripheral (exercise) and central (rTMS and exercise) mechanisms underpinning knee osteoarthritis pain and/or; (ii) 'priming' the brain to increase its responsiveness to the corticomotor benefits of exercise (i.e., increased cortical excitability, enhanced voluntary muscle activation, strength gains, improved motor control). [16] Although a recent meta-analysis showed that a combined rTMS and exercise intervention yielded a moderate pain reduction (2 trials, n=38, standardised mean difference=-0.76) for chronic pain conditions in general, [17] the effect of this intervention specific to knee osteoarthritis remains unknown. A rigorous and adequately powered randomised controlled trial (RCT) is needed to determine the efficacy of this combined intervention of rTMS and strengthening exercise for knee osteoarthritis. Before conducting a full-scale RCT, a pilot study is recommended to inform the feasibility of the processes essential to the success of a large RCT and the safety of the intervention. [18]

This study aimed to 1) examine the feasibility, safety and patient-perceived effect of a combined high-frequency rTMS and strengthening exercise intervention for knee osteoarthritis; 2) assess physiological mechanisms underlying the intervention; and 3) provide data to conduct a sample size calculation for a fully powered trial based on the results of pain and physical function outcomes.

METHODS AND ANALYSIS

Design

This was an assessor-, therapist- and participant-blinded, two-arm parallel group, pilot RCT. The outcome measures were assessed at baseline and upon treatment completion (six weeks post-randomisation). In addition, pain and function were also assessed three months post-intervention. The study was prospectively registered (ACTRN12621001712897) and approved by the University of New South Wales Human Research Ethics Committee (HC210954). The study protocol has been published. [19] All participants provided written informed consent. The study is reported using the Consolidated Standards of Reporting Trials statement extension for pilot trials (Supplementary Table S1). [20]

Participants

Participants were recruited from the community in Sydney, Australia. Inclusion criteria were: 1) people aged ≥50 years with knee osteoarthritis based on the American College of Rheumatology Clinical Criteria, [21] having at least one of the following: morning stiffness <30 minutes, crepitus, bony tenderness, bony enlargement, no palpable warmth; 2) knee pain for ≥3 months and on most days in the past month; 3) average pain intensity ≥4 on an 11-point numeric rating scale (NRS) in the past week. Exclusion criteria were: 1) previous knee joint replacement or high tibial osteotomy on the affected side; 2) knee surgery or joint injection in the past six months; 3) planned surgery in the next nine months; 4) using oral corticosteroids currently or in the past four weeks; 5) confirmed diagnosis of systemic arthritis (i.e., rheumatoid arthritis); 6) previous knee fracture or malignancy; 7) other conditions affecting lower limb function; 8) participating in any knee strengthening exercise for knee osteoarthritis in the past six months; 9) loss of sensation of the affected lower limb; 10) neurological or psychiatric disorders; 11) use of neuroactive drugs (e.g., tricyclic

antidepressant, Clozapine, Foscarnet); 12) contraindications to TMS (i.e., epilepsy, metal implant in the skull) using the TMS safety screening questionnaire[22]; 13) resting motor threshold (rMT) >80% measured at the baseline assessment as this would lead to a high stimulating intensity for the rTMS intervention and potential overheating of the coil. Participants were permitted to continue their usual medications during the trial.

Procedures

Potential participants completed an online screening questionnaire to determine eligibility. Eligible participants attended baseline assessment and were randomly allocated to the active rTMS+exercise (AR+EX) or sham rTMS+exercise (SR+EX) group. The assigned treatment was allocated through REDCap prior to the first treatment session, independently of the researchers involved with physiotherapy treatment and outcome assessment. Participants, treating physiotherapists and outcome assessors were blinded to group allocation. All participants received the same instructions and information about rTMS intervention. Participants received either active or sham rTMS immediately before 30 minutes of one-to-one supervised strengthening exercise twice weekly for six weeks (12 sessions). If bilateral symptoms were present, the most painful knee was assessed and treated. Six physiotherapists (at least 2 years' experience) delivered exercise therapies. All procedures were performed at Neuroscience Research Australia (NeuRA), Sydney, Australia.

Intervention

rTMS

The rTMS target is the motor hotspot, or the coil position inducing a maximal motor evoked potential (MEP) amplitude measured on electromyography (EMG) using a bipolar surface electrode (Ag-AgCl, Noraxon dual electrodes) on the first dorsal interosseous muscle

ipsilateral to the treated knee using a Magstim Rapid^2 (Magstim Ltd., UK) and a 70 mm figure-of-eight coil. Motor hotspots for the quadriceps muscles were not used as rTMS target as MEPs cannot be reliably elicited at rest, [23] and rTMS targeting motor hotspot for the hand has non-somatotopic analgesic effect. [24] At each session, 3000 stimuli (10 Hz, 30 trains of 10 seconds, 20-second intertrain interval) were delivered at 90% of rMT (the minimum intensity at which five out of ten stimuli delivered to the hotspot, evoked a MEP >50 μV). [25] rMT was assessed at the beginning of each session. For sham rTMS, a sham coil that looks identical to a real coil but produces no magnetic pulse and only audible clicks was used to deliver the same stimulation protocol as active rTMS.

Exercise

Participants performed standardised quadriceps strengthening exercises (Supplementary Table S2) with demonstrated effectiveness for knee osteoarthritis using ankle cuff weights or resistance bands as appropriate. [6 8] Each exercise was performed in 3 sets of 10 repetitions with a 30s rest between sets. The treating physiotherapists determined the starting level and when to progress the exercise based on participant's feedback and therapist's clinical judgement. Exercises were progressed as defined in the protocol. [19] Participants performed their supervised exercises at home at the same dosage using resistance bands twice per week. Home exercise diaries with instructions were provided for recording the number of sessions, type and number of exercises performed and adverse reactions and collected at the post-intervention assessment.

Outcome Measures

Primary Outcomes

Feasibility, safety and participant-perceived improvement to treatment were measured as: 1) the proportion of participants recruited from the total number screened; 2) the number of sessions attended by each participant; 3) the number of drop-outs in each group; 4) willingness of each participant to undergo therapy at baseline on an 11-point NRS with 'not at all willing' at 0 and 'very willing' at 10; 5) success of participant/outcome assessor/therapist blinding; 6) the number of adverse events and the details of each event; 7) the Global Perceived Effect Scale, where each participant rated their perceived response to treatments on a 7-point Likert scale ranging from "completely recovered" to "vastly worsened". [26] The success of participant blinding was assessed at the completion of the intervention using a Yes/No response to the question 'Do you believe you received real brain stimulation?' and an 11-point NRS of the individual's confidence in that judgement. Participants were also be asked 'Why do you believe you received the real/sham brain stimulation?' and 'Was it divulged to you whether you were receiving real brain stimulation or not?' The success of outcome assessor and treating physiotherapist blinding was determined using a Yes/No response to the question 'Did you know which intervention group the participant was assigned to before completion of the follow-up laboratory assessment?' and 'If you answer "yes", how was it divulged to you?'.

Secondary Outcomes

Pain and function

Knee pain and function were assessed using: 1) an 11-point NRS (0='no pain', 10='worst pain imaginable') for average pain in the past week; [27] 2) the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (24 items [0-4 scale, 0='none', 4='extreme'], total score=96) (Likert version 3.1) and its pain subscale (5 items, total score=20) and physical function subscale (17 items, total score=68), with higher scores indicating worse

pain and function; [28] 3) modified painDETECT (mPD-Q, 7 items, total score=38) to detect a neuropathic pain component (score ≥12) in people with knee osteoarthritis; [29] 4) the number of painful sites, measured by participants indicating the number of painful sites outside of the affected knee lasting >24 hours in the past week on a four-sided body map (total score=35) with higher scores indicating more widespread hyperalgesia; [30] and 5) the Pain Catastrophising Scale (PCS, 13 items, total score=0-52) to assess participants' thoughts and feelings about pain in the domains of magnification, rumination and helplessness, with higher scores indicating higher severity. [31] The minimum clinically important change (MCIC) to be detected in knee osteoarthritis trials is 1 unit for pain[32] and 6 units for function. [33]

Physiological mechanism investigations

1) Corticomotor excitability was measured using TMS mapping. [19] Single-pulse TMS was delivered over M1, evoking MEPs recorded on EMG by bipolar surface electrodes over the rectus femoris (RF), vastus lateralis (VL) and vastus medialis oblique (VMO) muscles while participants were seated. EMG signals were amplified (x2000), filtered (20-1000 Hz) and sampled at 2k Hz. Active motor threshold (aMT) was determined on the hotspot for the RF while participants maintained a muscle contraction of 10% averaged root mean square (RMS) EMG of three, 3-s maximal muscle contractions of the RF. During TMS mapping, 126 single-pulse biphasic stimuli (120% of RF aMT, 18 trains of seven stimuli, 2-s interstimulus interval) were delivered pseudorandomly over a 6 x 7 cm (7 rows and 8 columns) grid using Magstim Rapid^2 (Magstim Ltd., UK) and a 70 mm figure-of-eight coil, while participants activated the RF to 10% of the averaged RMS EMG of three, 3-s maximal muscle contractions with feedback provided on a monitor. The coil was placed tangentially to the skull with the handle pointing laterally 90 degrees. [23] The Neural Navigator (Neurosoft,

Russia) was used to track the positions of the TMS coil and participant's head and ensure stimuli were evenly distributed throughout the grid.

Maps for the RF, VL and VMO muscles were produced offline using a custom script in MATLAB 2023b (MathWorks Inc., USA) based on previously published methods. [23] RMS EMG amplitude of MEPs was extracted from a 26 to 46ms window after stimulation and background RMS EMG (55 to 5ms prior to stimulation) was subtracted. Surface maps within a transformed plane encompassing stimulation coordinates and their corresponding MEP amplitude were generated. The map was then divided into 2744 partitions (49 x 56), with each partition assigned an estimated MEP amplitude based on the nearest acquired MEP values using triangular linear interpolation. *Map volume*, a sum of the MEP amplitudes (μV) of all partitions with MEP amplitudes >10% of the maximum MEP amplitude, was used to index corticomotor excitability.

2) Maximum voluntary isometric contraction (MVIC) of the quadriceps muscles was measured when participants were seated with the hips and knees in 90 degrees flexion using a force transducer. Verbal encouragement was provided. Three attempts were recorded for each participant, and the highest value was used for analysis.

3) Pressure pain thresholds (PPTs) were assessed using a hand-held pressure algometer (Somedc, Hörby, Sweden, probe size 1cm^2) to quantify mechanical sensitivity. The probe (size 1 cm^2) was applied perpendicular to the skin (rate 40 kPa/s) until the participant first reported that the sensation of pressure had changed to pain. PPTs were measured at the side of the knee joint line of the most painful knee and ipsilateral thumbnail. Three measurements at each site were averaged for analysis. PPT assessment has good relative reliability (ICC=0.83, 95% confidence interval [CI] 0.72-0.90). [34]

4) Conditioned pain modulation (CPM) is a measure thought to reflect endogenous pain inhibition. The CPM response is quantified as a change in the threshold for a stimulus to become painful (test stimulus, TS) at one body site in the presence of pain during a second noxious stimulus (conditioning stimulus, CS) at another body site. In a normal CPM response, painful stimuli at one body site reduces perceived pain intensity induced by noxious stimuli at another body site. PPTs at the upper trapezius muscle contralateral to the painful knee were used as the TS and the cold pressor test (CPT) in the ipsilateral hand was used as the CS. Three PPTs (TS_1) were measured before the CPT. For CPT, participants immersed the hand in cold water (4 ºC) for a maximum of two minutes. [35] Three PPTs (TS_2) were re-assessed when CPT-evoked pain reached 50 on a NRS (0-100). If the pain became unbearable, participants were permitted to remove their hand before completing the CPT and a pain rating was obtained immediately after participants removed their hand. The magnitude of CPM was determined as (1) absolute value: TS_2 minus TS_1; and (2) precent change: $[(TS_2-TS_1)/TS_1]x100$, where a positive value indicated normal descending pain inhibitory function. [36] CPM paradigm has shown good relative reliability (ICC>0.75). [37]

Statistical Analysis

Although a sample size calculation is not required in a pilot RCT, 15 to 20 participants per treatment arm is recommended. [19] We selected a sample size of total 30 participants based as we successfully completed a previous pilot RCT with a similar design. [16] As a pilot study has low power, between-group statistical comparisons were not conducted. [38] Participant demographics and primary outcome measures were analysed and reported descriptively (mean and standard deviation [SD] or percentages). A full-scale RCT would be deemed to be feasible if the following predefined criteria thresholds are met: 1) attendance rate >80%; 2)

dropout rate <20%; 3) 80% of participants scored ≥7 on the 11-point willingness to undergo therapy scale at baseline. [19] For secondary outcome measures, within-group changes were calculated as follow-up minus baseline assessments (mean and 95% CI). Between-group differences (mean and 95% CI) were also calculated at post-intervention and three months. Two-sided T-tests were used for within-group comparisons between baseline and follow-up measures and effect sizes (*Cohen's d*, 0.2 as small, 0.5 moderate and 0.8 large) were calculated. All analyses were conducted using R, version 4.03 (R Development Core Team, Vienna, Austria). [39]

RESULTS

Feasibility

Between June 2022 and August 2023, 86 people were screened for eligibility, 35 (41%) were eligible and attended baseline assessment. Three participants were excluded at baseline assessment, and one withdrew after baseline assessment due to a wrist fracture unrelated to the study (Figure 1). Thirty-one participants (36% of screened participants) were enrolled and entered randomisation (AR+EX group N=17; SR+EX group N=14). All participants (100%) scored ≥7 on the willingness to undergo therapy (Table 1). The dropout rate was 10% at post-intervention assessment. In the AR+EX group, one participant withdrew due to work commitments. In the SR+EX group, one participant withdrew due to a flare-up of knee pain after the first treatment and another due to traveling distance. The dropout rate was 19% at three months (AR+EX group: N=3; SR+EX group: N=3). The treatment attendance rate was 98.4% (11.8±0.54 sessions) in the AR+EX group and 100% in the SR+EX group. No participant reported that treatment allocation was revealed before completing the post-intervention assessment. Thirteen participants (81%) in the AR+EX group and three (25%) in the SR+EX group correctly guessed their treatment group. In the AR+EX group, 11

participants thought they received “real” rTMS because their symptoms improved, and for the other two participants, because of perceived “stimulation” sensations in the hand or knee during rTMS. The outcome assessor and physiotherapists reported the treatment group allocation was not divulged before the trial completion.

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Table 1. Baseline characteristics of participants (mean and standard deviation).

	Active rTMS + Exercise (N = 17)	Sham rTMS + Exercise (N = 14)
Age (year)	64.2 ± 7.6	67.1 ± 9.6
Sex (male/female)	5/12	5/9
Body mass index (kg/meter^2)	28.3 ± 6.4	27.7 ± 5.1
Previous arthroscopy	3	2
Side of worse pain (left/right)	9/8	5/9
Duration of knee pain (year)	6.7 ± 5.0	7.5 ± 5.0
Previous injection (yes)	6	4
Cortisone	2	4
Hyaluronic acid	1	0
Platelet-rich plasm	3	0
Willingness to undergo treatment (out of 10)	9.8 ± 0.7	9.4 ± 1.2
Expected treatment effect		
No improvement	1	0
Minimal improvement	0	1
Moderate improvement	10	9
Large improvement	6	4

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Safety

No adverse event related to rTMS was reported. The AR+EX group reported mild side effects during rTMS: two episodes of transient feelings in a tooth filling and two episodes of transient sensation on the face. These side-effects did not impact rTMS and exercise treatment completion. One participant in the ST+EX group experienced an acute flare-up of knee pain after the first treatment and subsequently withdrew from the study. This acute episode of knee pain was attributed to strengthening exercise as it is unlikely that sham rTMS would yield negative effects on pain.

Participant-perceived improvement

Upon treatment completion, 13 (80%) participants in the AR+EX group and nine (75%) in the SR+EX group reported an improvement in their symptoms (Figure 2). One participant in each group reported worsened symptoms after treatment.

Pain and function

Average pain (11-point NRS) in the past week reduced after the six-week intervention in both groups (AR+EX group: $p<0.01$, $d=1.34$; SR+EX group: $p=0.03$, $d=1.07$) but did not change between baseline and three months ($p>0.11$) (Figure 3 and 4) (Table 2). WOMAC physical function subscale score improved after intervention in the AR+EX group ($p=0.02$, $d=1.02$) but not the SR+EX group ($p=0.23$). WOMAC physical function subscale score did not change between baseline and three months in either group ($p>0.12$).

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Table 2. Group data (mean and 95% confidence interval) for pain and functional outcomes.

	Baseline		Post-treatment		Difference between groups	3-month post-treatment		Difference between groups
	AR+EX	SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX
Pain (NRS, 0-10)	5.0 (6.1, 3.9)	4.4 (5.6, 3.2)	2.8 (3.8, 1.7)	2.6 (3.9, 1.3)	0.2 (1.9, -1.5)	3.7 (4.9, 2.5)	2.9 (4.3, 1.5)	0.8 (2.6, -1.0)
WOMAC								
Pain subscale	9.8 (11.7, 7.9)	8.0 (10.1, 5.9)	7.5 (9.4, 5.6)	7.4 (9.8, 5.0)	0.1 (3.0, -2.8)	7.5 (9.5, 5.5)	6.8 (9.2, 4.4)	0.7 (3.8, -2.4)
Physical function subscale	29.4 (35.9, 22.9)	25.6 (32.8, 18.4)	21.3 (28.0, 14.6)	20.2 (27.7, 12.7)	1.1 (11.2, -9.0)	23.2 (30.1, 16.3)	24.1 (32.3, 15.9)	-0.8 (-11.5, 9.9)
WOMAC total score	43.5 (52.4, 34.6)	37.3 (47.1, 27.5)	32.0 (41.1, 22.9)	30.1 (40.4, 19.8)	1.9 (15.6, -11.9)	34.1 (43.5, 24.7)	34 (45.1, 22.9)	0.1 (14.7, -14.4)
mPD-Q	12.7 (14.6, 10.8)	6.9 (9.0, 4.8)	9.5 (11.5, 7.5)	5.8 (8.1, 3.5)	3.7 (6.8, 0.6)	8.3 (10.5, 6.1)	4.6 (7.3, 1.9)	3.7 (7.2, 0.5)

Number of painful sites	2.6 (-2.6, 7.7)	3.0 (10.3, -4.3)	4.1 (11.2, -2.9)	3.4 (13, -6.1)	0.7 (3.8, -2.4)	5 (12.8, 2.8)	4.3 (17.7, -9.0)	0.4 (3.9, -3.2)
PCS	29.3 (34.3, 24.3)	25 (30.4, 19.6)	20.7 (26.0, 30.3)	24.6 (30.3, 18.9)	-3.89 (-11.5, 3.71)	23.9 (29.1, 18.6)	21.9 (28.0, -15.8)	2 (10.1, -6.1)

Note: AR+EX = active rTMS and exercise; SR+EX = sham rTMS and exercise; WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index; mPD-Q = modified painDETECT questionnaire; PCS = Pain Catastrophising Scale.

WOMAC pain subscale score reduced at post-intervention (p=0.03, *d*=0.97) and at three-month follow-up (p=0.04, *d*=0.97) in the AR+EX group but did not change in the SR+EX group (p>0.83). mPD-Q score reduced at post-intervention (p=0.04, *d*=0.89) and at three-month follow-up (p<0.01, *d*=1.23) in the AR+EX group but did not change in the SR+EX group (p>0.74). The PCS score reduced at post-intervention (p<0.01, *d*=1.54) and at three-month follow-up (p=0.046, *d*=0.97) in the AR+EX group but did not change in the SR+EX group (p>0.98). The number of painful sites did not change within groups at any timepoints (p>0.18).

Physiological Mechanisms

Map volume for quadriceps muscles was unchanged after intervention in both groups (p>0.18), except for an increase in the VL muscle in the SR+EX group (0.99 mV, 95% CI -0.05 to 1.93, p=0.047, *d*=0.90) (Supplementary Table S3). MVIC was unchanged after intervention in both groups (p>0.18). PPTs were unchanged in both groups at the knee (p>0.30) and the thumb (p>0.34). Similarly, CPM was unchanged in both groups (p>0.45).

Sample Size Calculation

A study with 55 participants per arm would achieve 80% power considering a two-sided significance level of 0.05 and a correlation between pre- and post-measurements of 0.21 for pain. Accounting for a 20% dropout rate, a total of 138 participants would be required to detect the minimum clinically important between-group difference of 1.8 units for pain. [33]

DISCUSSION

This is the first study to evaluate the addition of rTMS to quadriceps strengthening exercise in knee osteoarthritis. The findings suggested the combined intervention is feasible, safe and

well-received to this population, and adding rTMS to quadriceps strengthening exercises might improve pain and function in knee osteoarthritis. Thus, our results support a definitive trial to examine the effects of this intervention on the symptoms in knee osteoarthritis.

Attendance was nearly 100% for treatments and 90% for the post-intervention assessment and all participants rated ≥7 on the willingness to undergo therapy. These findings met our predetermined criteria thresholds, [19] supporting the feasibility of a full-scale clinical trial. Although dropout rate at three-month follow-up was 19%, a full-scale trial with more resources could reduce the dropout rate. The proportion of participants thought they received active rTMS in both groups (AR+EX 81% vs SR+EX 75%) was similar. A recent study applying electrical stimulation synchronised to rTMS pulses on the head, mimicking scalp tapping sensation induced by active rTMS, for all participants, reported that 58% in the active rTMS and 44% in the sham rTMS groups thought they received active treatments. [40] Similar to that study, most our participants based their judgement on perceived analgesic effects. Future trials might consider this approach to strength participant blinding. Adverse reactions to rTMS during (e.g. seizure, syncope) and after (headache or pain at the stimulation site, hearing-related complaints) stimulation were reported previously, although occurring rarely (e.g. 0.1% for seizure). [41] No participant reported rTMS-related adverse reactions in this study. One participant in the SR+EX group reported an adverse reaction (flare-up of knee pain) attributed to exercise after the first treatment and discontinued the study. Our incidence rate of adverse reactions is lower than previous findings for the rTMS (i.e., 15% headaches) [13] or exercise therapy (23-30%)[42]. Generally, we found no barriers to implementation of the interventions or outcome measures and the rTMS and exercise intervention appears to be safe and well tolerated.

Participants received 12 supervised exercise sessions recommended for knee osteoarthritis[43] over six weeks. Notably, recent meta-analyses found that at least three months of strengthening exercise are needed to improve pain and disability in this condition, regardless of exercise volume (i.e., frequency, intensity). [44] Future definitive trials may consider a three-month intervention duration. We did not identify any issue with the rTMS protocol. A recent RCT demonstrated that a 22-week rTMS intervention of the same rTMS parameters (15 sessions) had long-term analgesic effects on chronic neuropathic pain, [40] The authors suggested the efficacy could be attributed to the cumulative effects of rTMS sessions over time, further supporting a longer intervention duration in future trials.

Our results of pain outcomes suggest that AR+EX might induce larger and longer-lasting analgesic effects than SR+EX. At post-intervention assessment, the AR+EX group demonstrated improvements in pain (11-point NRS) and physical function (WOMAC physical functional subscale) exceeding the MCIC for these outcomes whereas the SR+EX group only improved in pain and this improvement was below the MCIC. Further, WOMAC pain subscale, mPD-Q and PCS scores at the post-intervention assessment and at three-month follow-up suggest that adding rTMS to quadriceps strengthening could lead to long-term benefits for osteoarthritic pain, neuropathic-like pain (measured by the mPD-Q) and pain catastrophisation (measured by the PCS) in knee osteoarthritis. Notably, baseline mPD-Q score in the AR + EX group was higher than the SR + EX group (see Figure 3). Based on the cut-off points for mPD-Q, [29] the AR + EX group displayed a possible neuropathic pain profile (13-18) whereas the SR + EX group displayed a nociceptive pain profile (≤ 12). While a recent clinical trial has demonstrated the efficacy of rTMS in chronic neuropathic pain, [24] whether this combined intervention is more efficacious in people with a neuropathic component of osteoarthritic knee pain cannot be inferred in this polit study. To evaluate

clinical efficacy of a combined rTMS and strengthening intervention on pain and physical function for knee osteoarthritis, full-scale trials may consider a sample size of 138, 12 treatment sessions over three months and assessing the primary outcomes of pain (11-point NRS) and physical function (WOMAC physical function subscale) at baseline and three months post-intervention.

rTMS can induce long-lasting neuroplastic changes (i.e., decreasing or increasing cortical excitability) by modulating N-methyl-D-aspartate receptor activity, hypothesised as the underlying mechanism of analgesic effects. [45 46] Despite improvements in pain and function, the AR+EX group (10-Hz M1-rTMS) did not display an increase in corticomotor excitability observed in previous research. [46] Another study also showed a pain reduction but no change in corticomotor excitability after10-Hz M1-rTMS (five consecutive days). [47] It is likely that analgesic effects of rTMS might be driven by neuroplastic effects at remote cortical regions connecting to M1, not M1 itself, unrelated to modulating corticomotor excitability and that were not measured here. [47] Future studies should evaluate rTMS-induced neuroplastic changes using other measures (i.e., altered brain oscillations on electroencephalography) and their relationship with pain outcomes. [48] Further, increased quadriceps strength, reduced pressure pain sensitivity and improved descending pain inhibition after quadriceps strengthening exercises (alone or with adjunct treatments) were reported in knee osteoarthritis. [16 49] However, we found no changes in MVIC, PPTs and CPM in either group, regardless of observed within-group changes in pain and function. It is plausible that a longer intervention duration might be necessary to induce physiological changes similar to previous research. Alternatively, the interventions might act through other mechanisms such as placebo, pain catastrophisation or other pain-related psychological factors. As this is a

feasibility study, future full-scale studies are needed to determine underlying physiological mechanisms of this novel intervention in knee osteoarthritis.

Limitations

This study has some limitations. First, this pilot RCT was not powered to determine clinical efficacy, effects of the combined intervention of rTMS and strengthening exercise on pain and function in knee osteoarthritis cannot be inferred. Second, while self-reported WOMAC (physical function subscale) was used to assess function, objective outcome measures of physical function were not included in this study. The 2013 OARSI consensus recommends a set of performance-based tests for physical function in people with knee osteoarthritis. [50] According to this consensus, a minimal core set of three tests (i.e., 30-s chair-stand test, 40 m fast -paced walk test and stair-climb test) should be included as outcome measures to complement patient-reported measures in future large clinical trials.

In conclusion, data from this pilot study support a definitive trial examining a combined rTMS and quadriceps strengthening exercise intervention for knee osteoarthritis. Despite no identified barriers to implementing this study methodology in future trials, a three-month intervention duration should be considered to yield long-term benefits. Based on our findings, a fully powered clinical trial is justified to evaluate the clinical benefits of this novel treatment in knee osteoarthritis.

Patient and public involvement

We engaged a consumer representative from the Musculoskeletal Health Clinical Academic Group Consumer Community Council, Australian & New Zealand Musculoskeletal Clinical Trial Network and received feedback on the study including the proposed intervention and

potential barriers to participant recruitment. The feedback from the consumer representative was used to guide the design of intervention and recruitment strategies.

AUTHOR'S CONTRIBUTION

WJC, SA, JMN and SMS were involved in the conception and design of the study. WJC, SA, JMN, NC, HF, RRNR, EG, EO and SMS contributed to methodology of the study. WJC conducted recruitment, eligibility screening, and baseline and post-intervention assessment. AC and NC performed rTMS intervention. WJC performed the analysis and drafted the manuscript. All authors edited, reviewed and approved the final protocol.Guarantor - WJC.

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COMPETING INTERESTS

None

DATA AVAILABILITY STATEMENT

Individual participant data that underlie the results reported in this study—including text, tables, figures, and appendices—will be made available following deidentification. This

includes deidentified participant data and associated data dictionaries. A published study protocol including planned statistical analysis is available to provide full methodological transparency, along with related supplementary documents. The data will be made available immediately upon publication of the study findings, with no end date for access. Access to the data will be granted to researchers for the purpose of conducting secondary analyses. Requests must include the evidence of ethical approval from a recognised Human Research Ethics Committee.

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FIGURE LEGENDS

Figure 1. Flow of participants through the trial. *Note: rTMS - repetitive transcranial magnetic stimulation; TMS - transcranial magnetic stimulation*.

Figure 2. Percentage of participants reporting perceived change across categories from 'vastly worse' to 'completely recovered' after six-week interventions.

Figure 3. Pain and function (mean and 95% confidence interval) at baseline, post-intervention and three-month follow-up (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). *Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.*

Figure 4. Within-group changes in pain and function pre- and post-intervention (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). *Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.*

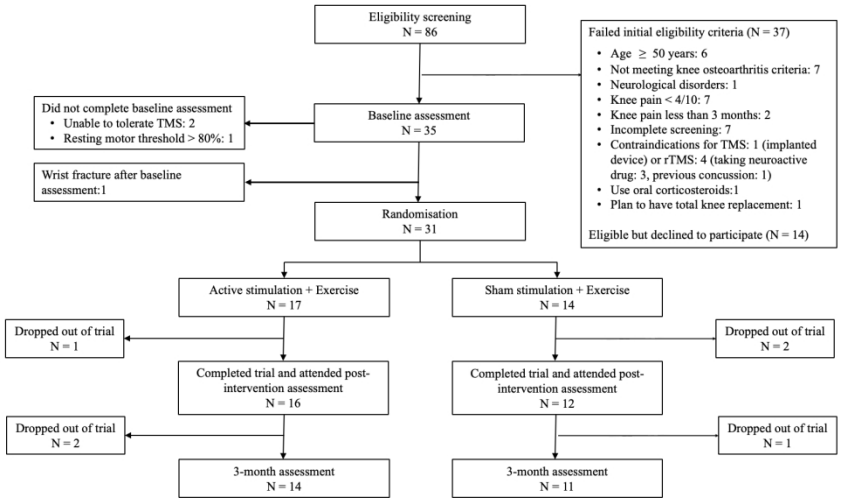

Figure 1. Flow of participants through the trial. Note: rTMS - repetitive transcranial magnetic stimulation; TMS - transcranial magnetic stimulation.

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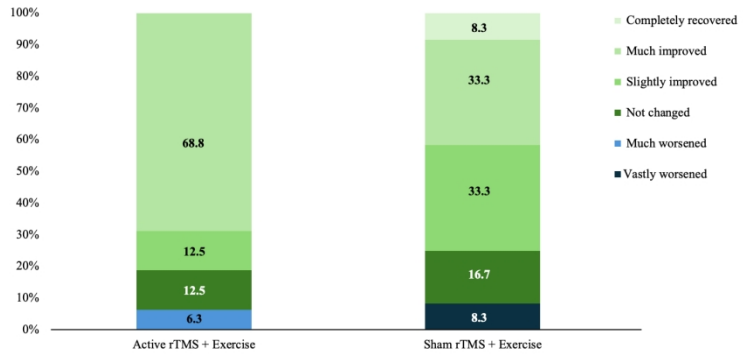

Figure 2. Percentage of participants reporting perceived change across categories from 'vastly worse' to 'completely recovered' after six-week interventions.

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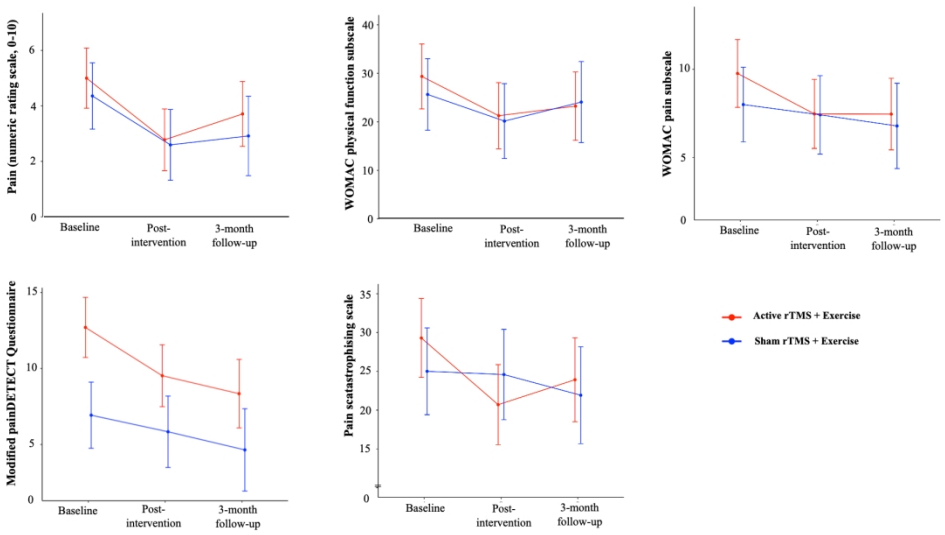

Figure 3. Pain and function (mean and 95% confidence interval) at baseline, post-intervention and three-month follow-up (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.

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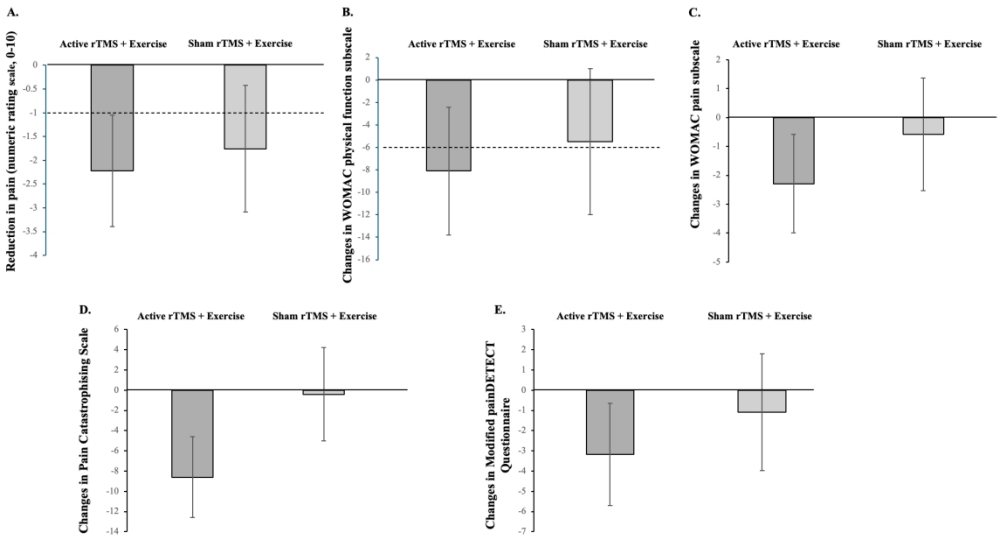

Figure 4. Within-group changes in pain and function pre- and post-intervention (A. Average pain in the past week; B. WOMAC physical function subscale; C. WOMAC pain subscale; D. modified painDETECT Questionnaire; E. Pain Catastrophising Scale). Note: WOMAC = the Western Ontario and McMaster Universities Osteoarthritis Index.

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SUPPLEMENTARY FILES

SUPPLEMENTARY Table S1. CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial.

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (specific guidance see CONSORT abstract extension for pilot trials)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial and reasons for randomised pilot trial	6-7
	2b	Specific objectives or research questions for pilot trial	7
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	7-8
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8-9
	4b	Settings and locations where the data were collected	9
	4c	How participants were identified and consented	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-10
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	10-14
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	14

Sample size	7a	Rationale for numbers in the pilot trial	14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	9
	11b	If relevant, description of the similarity of interventions	9-10
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	14-15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	15
	13b	For each group, losses and exclusions after randomisation, together with reasons	15
Recruitment	14a	Dates defining the periods of recruitment and follow-up	15
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	15-20
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	15-20
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	15-20
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	17
	19a	If relevant, other important unintended consequences	NA

Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	20-24
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	20-24
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	20-24
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	20-24
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	8
Protocol	24	Where the pilot trial protocol can be accessed, if available	8
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1
	26	Ethical approval or approval by research review committee, confirmed with reference number	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

SUPPLEMENTARY Table S2. Strengthening exercise program with progression and repetitions.

Exercise Description	Progression	Repetitions
1. Knee extensor strengthening Seated knee extensions with ankle weights. In a seated position, slowly straighten symptomatic knee until it is fully straight. Hold for 5 seconds and then lower slowly.	Ankle weights.	3 sets of 10. 30 second break period in between sets.
2. Hip abductor strengthening Level 1: Side lying hip abduction with ankle weights. Keep body still and knee straight and life affected leg up. Do not swing affected leg forward. Keep heel of foot higher than toes and behind hips while lifting straight upwards towards the ceiling. Hold for 5 seconds and then lower slowly.	Increase ankle weights or progress to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Standing hip abduction with thera elastic resistance band. Place looped thera elastic resistance band around both legs just above the ankle. Adequate tension on the elastic band and correct upright posture with shoulders and hips both facing forward is required prior to starting the exercise. The back of a chair or a wall can be used to provide support. Hold for 5 seconds and then lower slowly.	Increase thera elastic band resistance.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
3. Weight-bearing knee/hip extensor strengthening Level 1: Partial wall squats (option shown is to add thera elastic band around knees to incorporate the hip abductor muscles). Stand with one foot 30cm away from the wall with feet apart and turned inwards. With back straight and trunk and buttocks against a wall, slowly slide down the wall (as if to sit) to approximately 60° (less if painful) and then back up again while keeping contact with the wall at all times. Knees must go past the toes during the squat exercise. Hold position for 5 seconds.	Increase resistance by adding thera elastic resistance band or if already in use increase elastic band resistance strength. Progress further to level 2.	3 sets of 10. 30 second break period in between sets.
Level 2: Sit-to-stand (option to add thera elastic band around knees to incorporate hip abductor muscles). Seated with back against a chair of standard height with firm seat, slowly stand up without using hands for support. Lean forward over toes so that the buttocks are lifted and hips go under the trunk. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.	Increase resistance by adding thera resistance elastic band. If already in use increase elastic band resistance strength. Progress further to level 3.	3 sets of 10. 30 second break period in between sets.
Level 3: Alternate split sit-to-stand Place the foot of the unaffected leg 10cm in front of the other foot.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.

Exercise Description	Progression	Repetitions
Slowly stand by leaning forward with back straight (nose in front of the toes) and squeeze buttock muscles. Most weight bearing must be on the symptomatic knee. Hold for 3 seconds with buttocks slightly off the chair before sitting back down slowly.		
Level 3+: Split partial wall squats Slowly slide down the wall (as if to sit) keeping the trunk and buttocks in contact with the wall. Knees must move over the toes. Most weight bearing must be on the symptomatic knee. Stop when symptomatic knee is bent to approximately 60° (less if painful) Hold for 5 seconds and then slowly slide back up keeping the trunk and buttocks in contact with the wall at all times.	Increase depth of squat.	3 sets of 10. 30 second break period in between sets.
4. Hamstring strengthening seated knee extensions Place a looped thera band elastic resistance band around the leg of a heavy table or chair. Seated in a chair, place the symptomatic leg in the looped thera elastic band with the knee slightly bent. Slowly pull the leg backwards into the elastic band until the knee is bent and a strong resistance is felt. Hold for 5 seconds.	Increase elastic band resistance.	3 sets of 10. 30 second break period in between sets.
5. Steps: a. Step ups: Place symptomatic leg onto the step. Slowly step up onto the step.	First increase the height of the step and second add weight.	3 sets of 10. 30-60 second break period in between sets.

Exercise Description	Progression	Repetitions
Touch foot of non-affected leg onto the step then place both feet back onto the starting position on the ground. b. Step downs: Start with both legs standing on top of the step. Bend the knee of the affected leg slowly to lower the non-affected leg towards the ground. Then straighten the affected knee slowly to return to the starting position. The knee of the affected leg must point forward during the movement.	Weight can be held across the chest with both hands or use two hand weights. First increase the height of the step and second add weight. Weight can be held across the chest with both hands or use two hand weights.	3 sets of 10. 30-60 second break period in between sets.

SUPPLEMENTARY TABLE S3. Group data (mean and 95% confidence interval) for physiological measures.

	Baseline		Post-treatment		Difference between groups
	AR+EX	SR+EX	AR+EX	SR+EX	AR+EX minus SR+EX
Map volume					
Rectus femoris	0.6 (1.0, 0.1)	0.7 (1.2, 0.3)	0.9 (1.4, 0.5)	1.0 (1.5, 0.5)	-0.1 (-0.8, -0.6)
Vastus lateralis	0.8 (1.3, 0.2)	0.8 (1.4, 0.2)	1.1 (1.7, 0.5)	1.8 (2.7, 1.0)	-0.7 (-1.6, -0.3)
Vastus medialis oblique	1.1 (1.9, 0.3)	1.4 (2.3, 0.5)	1.3 (2.2, 0.4)	1.6 (2.7, 0.5)	-0.3 (-1.7, -1.1)
Pressure pain threshold					
Knee	662 (754.9, 569.1)	587 (689.3, 484.7)	686 (780.1, 591.9)	633 (739.2, 526.8)	53.3 (195.2, -88.6)
Thumb	379 (431.1, 326.9)	386 (443.4, 328.6)	393 (446.1, 339.9)	410 (470.0, 350.0)	-17.3 (62.9, -97.4)
Condition pain modulation	72.2 (108.9, -35.5)	97 (137.4, 56.6)	51.3 (90.5, 12.1)	90.5 (212.6, 46.6)	-39.2 (37.6, -98.2)
Maximum voluntary isometric contraction	298 (353.9, 242.1)	349 (408.8, 289.2)	331 (389.6, 272.4)	360 (420.8, 299.2)	-29.1 (55.4, -113.6)

Note: AR+EX = active rTMS and exercise; SR+EX = sham rTMS and exercise.