ISRCTN88737146 https://doi.org/10.1186/ISRCTN88737146

Are there differences in central nervous system processing in patients with refractory chronic cough?

Submission date 28/11/2018	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 10/12/2018	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 25/06/2024	**Condition category** Respiratory	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Cough is one of the most common conditions for which treatment is sought, but treatment options are very limited. Some people experience chronic cough, which persists despite attempts to treat. This can be very distressing and disruptive to sufferers. It is suspected that these patients suffer from a hyper-sensitivity of the cough reflex, affecting the nerves either in the peripheral or central nervous system (CNS). Some drugs which act on the CNS have been shown to reduce cough in some patients, but not all. The aim of this study is to investigate the CNS by comparing brain activity in chronic cough patient to that of healthy volunteers. Resting-state functional magnetic resonance scanning (fMRI) is used to look at which areas of the brain interact with each other in chronic cough and if this differs from activity seen in healthy volunteers.

Who can participate?
Healthy volunteers and chronic cough patients, aged between 18 and 80

What does the study involve?
The study involves two visits for healthy volunteers and three visits for cough patients. Participants are asked to complete some questionnaires about cough and other symptoms they may experience. Their blood pressure, heart rate and oxygen saturation are measured, as are their height and weight. A blood sample and urine sample are taken. Chronic cough patients are asked to wear a cough monitor - a device which records the number of times they cough in 24 hours. This visit takes place at Wythenshawe Hospital, Manchester. All volunteers are asked to complete a cough challenge at Wythenshawe Hospital. This involves inhaling different concentrations of saline which can cause cough. The challenge is stopped when the participant has reached the maximum dose that they can tolerate. Chronic cough patients are asked to complete this after the 24-hour cough monitoring period. Healthy volunteers can complete the challenge as part of the screening visit. Volunteers are asked to attend a visit at the PET-MR unit at St Mary's Hospital, Manchester. A resting-state fMRI scan is carried out. This involves lying in an MRI scanner for 20 minutes, split over two 10-minute sessions, and relaxing without falling to sleep. While the participant is being scanned, their breathing rate and depth are measured using

a respiratory band around the chest, their heart rate is measured, and their blood oxygen levels are measured using a clip on their finger. Their exhaled carbon dioxide is also measured. The day after the scan, the researcher calls the volunteer to make sure that they are well after taking part in the study.

What are the possible benefits and risks of participating?
There are no benefits of participating in the study. All of the research methods have been used many times and only carry minimal risks. Giving a blood sample may be uncomfortable and might leave a small bruise.

Where is the study run from?
Wythenshawe Hospital (UK)

When is the study starting and how long is it expected to run for?
February 2017 to September 2022

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Rachel Dockry
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Contact information

Type(s)
Scientific

Contact name
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Type(s)
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
258150

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
18/CoCen/001, 207504/B/17/Z, IRAS 258150

Study information

Scientific Title
Are there differences in central nervous system processing in patients with refractory chronic cough?

Acronym
Cough Central

Study objectives
Patients suffering from chronic treatment-refractory cough have different brain activity than seen in healthy volunteers.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/03/2019, North West - Greater Manchester West Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ; 0207 104 8021; nrescommittee.northwest-gmwest@nhs.net), ref: 19/NW/0105

Study design
Observational case-control study

Primary study design
Observational

Secondary study design

Case-control study

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet

Health condition(s) or problem(s) studied
Chronic cough

Interventions
Volunteers will be asked to attend a screening visit to determine eligibility for the study. Here their medical history and demographics will be recorded; their blood pressure and heart rate will be measured; and their height and weight will be measured. The volunteer will be asked to complete some questionnaires and perform a spirometry test. If the results of all of these tests show that the subject is suitable, the chronic cough patients will be asked to wear a cough monitor to record their coughing for 24 hours. After the completion of the cough monitoring period, the patient will be asked to return to the clinical trials unit to complete a cough challenge. Healthy volunteers will be asked to complete the cough challenge as part of the screening visit.

A cough challenge involves inhaling increasing doses of an agent which may make the volunteer want to cough. In this case, we are using hypotonic saline. The test continues until the volunteer reached their maximum tolerated dose of saline. Spirometry is performed both before and after the challenge test as a safety precaution.

The final visit involves an MRI scan of the brain. This visit will take around 35 minute and involves the participant lying in the scanner and thinking about nothing for two sessions, 10 minutes each. Whilst in the scanner the volunteers will have their breathing rate measured by a band about their chest, their heart rate and blood oxygen saturation measured by a finger clip and their exhaled carbon dioxide measured by a tube which sits under their nose.

Intervention Type
Other

Primary outcome measure
Brain connectivity assessed using an fMRI scan at the final visit

Secondary outcome measures
All outcomes are only measured once (baseline):
1. Cough frequency, recorded by an ambulatory cough monitor
2. Cough reflex sensitivity, as determined by a cough challenge
3. The impact of cough on daily life and activities, measured using the Cough Quality of Life Questionnaire (CQLQ)
4. Depression, measured using The Centre for Epidemiological Studies depression scale (CED-S)
5. Interoception, measured using The Multidimensional Assessment of Interceptive Awareness (MAIA)

Overall study start date
28/02/2017

Completion date
09/09/2022

Eligibility

Key inclusion criteria
1. Males and females 18-80 years, inclusive
2. Non-smokers >6 months; ex-smokers <20 pack years

Healthy Volunteers
3. No clinically relevant abnormalities based on the medical history, physical examination, vital signs
4. No history of current or significant past respiratory disease, specifically a diagnosis of asthma
5. Spirometry within normal limits

Chronic Cough Patients
6. Have a refractory chronic cough as defined by BTS guidelines
7. No evidence of asthma

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
70: 20 healthy volunteers and 50 chronic cough patients

Total final enrolment
74

Key exclusion criteria
1. Routine contraindications to fMRI scanning e.g. certain metal implants, recent surgery, extreme claustrophobia etc
2. Any condition that may increase airway/circulating levels of ATP/adenosine e.g. chronic cardiac failure, chronic hypoxia, vigorous exercise within 48 hours
3. Pregnant or breastfeeding
4. Upper or lower respiratory tract infection or significant change in pulmonary status within 4

weeks of enrolment
5. Any therapy that may modulate cough (e.g. ACE inhibitors, opioids, gabapentin). Patients can be included if they are willing/able to discontinue these for the study duration and a suitable washout period

Date of first enrolment
01/02/2020

Date of final enrolment
02/09/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
MFT Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Sponsor information

Organisation
Wythenshawe Hospital Research and Development Directorate

Sponsor details
Manchester University NHS Foundation Trust
Southmoor Road
Manchester
United Kingdom
M23 QZ

Sponsor type
Hospital/treatment centre

Website
www.researchdirectorate.org.uk

ROR

https://ror.org/05vpsdj37

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The trialists plan to publish the results of this study in leading peer-reviewed journals. They may also present the data at conferences. They will also publish their results in our newsletter 'Cough in Focus' to distribute to the study participants and other patient who are interested in our research.

Intention to publish date
30/06/2025

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No