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Brain connectivity to optimise and assess noninvasive brain stimulation for central pain modulation

Submission date
10/02/2022

Recruitment status
No longer recruiting

Registration date
24/02/2022

Overall study status
Completed

Last Edited
24/03/2025

Condition category
Musculoskeletal Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
There is more and more evidence that effective pain treatments need to also focus on any disturbed communication between brain areas that are fundamental to the perception of pain. Logically, if abnormal brain connectivity patterns are reversed, this should help to alleviate chronic pain. Transcranial magnetic stimulation (TMS) offers the possibility to do so non-invasively, safely and with practically no side effects, and has already been approved by the National Institute of Clinical Excellence (NICE) for treatment-resistant depression. Many studies recently have testified promising results for pain relief with this method. Researchers at the University of Nottingham have identified a few factors that likely elevate this approach's success rate. This is what they would like to verify in the current study.

Who can participate?
Patients aged 18-75 years of age with chronic knee pain

What does the study involve?
The study involves completing questionnaires, undergoing an MRI scan of the brain, undergoing TMS treatment, and doing some sensory testing. As the study aims to assess the benefits of a TMS stimulation protocol aiming for longer-term effects, the core study schedule is fairly intense over 2 weeks. Participants will be asked to come to a first visit then 4 treatment days with a session length of about 6 hours each but with long breaks with refreshments in a comfortable waiting area. The sixth and final study visit is about 2 hours long. Participants may be asked to complete pain and wellbeing questionnaires up to 16 weeks after the last visit.

What are the possible benefits and risks of participating?
There are no direct anticipated effects from taking part in the study as the researchers do not know whether the TMS will have an effect on pain and whether or not participants will be allocated to the active or sham TMS arm. There is the possibility that the active TMS may help with pain as the protocol is designed specifically for pain reduction. The staff operating the TMS device are professionally trained and adhere to all safety instructions. As it directly influences the activity of nerve cells, theoretically there is the risk of a seizure. Practically this has occurred

only in 1 out of 4500 sessions with healthy volunteers in a different research centre and the TMS intensity applied in that incident was higher than standard. No such incident was reported in any of the many studies on chronic pain or depression; this study does not use any new TMS protocol that has not been tested on humans yet. The researchers also screen thoroughly for any risk factors (e.g., certain drugs) that would increase the risk for a seizure and do not enrol anyone into the study who could be at higher risk. TMS in this study is therefore considered to be very safe and the risk of a seizure is very low. The majority of TMS treatments are very well tolerated, occasionally however a short-lasting headache can occur. Depending on an individual's facial anatomy, facial nerves can be stimulated at the same time which would result in muscle twitches in the face; these however cease as the stimulation is stopped. If participants find it too uncomfortable, the session can be stopped immediately. As explained above, there is very brief discomfort associated with some sensory assessment tasks but no harm to any part of the body, but participants will always be in the control to stop tasks if they do not like to do them. MRI is noisy and thus the researchers will take extra care to protect participants' ears. Despite this participants will still hear some noise and thus it is not recommended for people who are very sensitive to/easily annoyed by noise. Apart from that, being in the tube is not comfortable for people who get anxious when in enclosed spaces (claustrophobia). Participants will however always be able to tell the researchers to stop the scan, should they feel too uncomfortable. Scanning pregnant women is avoided although this is just to be careful as there is no known risk using this strength of magnetic field. Women who are pregnant you should not take part in the study. It is extremely unlikely that the scan will show any abnormality. Even if there were an abnormality, it is unlikely that the researchers would notice it since they are taking these scans for scientific research, so they are not the same as scans collected by doctors for medical purposes. Furthermore, the pictures will not be looked at by a radiologist (a doctor qualified to find abnormalities in scans). If the researchers did find anything abnormal on the scan, the investigator would arrange for an appropriately qualified doctor from a healthcare provider (e.g. an NHS Trust or a private doctor) to look at them. That specialist doctor would contact the participant's GP to explain the situation, so that the GP could then advise the participant.

Where is the study run from?
University of Nottingham (UK)

When is the study starting and how long is it expected to run for?
July 2021 to July 2024

Who is funding the study?
Versus Arthritis (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
298509

Central Portfolio Management System (CPMS)
49664

Study information

Scientific Title
Brain connectivity guided, optimised theta-burst transcranial magnetic stimulation to improve central pain modulation in knee osteoarthritis pain

Acronym
BoostCPM

Study objectives
Current study hypothesis as of 04/05/2023:
Chronic pain is a major burden for society, the economy, health systems and individuals. There is a lack of effective analgesic treatments in chronic pain with an urgent need for novel treatments. Maladaptive brain mechanisms are increasingly recognised as key contributors to the development and persistence of pain. A feature is the altered communication between brain areas that are involved in the processing of pain signals and the modulation of the associated pain perception, which partially overlap with the observed brain connectivity changes in major depression.

These maladaptive functional brain network changes are (i) thought to drive the experience of chronic pain, and (ii) potentially reversible, thereby supporting the notion that non-invasive neuromodulation that normalises the brain’s connectivity will also reverse the pain behaviour.

Transcranial Magnetic Stimulation (TMS) is a promising method to non-invasively change brain networks and thus restore normal connectivity patterns which has already been approved by the National Institute of Clinical Excellence (NICE) for treatment-resistant depression. Treatment-resistant depression shares brain network alterations with chronic pain which may explain the known comorbidity between both conditions and suggests that TMS could become equally effective in treating chronic ‘treatment-resistant’ pain as shown for treatment-resistant depression.

Pain and depression are closely related from the perspective of involved brain regions, which may explain the known comorbidity between both conditions. This suggests that TMS could become useful in treating 'refractory' pain (i.e. chronic pain that failed to get better in multiple treatment attempts) as it is effective for treatment-resistant depression. Efficacy might be higher in patients with higher associated affective symptoms including higher levels of reported pain catastrophizing, low mood or anxiety.

There is evidence that invasive neuromodulation is effective in selected indications (3). There is also considerable recent interest in non-invasive brain stimulation (NIBS) trials in chronic pain with mixed results to date. Meta-analyses and systematic reviews have described NIBS as having 'poor or inconclusive' analgesic effects across sites and pain disorders (3-5), "minimally clinically relevant"(5), to "promising"(6) and "probable efficacy" for either motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) stimulation (7). There are major quality concerns with most studies considered poor (3) due to underpowered sample sizes, lack of blinding, inadequate randomization, or missing sham for comparisons.

Importantly, recently an accelerated, optimised TMS protocol was reported to achieve a remarkably better outcome than any other treatment including standard TMS protocols in treatment-resistant depression with over 90% of participants reaching clinical response (Cole et al., 2020).
While only a small study and using an open design, the main benefits were considered to come from the combination of (i) a higher cumulative dose (90,000 iTBS pulses), (ii) administered over a shorter period of time (5 days) and (iii) individually optimised treatment target (Iwabuchi et al., 2019). The researchers aim to translate this highly promising approach to chronic musculoskeletal pain, which if effective would greatly improve clinical interest in this technique both for cost and practical reasons.

To address the remaining fundamental questions before undertaking full clinical analgesic trials, there is a need for sham-control optimisation of the stimulation protocol in healthy controls, and then for high-quality mechanistic assessment of the optimised protocol in the target population.

The researchers will make use of the latest advances in individual imaging-guided optimisation of the brain stimulation target that they have established in collaboration with IMH and the clinical neuromodulation service at QMC, and additionally develop an improved stimulation protocol that optimises 'dosing' and 'timing' of brain stimulation to achieve the desired modulatory effects on pain inhibitory brain circuits. This will be done in three steps: First, the researchers will undertake an acute single cross-over sham-controlled TMS study in healthy participants to optimise the intersession interval in line with current neurophysiological and neuroimaging evidence of metaplasticity and homeostatic plasticity that can enhance or decrease the cumulative effect of repeated TMS stimulation over one day/research visit. Stimulation efficiency will be assessed using serial MRI post-stimulation protocols. The optimised protocol for one day will then be assessed for feasibility and tolerability in chronic musculoskeletal (MSK) patients if applied over a week, and finally the researchers will undertake a sham-controlled mechanistic parallel design efficacy study in participants with chronic knee pain, enriched for reports of negative effect. The mechanistic assessment will be done by investigating the modulatory effects of dlPFC TMS on the descending pain modulatory system using a range of brain imaging metrics and on quantitative sensory testing that inform on the efficacy of central pain modulation.

Previous study hypothesis:
Chronic pain is a major burden for society, the economy, health systems and individuals. There is a lack of effective analgesic treatments in chronic pain with an urgent need for novel

treatments. Maladaptive brain mechanisms are increasingly recognised as key contributors to the development and persistence of pain. A consistent feature is the altered communication between brain areas that are involved in the processing of pain signals and the modulation of the associated pain perception, which partially overlap with the observed brain connectivity changes in major depression.

These maladaptive functional brain network changes are (i) thought to drive the experience of chronic pain, and (ii) potentially reversible, thereby supporting the notion that non-invasive neuromodulation that normalises the brain's connectivity will also reverse the pain behaviour.

The best-established method to non-invasively change brain networks and thus restore normal connectivity patterns is Transcranial Magnetic Stimulation (TMS) which has already been approved by the National Institute of Clinical Excellence (NICE) for treatment-resistant depression. Treatment-resistant depression shares brain network alterations with chronic pain which may explain the known comorbidity between both conditions and suggests that TMS could become equally effective in treating chronic 'treatment-resistant' pain as shown for treatment-resistant depression.

This led to recent interest in TMS trials in chronic pain with mixed success to date: the judgement in meta-analyses and systematic reviews ranged from poor or inconclusive analgesic effects from TMS across sites and pain disorders (Cruccu et al., 2016; O'Connell, Marston, Spencer, DeSouza, & Wands, 2018), "minimally clinically relevant" (Saltychev & Laimi, 2017), to "promising" (Yang & Chang, 2020) or even "definite efficacy" after motor cortex (M1) stimulation (Lefaucheur et al., 2014) (but see a later review from the same group (Lefaucheur et al., 2020) concluding "probable efficacy" for either M1 or dorsolateral prefrontal cortex as in treatment-resistant depression) stimulation. There are major quality concerns with these studies and quality overall has been considered poor (Cruccu et al., 2016) with most studies being underpowered, and uncertainties regarding the best brain stimulation site, type of stimulation, target population. Nevertheless, pain relief was frequently found to be >30% (Galhardoni et al., 2015) which encourages seeking further improvements and addressing limitations in order to unlock the potential that this technology may hold for pain treatment. In particular, the dorsolateral prefrontal cortex (dlPFC) as the target site for TMS is relatively understudied despite promising efficacy rates seen in treatment-resistant depression when using optimised imaging-guided neuromodulation (Iwabuchi, Auer, Lankappa, & Palaniyappan, 2019) (Ahdab, Ayache, Brugieres, Goujon, & Lefaucheur, 2010).

Importantly, recently an accelerated, optimised TMS protocol was reported to achieve a remarkably better outcome than any other treatment including standard TMS protocols in treatment-resistant depression with over 90% of participants reaching clinical response (Cole et al., 2020).
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To address the remaining fundamental questions before undertaking full clinical analgesic trials, there is a need for sham-control optimisation of the stimulation protocol in healthy controls, and then for high-quality mechanistic assessment of the optimised protocol in the target population.

The researchers will make use of the latest advances in individual imaging-guided optimisation of the brain stimulation target that they have established in collaboration with IMH and the clinical neuromodulation service at QMC, and additionally develop an improved stimulation protocol that optimises 'dosing' and 'timing' of brain stimulation to achieve the desired modulatory effects on pain inhibitory brain circuits. This will be done in three steps: First, the researchers will undertake an acute single cross-over sham-controlled TMS study in healthy participants to optimise the intersession interval in line with current neurophysiological and neuroimaging evidence of metaplasticity and homeostatic plasticity that can enhance or decrease the cumulative effect of repeated TMS stimulation over one day/research visit. Stimulation efficiency will be assessed using serial MRI post-stimulation protocols. The optimised protocol for one day will then be assessed for feasibility and tolerability in chronic musculoskeletal (MSK) patients if applied over a week, and finally the researchers will undertake a sham-controlled mechanistic parallel design efficacy study in participants with chronic knee pain, enriched for reports of negative effect. The mechanistic assessment will be done by investigating the modulatory effects of dlPFC TMS on the descending pain modulatory system using a range of brain imaging metrics and on quantitative sensory testing that inform on the efficacy of central pain modulation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/07/2021, South West – Cornwall and Plymouth Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8071, +44 (0)207 104 8370, +44 (0)207 104 8019; cornwallandplymouth.rec@hra.nhs.uk), REC ref: 21/SW/0079

Primary study design
Interventional

Study design
Randomized Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Knee osteoarthritis

Interventions
Current interventions as of 01/06/2023:
Six research visits for pain-free healthy control pilot (baseline, 4 days intermittent theta-burst stimulation [TBS]/sham over 3-5 weeks).
Six research visits over 3-5 weeks for tolerability study and mechanistic study (baseline, 4 days TBS/sham and post-treatment assessment).

TMS/iTBS: For all treatments, the intermittent theta burst stimulation (iTBS) protocol will be delivered using a fixed 7 cm diameter coil
(E-z Cool Coil and support arm) consisting of three pulses (aimed at 80% RMT, but may be lowered to avoid participant discomfort) of 50 Hz repeated at 200 ms (5 Hz) intervals with a total 1800 pulses per block/session, and 36,000 pulses over the treatment week.

Previous interventions from 04/05/2023 to 01/06/2023:
Six research visits for pain-free healthy control pilot (baseline, 4 days intermittent theta-burst stimulation [TBS]/sham over 3-5 weeks).
Six research visits over 3-5 weeks for tolerability study and mechanistic study (baseline, 4 days TBS/sham and post-treatment assessment).

TMS/TBS: Intermittent theta burst stimulation (90% motor threshold) with 50Hz bursts at 5Hz in runs of 600 pulses, 5' inter-run time, intersession time of up to 60 minutes (to be optimised as well as the number of daily sessions during the pilot) with maximum total dose 48,000-60,000 within FDA approved limits.

Previous interventions:
Three research visits for pain-free healthy control pilot (baseline, intermittent theta-burst stimulation [TBS]/sham 1 week apart)
Six research visits over 2 weeks for tolerability study and mechanistic study (baseline, 4 days TBS /sham and post-treatment assessment (24 hours after last treatment) treatments may not be interrupted for more than 3 days.

TMS/TBS: Intermittent theta burst stimulation (90% motor threshold) with 50Hz bursts at 5Hz in runs of 600 pulses, 5' inter-run time, intersession time of up to 60 minutes (to be optimised as well as the number of daily sessions during the pilot) with maximum total dose 48,000-60,000 within FDA approved limits.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Current primary outcome measures as of 04/05/2023:
1. Variance of changes in pre-selected neuroimaging functional markers of the descending pain modulatory system (MRI) at final (T6) vs baseline visit (T1)
2. Variance of change in conditioned pain modulation (pain intensity change with/without conditioned pain stimulus) (QST) at final vs baseline visit
3. Number of participants recruited and retained on the trial
4. Number of iTBS sessions completed at 80% RMT (TMS data collected T2-T4)

Previous primary outcome measures:
1. Brain activity and connectivity changes in areas of the descending pain modulatory system measured using MRI (3Tesla): 0.5 – 1 hour duration (1.5 hours for controls), at baseline and 2 weeks
2. Extent of conditioned pain modulation (pain intensity change with/without conditioned pain stimulus): quantitative sensory testing for conditioned pain modulation (CPM) and temporal summation of pain (TSP) at baseline and 2 weeks
3. Number of participants recruited and retained on the trial, measured at the end of the trial

Key secondary outcome(s)
Current secondary outcome measures as of 04/05/2023:
1. Variance of change in reported pain intensity, burden and catastrophizing (ICOAP, PCS) at final versus baseline study visit
2. Change in negative affect (HADS) at final versus baseline study visit
3. Variance in physiological and psychophysical changes (acute experimental pain) at final vs baseline study visit

4. Variance of PROMS (daily online recording pain, wellbeing, sleep) over 16 weeks from treatment versus enrolment-baseline

Previous secondary outcome measures:
1. Physiological and psychophysical effects (acute experimental pain) measured at the final study visit
2. Reported pain intensity, burden and catastrophizing measured using Intermittent and Constant Osteoarthritis Pain (ICOAP), Pain Catastrophizing Scale (PCS) questionnaires at baseline and 2 weeks
3. Mood measured using Depression Anxiety Stress Scale-21 (DASS21) at baseline and 2 weeks
4. Anxiety measured using Hospital Anxiety and Depression Scale (HADS) at baseline and 2 weeks
5. Patient-Reported Outcome Measures (PROMs) (daily online recording pain, wellbeing, sleep) measured over 16 weeks from treatment versus enrolment-baseline
6. Pain phenotype measured using Quantitative Sensory Testing (QST) at baseline and 2 weeks

Completion date
31/07/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/08/2023:
1. 18-75 years of age and able to consent
2. Chronic knee pain (minimum 6 months duration) with VAS score >=4/10
3. Able to accommodate the study visits without disruption to their jobs or other responsibilities and without experiencing excessive physical strain or other distress.

Previous inclusion criteria from 01/06/2023 to 21/08/2023:
1. 18-75 years of age and able to consent
2. Chronic knee pain (minimum 6 months duration) with VAS score ≥4/10
3. Predominant knee pain
4. Able to accommodate the study visits without disruption to their jobs or other responsibilities and without experiencing excessive physical strain or other distress.

Previous inclusion criteria:
1. 18-75 years of age
2. Chronic knee pain (minimum 6 months duration) with VAS score ≥4/10
3. Predominant knee pain
4. Reporting low mood, high anxiety or pain catastrophizing with scores above population average in one of three domains (mood, anxiety, PCS)
5. Able to accommodate the study visits without disruption to their jobs or other responsibilities
6. Able to come for the study visits without experiencing excessive physical strain or other distress.
7. Able to consent
8. No contraindication to MRI
9. No contraindication to TMS
10. Must be free from major medical or neurological conditions unrelated to the pain condition

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 21/08/2023:
1. Contraindication to MRI and TMS
2. Major medical or neurological conditions unrelated to the pain condition
3. Scheduled for total knee replacement surgery (TKR) within 1 month of study visits or other considerable treatment change
4. Change in pain medication in the past four weeks
5. On centrally active medication other than stable antidepressants or on opioidergic analgesic treatment
6. On medication, alcohol or recreational drugs thought to increase risk of seizure and/or syncope
7. Experiencing frequent headaches

Previous exclusion criteria from 01/06/2023 to 21/08/2023:
1. Contraindication to MRI or contraindication to TMS
2. Major medical or neurological conditions unrelated to the pain condition
3. Scheduled for total knee replacement surgery (TKR) within 1 month of study visits or other considerable treatment change
4. Unstable pain medication over the past 4 weeks, or on centrally active medication other than stable antidepressants or on opioidergic analgesic treatment
5. Patients on medication, alcohol or recreational drugs, thought to increase risk of seizure and /or syncope
6. Patients experiencing frequent headaches

Previous exclusion criteria:
1. Scheduled for total knee replacement surgery (TKR) within 1 month of study visits or other considerable treatment change
2. Claustrophobia
3. Safety concerns regarding TMS or MRI
4. Unstable pain medication over the past 4 weeks
5. Centrally active medication other than stable antidepressants or non-opioidergic analgesic treatment

Date of first enrolment
12/05/2022

Date of final enrolment
31/12/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Sponsor information

Organisation
University of Nottingham

ROR
https://ror.org/01ee9ar58

Funder(s)

Funder type
Charity

Funder Name
Versus Arthritis; Grant Codes: 20777

Alternative Name(s)
Arthritis UK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plan is guided by the principles of openness, transparency and protection of personal data in accordance with the NIHR policy documents. All data will be stored securely and will not be made available to the public. Data will be protected through the use of passwords, encryption, and other technical safeguards.

Access to and use of personal and medical data will be restricted, limiting content that will be accessed and individuals within the research team who have access to what is necessary to safely and effectively conduct the trial. Access to and use of research data collected as part of the research trial will be limited to individuals within the research team including additional collaborators compliant with the Ethics and sponsor's requirements. In addition, anonymised research data may be shared with researchers who are not affiliated with the research team subject to participants' consent and appropriate data-sharing agreement with the University of Nottingham.

Relevant information regarding protocols and research design of the study, data collection, and analysis will be made available in open-access publications and prospective statistical analysis plans will be shared using appropriate open repositories.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		10/03/2025	24/03/2025	Yes	No
Protocol article		16/10/2023	17/10/2023	Yes	No
HRA research summary			28/06/2023	No	No