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Brain response to light stimulation in people with myalgic encephalomyelitis/chronic fatigue syndrome

Submission date
12/11/2025

Recruitment status
No longer recruiting

Registration date
21/11/2025

Overall study status
Completed

Last Edited
18/11/2025

Condition category
Nervous System Diseases

[ ] 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
Literature suggests that impairments in cellular energy processes involving mitochondria may play an important role in the pathophysiology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). A marker for this is the accumulation of a biochemical called lactate, resulting from the mitochondria not being able to use lactate as the energy source, or cellular respiration switching from normal oxidative mechanisms to another process, glycolysis, whose waste product is lactate.
Using magnetic resonance spectroscopy (MRS), it is possible to measure lactate in the brain. Our pilot MRS study showed an overall increase in lactate in the anterior cingulate cortex (ACC) in people with ME/CFS compared with healthy controls. Studies in people with ME/CFS, however, lack replication; also, the results usually show much overlap between the lactate levels in ME /CFS patients and healthy controls.

One possible explanation for this overlap is that neural systems compensate at rest, while the capacity for compensation is exceeded during physiological challenge; thus, during physiological challenge, the differences between ME/CFS patients and healthy controls may become much more pronounced. This would mirror clinical changes in patients with ME/CFS, who may feel comfortable at rest but even simple physical/cognitive challenges (such as reading) may rapidly lead to exhaustion.

The research team recently developed a functional MRS (fMRS) approach, where MRS is used to measure lactate concentrations in the visual cortex during rest and stimulation with flashing light. This method is safe and requires minimal active effort as participants are simply asked to look at the flashing checkerboard for a few minutes; hence, this can be easily applied in patient populations. This study aims to 1) replicate those findings of increased lactate concentration in the ACC of ME/CFS patients compared to healthy controls, and to 2) apply the above-described fMRS method to explore differences between ME/CFS patients and healthy controls during activation with flashing lights. It is expected that the difference during activation will be more pronounced than at rest.

Who can participate?
Adult patients with ME/CFS and healthy control volunteers.

What does the study involve?
The study involves a screening assessment that can be done either in person or remotely through a video or telephone call, and one in-person visit at the John Radcliffe Hospital in Oxford. During this visit, participants will have an MRI scan (about 1.5 hours) and will be asked to fill out questionnaires asking about their symptoms. Testing will take about 2 hours.

What are the possible benefits and risks of participating?
While there are no individual benefits from participating in the study, if there is a difference between people with ME/CFS and healthy participants, this could guide the search for biomarkers for ME/CFS and facilitate thinking about therapeutic approaches.

Possible risks of participating:
• Clinical Interview
Sometimes, clinical interviews during the screening session can ask for information that might be potentially upsetting (for example, information about mood). All clinical assessments will be performed by a trained researcher who can provide adequate information and treat any sensitive issues with care. Participants will be under no obligation to answer the questions if they make them uncomfortable.

• MRI/MRS
MRI is safe and does not involve any ionising radiation (x-rays). However, because it uses a large magnet to work, MRI scans are not suitable for everybody. Participants will be asked to answer some safety questions to determine if they can take part. For example, people with a heart pacemaker or stent, a mechanical heart valve, mechanical implants such as an aneurysm clip, joint replacement (e.g. hip/knee), or with other pieces of metal that have accidentally entered the body, cannot be scanned.

While there is no evidence that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. The study does not routinely test for pregnancy, so if a participant thinks they may be pregnant, they should not take part in this research.

While very rare, tattoos can occasionally warm up in the scanner. As a safety measure, people with tattoos above their shoulders will be excluded, as this is too close to the head. People should not take part in a scan until 48 hours after receiving the new tattoo.

The enclosed space of the scanner can induce feelings of claustrophobia. People who declare they suffer from claustrophobia will be excluded. All operators and radiographers are accustomed to dealing with participants who may be claustrophobic and have a variety of strategies to employ with people who exhibit feelings of claustrophobia but who still wish to participate in the study.

Comfort: As certain MRI sequences can be very noisy so participants will be given earplugs. Lying on the scanner table for prolonged periods can induce lower back pain. This will be minimised by means of comfortable padding and positioning.

Participants will be introduced carefully to the scanner and allowed to leave at any stage. Whilst in the scanner, they will have a call button, which they can press if they need to stop the scan or speak with the person operating the scanner.

It is important to note that the scans will not be carried out for diagnostic purposes, only for research. The scans are not routinely looked at by a doctor and are therefore not a substitute for a doctor's appointment. Occasionally, however, a possible abnormality may be detected. In this case, the study team would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, participants would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information will be kept strictly confidential.

• Flickering Checkerboard Stimulation
This visual stimulation is a succession of alternating black and white squares on a small monitor in the scanner; the black and white checkerboard creates the effect of flickering lights. It is not a harmful or painful stimulus. However, it is important to exclude participants who have a history of epilepsy as the flickering produced by the checkerboard may be intense enough to induce an epileptic seizure. There is a small possibility that the visual stimulation could also evoke a mild headache, and as such, participants are given the option to stop the flickering checkerboard at any moment during the scan by squeezing the call button. For this reason, individuals who suffer from photosensitive migraines will also be excluded. Any effect would be temporary and should rapidly fade once the monitor is turned off. This flickering checkerboard stimulation has been used in many previous research studies and has not been harmful to the participant.

Where is the study run from?
Department of Psychiatry, University of Oxford, UK.

When is the study starting and how long is it expected to run for?
September 2024 to December 2025

Who is funding the study?
Medical Research Council, UK

Who is the main contact?
Dr Beata Godlewska, beata.godlewska@psych.ox.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Study information

Scientific Title
Lactate response to light stimulation in people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Acronym
OxLac

Study objectives
1. Apply fMRS to explore differences in lactete concentrations between ME/CFS patients and healthy controls during activation with flashing lights; we expect the difference during activation will be more pronounced than at rest;
2. Replicate our previous finding of increased lactate concentration in the ACC of ME/CFS patients compared to healthy controls (doi: 10.1038/s41380-025-03108-8).

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/08/2024, Medical Sciences Interdivisional Research Ethics Committee (Research Services, Boundary Brook House, Churchill Drive, Oxford, OX3 7GB, United Kingdom; +44(0)1865 616575; ethics@medsci.ox.ac.uk), ref: R93723/RE001

Study design
Single-centre observational cross-sectional cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Interventions
Participants undergo an MRI scan, which allows the measurement of lactate. During this scan, they undergo a simple task, which includes looking at the flickering checkerboard for 7.5 min; this is preceded and followed by 11 min of rest with eyes closed. Participants are also asked to fill out a number of questionnaires to collect information about their symptoms.

Intervention Type
Mixed

Primary outcome(s)
1. Lactate concentration in the occipital cortex measured using functional magnetic resonance spectroscopy (fMRS) at baseline and after stimulation with a flashing checkerboard

Change in lactate concentration in the occipital cortex from basline to stimulation with flashing checkeboard using functional MRS - ME/CFS patients compared to healthy controls.

Key secondary outcome(s))
1. Resting lactate concentration in the anterior cingulate cortex measured using magnetic resonance spectroscopy (MRS) at baseline

Resting lactate concentration in the anterior cingulate cortex measured with MRS - ME/CFS patients compared to healthy controls.

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Males or females aged 18 years or over
2. Willing and able to give informed consent to participate in the study
3. Diagnosis of DSM-V major depression based on the affective disorder sections of the SCID-5. N.b. comorbid anxiety disorder is not an exclusion criterion
4. Quick Inventory of Depressive Symptomatology self-report version (QIDS-SR16) score >10 (moderate, severe or very severe depression)
5. Currently taking an antidepressant medication and on a stable dose of an antidepressant for at least 4 weeks
6. A lack of response to at least two antidepressants at therapeutic doses (based on Maudsley Prescribing Guidelines and/or British National Formulary) in the current episode (including the current one)
7. An indication for a change in treatment
8. Willing to continue antidepressant treatment
9. Having access to a smartphone
10. Women of child-bearing potential (WOCBP) only – a negative urine pregnancy test result

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
18 years

Upper age limit
99 years

Sex
All

Total final enrolment
49

Key exclusion criteria
1. Clinical diagnosis of current or previous psychosis (including psychotic depression), bipolar disorder or Parkinson's Disease
2. Currently taking an antipsychotic medication
3. Clinically significant current or previous impulse control difficulties
4. Serious suicide or homicide risk
5. Current treatment with any medication known to interfere with pramipexole metabolism including cimetidine, memantine and methyldopa
6. Contraindications to pramipexole including history of or current treatment for glaucoma or retinal degeneration, significant, symptomatic cardiovascular or renal disease or significant, symptomatic orthostatic hypotension
7. Previous course of pramipexole (>2 weeks)
8. Untreated or unstable medical condition which, in the judgement of the investigator, could interfere with the safety of receiving pramipexole or ability to complete the study
9. Pregnancy, breast-feeding or planning pregnancy
10. WOCBP not willing to use effective contraception
11. Male participants not willing to refrain from donating sperm
12. Planning to start other mental health treatments or psychotherapy started in past 4 weeks or planned to start within next 12 weeks
13. Participants will be excluded if they participated in a psychological or medical study involving the same reward processing tasks within the last 3 months.

Date of first enrolment
23/09/2024

Date of final enrolment
27/10/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
University Offices
Oxford
England
OX1 2JD

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Not defined

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be available upon request from Dr Beata Godlewska, beata.godleska@psych.ox.ac.uk. The data will include MRI data (in particular MRS data). Participants' consent to sharing data was acquired. The data will be shared in anonymised form.

IPD sharing plan summary
Available on request