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The effects of morphine treatment on functional brain scans in patients with chronic cough

Submission date
08/07/2025

Recruitment status
Not yet recruiting

Registration date
15/07/2025

Overall study status
Ongoing

Last Edited
23/01/2026

Condition category
Signs and Symptoms

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Refractory chronic cough (RCC) is a distressing condition defined as excessive coughing that lasts for more than 8 weeks with no underlying cause or does not respond to treatment of underlying conditions (e.g. asthma, gastro-oesophageal reflux). The causes of RCC are poorly understood, and specific, effective treatments are lacking. RCC is thought to be caused by heightened sensitivity of nerves in the airways and/or an impairment in the brain pathways that would normally control how much a person coughs (called descending inhibitory control pathways). One treatment currently used 'off-label' for RCC is the opioid painkiller morphine sulphate (MST), which can provide some relief and reduce coughing in RCC patients when taken at low doses. However, the mechanism by which MST reduces coughing is poorly understood. The study hypothesis is that MST partly regulates the descending inhibitory control pathways in chronic cough patients, which is a similar way to how MST relieves pain. Networks of the brain, including inhibitory control pathways, can be studied by scanning the brain using functional magnetic resonance imaging (fMRI). Recently, 50 baseline resting fMRI brain scans were performed in patients with RCC, which showed differences in brain network activity compared with healthy volunteers. This study aims to carry out fMRI brain scanning in RCC patients, before and after taking MST, to assess how the treatment influences brain networks and ultimately better understand the mechanisms involved in RCC. There will also be assessments of how changes in the brain relate to MST-related improvements in daily coughing.

Who can participate?
Patients with RCC at the North West specialist cough clinics, UK

What does the study involve?
Participants will attend six visits over a maximum of 23 days. The final visit will be a follow-up over the telephone. Procedures will include vital signs, breathing tests, urine tests, questionnaires, cough monitoring (to measure coughing), and fMRI brain scans.

What are the possible benefits and risks of participating?
There will be no immediate direct benefit to the participants taking part in this study. However,

it is hoped that the results will improve knowledge of the underlying mechanisms of chronic cough to ultimately better understand the condition and develop more effective treatment options in the future.

Participants will be made aware of any potential risks before enrolment, which are summarised as follows:
- fMRI scanning uses magnets, not radiation; therefore, there is no exposure risk. Other risks include the presence of metal elements on or inside the body and claustrophobia. Suitability for scanning will be screened before enrolment, and participants will be able to leave the scanner at any point they feel uncomfortable by pressing an alert button. There is also a small risk of incidental findings on the scan results. Such occurrences will be referred to a named medical radiologist for advice, and this will be followed up as appropriate, for example, with the participant's GP.
- Morphine treatment can cause some side effects such as constipation, upset stomach and drowsiness. However, a very low dose is being used in this study, and it is a controlled-release formulation, which does not usually cause side effects. Any side effects that do occur will be managed accordingly by the study physician(s).
- Ambulatory cough monitoring poses potential data protection and confidentiality risks as the device records all sounds made by the participant, including speech; therefore, sensitive or personal information may be captured. The recordings are handled and stored securely with limited access to the immediate research team. All staff who have access to the recordings are trained in information governance and data protection policies and are bound by strict confidentiality rules. This is explained to the participants at the point of enrolment.
- Adverse events will be recorded throughout the study, and any serious adverse events will be reported to the Sponsor within the specified timeframe.

Where is the study run from?
The study will be sponsored by the University of Manchester, UK. Visits will be carried out either at the Manchester Clinical Research Facility at Wythenshawe Hospital, the University of Manchester MRI scanning unit (Oxford Road, Manchester) or over the telephone. Participants will be recruited from specialist cough clinics at Manchester University NHS Foundation Trust (MFT) and Lancashire Teaching Hospitals NHS Foundation Trust (LTH).

When is the study starting and how long is it expected to run for?
January 2025 to January 2027

Who is funding the study?
The North West Lung Centre Charity, UK
The NIHR Manchester Biomedical Research Centre, UK

Who is the main contact?
Dr Rachel Dockry (Research Associate), University of Manchester, rachel.dockry@manchester.ac.uk

Contact information

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Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
356572

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Neural correlates of low dose opioid therapy in chronic cough

Acronym
NEUTRINO

Study objectives
Low-dose morphine treatment causes changes to resting state network connectivity in the brains of chronic cough patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 03/11/2025, North West - Preston Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; -; preston.rec@hra.nhs.uk), ref: 25/NW/0275

Study design
Single-centre observational prospective cross-sectional study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Refractory chronic cough

Interventions
Participants diagnosed with refractory chronic cough will be recruited from specialist chronic cough service clinics in Manchester and Preston. Screening tests will include physical examination, spirometry, urine pregnancy test, vital signs and scanning suitability questionnaires. Participants who pass screening and are enrolled will be treated with low-dose morphine therapy. The morphine will not be tested as an investigational medicinal product for efficacy, but will be used to study mechanistic changes to networks in the brains of chronic cough patients by performing functional magnetic resonance imaging (fMRI) scans. Questionnaires will be completed, and objective cough frequency will also be measured by ambulatory cough monitoring for correlation with the fMRI results. The measurements will be made prior to commencing morphine treatment and repeated following the treatment period.

Participants will attend 6 visits over a maximum period of 23 days. Visits will take place either at the Manchester Clinical Research Facility or the University of Manchester PET-MR scanning facility. Visit 6 is a follow-up phone call.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Morphine slow release (MST)

Primary outcome(s)
Changes in central nervous system (CNS) connectivity with low-dose morphine therapy measured by the blood-oxygen-level dependent (BOLD) signal using functional magnetic resonance imaging (fMRI), specifically the sensorimotor resting state network, the precuneus and the default mode resting state network following 6-8 days of low-dose morphine therapy

Key secondary outcome(s))
1. Changes in objective daytime cough frequency (coughs per hour), cough severity visual analogue scale (VAS), Leicester Cough Questionnaire (LCQ) score, and the Triggers and Sensations Provoking Cough (ToPIC) questionnaire score following 6-8 days of low-dose morphine therapy.
2. Correlations between the changes in CNS connectivity (as measured by BOLD signal) and changes in objective daytime cough frequency per hour following 6-8 days of low-dose morphine therapy, reported cough severity VAS and measures of expectation.
3. Correlations between resting state network activity (as measured by BOLD activity) and changes in daytime cough frequency following 6-8 days of low-dose morphine treatment, reported cough severity, ToPIC score and measures of expectation.
4. Changes in cerebral blood flow following 6-8 days of low-dose morphine therapy as measured by arterial spin labelling (ASL) fMRI methods.

Completion date
01/01/2027

Eligibility

Key inclusion criteria
1. Males and females aged 18-80 years inclusive
2. Non-smokers and ex-smokers with <20 pack years smoking history and >6 months abstinence
3. Diagnosis of refractory chronic cough (RCC) as per guidelines
4. Right-handedness
5. No substantial abnormalities on chest radiograph or CT scan of the thorax in the 5 years prior, which, in the opinion of the investigator, may have contributed to chronic cough
6. No evidence of lung disease, which may contribute to chronic cough (including COPD and asthma)
7. Normal spirometry; forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) predicted values ≥70% and FEV1/FVC ratio of ≥70%

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit

80 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Taking any medications likely to alter cough (including ACE inhibitors) within 2 weeks of enrolment
2. Pregnant/breastfeeding
3. Significant change in pulmonary status or respiratory tract infection within the prior 4 weeks
4. Contraindications to fMRI scanning (e.g. metal plates, claustrophobia)
5. Previous opiate or pharmacological anti-tussive therapy use
6. Chronic pain/taking regular analgesia (if using as required, must be able to omit for the duration of the study)
7. Previous stroke and diagnosis of dementia
8. Other severe, acute, or chronic medical or psychiatric conditions that may increase the risk associated with trial participation or may interfere with the interpretation of trial results

Date of first enrolment
16/02/2026

Date of final enrolment
31/10/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
North West Lung Research Centre
Wythenshawe Hospital
Southmoor Road
Manchester
England
M23 9LT

Study participating centre
Royal Preston Hospital
Sharoe Green Lane

Preston
England
PR2 9HT

Study participating centre
University of Manchester PET-MR Imaging Unit
Oxford Road
Manchester
England
M13 9PT

Sponsor information

Organisation
University of Manchester

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Charity

Funder Name
North West Lung Centre Charity

Funder Name
Manchester Biomedical Research Centre

Alternative Name(s)
NIHR Manchester Biomedical Research Centre, Manchester BRC, NIHR Manchester BRC, NIHR Manchester Biomedical Research Unit, Manchester NIHR BRC, Manchester NIHR Biomedical Research Centre, Biomedical Research Centre, BRC, NIHR BRC

Funding Body Type
Government organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available