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Mechanisms of chronic pain and fatigue

Submission date
04/09/2017

Recruitment status
No longer recruiting

Registration date
19/09/2017

Overall study status
Completed

Last Edited
11/10/2023

Condition category
Musculoskeletal Diseases

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Fibromyalgia is a musculoskeletal condition affecting around 5% of the UK population. Patients often experience pain with tiredness (fatigue) and clouded thoughts ('fibro-fog'), which can stop them from enjoying a normal active life. As a result, patients with fibromyalgia have significantly lower quality of life than the general population and even patients with other musculoskeletal conditions, including rheumatoid arthritis. Despite its prevalence, fibromyalgia remains poorly recognized and understood, by doctors and patients alike. Medical test show that patients with fibromyalgia may have problems with their bodies own arousal 'fight and flight' response to stress. Furthermore, there is evidence to suggest that inflammatory responses may be abnormal in fibromyalgia, and patients may be more sensitive to inflammation. The aim of this study is to understand how the body and brain affect each other to cause pain and fatigue in fibromyalgia. First, this study will investigate how pain and fatigue change when the flight and fight nervous system is activated by a mild inflammatory challenge, lying in a tilted position. Second, we will induce a mild state of inflammation using a routine clinical Typhoid vaccination, and use brain scanning to measure differences in brain structure and function (with blood markers) between people with pain and/or fatigue, and healthy people. The detailed insights obtained from this work will help improve doctor-patient communication, reduce stigma and improve patient experience. This research has great potential to identify mechanisms of pain and fatigue in fibromyalgia and therefore in the longer term may lead to better interventions to improve quality of life and inform further research toward treatments and cures for the disorder.

Who can participate?
1. Adults aged 18 or over, who have a diagnosis of Fibromyalgia and/or ME/Chronic Fatigue Syndrome.
2. Healthy adults (aged 18 or over) with no history of fibromyalgia and/or ME/Chronic Fatigue Syndrome.

What does the study involve?
The study involves three visits on separate occasions. Each visit lasts approximately three hours and includes breaks. The first visit involves measuring heart rate and blood pressure. The other two visits involve going in the brain scanner and receiving a Typhoid injection or placebo (a dummy medication) which are randomised between visits. All study visits involve blood tests, questionnaires and performing some simple tasks.

What are the possible benefits and risks of participating?
There are no direct benefits to participants for their participation in this study. However, receiving a free Typhoid vaccination would be beneficial to any participants that plan to travel abroad to a country for which this vaccination is required. Although this research may not directly benefit the participant, it could result in a better understanding of the biological bases of chronic pain and fatigue and help Fibromyalgia and ME/Chronic Fatigue Syndrome and inform new treatments. There are no direct risks to taking part. All procedures (blood sampling, tilt table, typhoid vaccination injection, and MRI brain scanning) are safe and routinely used in clinical care. At all study visits at both sites a medical doctor will be on site at all times.

Where is the study run from?
The first study visit takes place at the Clinical Investigation and Research Unit at Royal Sussex County Hospital (UK). The other two study visits take place at the Clinical Imaging Sciences Centre at Brighton and Sussex Medical School at The University of Sussex (UK).

When is the study starting and how long is it expected to run for?
February 2015 to March 2019

Who is funding the study?
Arthritis Research UK (UK)

Who is the main contact?
Dr Jessica Eccles
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Study website
N/A

Contact information

Type(s)
Public

Contact name
Dr Jessica Eccles

Contact details
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
34733, IRAS

Study information

Scientific Title
Viscero-sensory processes and neural responses to inflammation: mechanisms of pain and fatigue in fibromyalgia

Study objectives
The main aim of the project is to investigate how viscero-sensory processes and neural responses to inflammation may contribute to pain and fatigue in fibromyalgia.

Hypotheses:
1. That patients with fibromyalgia with both pain and fatigue will exhibit different but overlapping symptom profiles compared to patients with fibromyalgia without fatigue and patients who have fatigue but not pain and healthy controls
2. That pain and fatigue symptoms will correlate with markers of peripheral inflammation and quality of life measurements in patients with fibromyalgia
3. That patients with fibromyalgia will show differentially altered pain sensitivity, interoceptive and cognitive profiles (including attention and fatigue) when under sympathetically mediated challenge, demonstrating the role of viscero-sensory processes in underlying pain and fatigue
4. Correlation between qMT parameters and fatigue and pain ratings as well as a correlations between qMT parameters and autonomic and interoceptive indices

Ethics approval required
Old ethics approval format

Ethics approval(s)
London-Brighton & Sussex Research Ethics Committee, 18/08/2017, ref: 17.LO.0845

Study design
Non-randomised; Interventional; Design type: Prevention, Vaccine, Imaging, Psychological & Behavioural

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Specialty: Musculoskeletal disorders, Primary sub-specialty: Musculoskeletal Pain Disorders; UKCRC code/ Disease: Musculoskeletal/ Other soft tissue disorders

Interventions
The study recruits hundred people in total: 25 patients with pain-prominent disease (from fibromyalgia populations), 25 patients with fatigue-prominent disease (from ME/Chronic Fatigue Syndrome populations), 25 patients with both pain and fatigue (from fibromyalgia and ME /Chronic Fatigue Syndrome populations), and 25 healthy participants).

Participants are asked to attend three study visits lasting between 2.5 and 4 hours each. The first study visit always involves a sympathetic challenge (head up tilt). For study visit two and three, participants are randomised using a computer algorithm, to either receive a typhoid injection (inflammatory challenge) or a saline (placebo/dummy) injection and will involve going in the brain scanner.

Intervention Type
Other

Primary outcome measure
The effects of a systemic inflammatory challenge (typhoid injection) on human brain microstructure is measured using quantitative magnetization transfer (qMT) imaging at visit two or visit three (randomized).

Secondary outcome measures
1. Pain is measured using a Pain Visual Analogue Scale before and after the intervention at visit 1, 2, and 3
2. Fatigue is measured using a Fatigue Severity Scale before and after the intervention at visit 1, 2, and 3
3. Quality of life is measured using the 36-Item Short Form Survey (SF-36) at baseline at visit 1
4. Depression and anxiety is measured using the MINI diagnostic criteria at visit 1
5. Heart rate and blood pressure is measured using a non-invasive blood monitor during the autonomic function test at visit 1
6. Inflammatory markers are measured using blood tests at baseline at visit 1 and before and after the intervention at visit 2 and 3
7. Pressure Pain Thresholds are measured using an algometer before and after the intervention at visit 1, 2, and 3
8. Autonomic symptoms score is measured using the Autonomic Symptoms and Quality of Life Score at baseline
9. Cognition is measured using a Working Memory Assessment (subscale of WAIS-III) before and after the intervention at visit 1 and is measured using a short STROOP task at visit 2 and 3
10. Interoceptive function is measured using an interoceptive accuracy task (mental tracking) before and after the intervention at visit 1, 2, and 3
11. BOLD signal during fMRI is measured using a 3T scanner at visit 2 and 3.

Overall study start date
01/02/2015

Completion date
31/03/2019

Eligibility

Key inclusion criteria
1. Participants must be capable of giving informed consent
2. All participants must be aged 18 or over
3. Healthy controls – free from major medical or psychiatric illness
4. Patients – meet diagnostic criteria for Fibromyalgia and/or ME/Chronic Fatigue Syndrome; they will then be stratified into the above groups

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 100; UK Sample Size: 100

Total final enrolment
105

Key exclusion criteria
All participants:
1. Not able to give informed consent
2. Age under 18
3. Needle phobia
4. MRI incompatibility
5. Presence of metal work (e.g pacemaker) in body
7. Claustrophobia
8. Inability to lie still for one hour
9. Pregnancy
10. Previous adverse reaction to Typhoid Vaccination

Healthy controls:
Major medical or psychiatric illness

Patient participants:
Major neurological illness

Date of first enrolment
20/09/2017

Date of final enrolment
02/11/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Sussex
BSMS
Clinical Imaging Sciences Centre (CISC),
Falmer
Brighton
United Kingdom
BN1 9RR

Study participating centre
Royal Alexandra Children's Hospital
Clinical Investigation and Research Unit (CIRU)
Level 10
Eastern Road
Brighton
United Kingdom
BN2 5BE

Sponsor information

Organisation
Brighton and Sussex University Hospitals NHS Trust

Sponsor details
Royal Sussex County Hospital
Eastern Road
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BN2 5BE

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Sponsor type
Hospital/treatment centre

Funder(s)

Funder type
Government

Funder Name
Arthritis Research UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Findings will be presented at conferences and to patient audiences with planned publication in high-impact peer-reviewed journals.

Intention to publish date
31/03/2021

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?
Participant information	version V2	09/06	19/09	No	Yes

sheet		/2017	/2017		
Participant information sheet	version V2	09/06 /2017	19/09 /2017	No	Yes
Preprint results	non-peer-reviewed results in preprint	23/02 /2020		No	No
Other publications	Beyond bones: The relevance of variants of connective tissue (hypermobility) to fibromyalgia, ME/CFS and controversies surrounding diagnostic classification: an observational study	01/01 /2021	11/10 /2023	Yes	No