ISRCTN13121654 https://doi.org/10.1186/ISRCTN13121654

A multidimensional approach to pain in rheumatoid arthritis to understand sex differences using functional brain imaging and joint ultrasound

Submission date
18/11/2025

Recruitment status
Recruiting

Registration date
24/03/2026

Overall study status
Ongoing

Last Edited
24/03/2026

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
This study is about understanding why many people with Rheumatoid Arthritis (RA) continue to feel pain even when their inflammation is under control, especially women, who often report more severe and long-lasting pain than men. RA is an autoimmune disease that causes joint inflammation, stiffness, and pain. Doctors usually monitor RA using a checklist that combines joint exams, blood tests, and how the patient feels. But sometimes, this checklist doesn't explain why a patient is still in pain.
We want to explore whether the ongoing pain is caused by joint inflammation or if it's more about how the brain processes pain. They will use two advanced tools: musculoskeletal ultrasound (MSUS), which can see inflammation in the joints, and functional MRI (fMRI), which shows how the brain reacts to pain.
The study will compare brain responses in men and women with RA when mild pressure is applied to their painful and non-painful joints. They'll also look at whether patients have fibromyalgia, a condition that causes widespread pain and might affect how the brain processes pain.
The goal is to find out if men and women with RA experience and process pain differently, and whether this difference is linked to joint inflammation, brain activity, or both. Understanding this could help doctors personalize treatment better, especially for patients whose pain doesn't match what the typical RA tests show.

Who can participate?
Adult patients (≥18 years) having RA fulfilling the 2010 ACR/EULAR classification criteria (21) with Moderate-to-high disease activity according to DAS28ESR (22) and Tenderness and swelling in any metacarpophalangeal joint in the right hand

What does the study involve?
Ultrasound , fMRI procedure of the brain and application of mild pressure using a vector-adjusted vascular cuff. Questionnaires (HAQ, McGill Pain Questionnaire, Widespread Pain Index, Symptom Severity Scale, and Polysymptomatic Distress (PSD) Score)

What are the possible benefits and risks of participating?
There are no direct benefits for participants. There should be no long term risks from participating in this study. Potential risks from fMRI include discomfort from claustrophobia, loud noises, and prolonged stillness.

Where is the study run from?
Riverside Rheumatology Clinic, The Ottawa Hospital, Ottawa, ON.

When is the study starting and how long is it expected to run for?
March 2026 to December 2027

Who is funding the study?
The Ottawa Hospital, Department of Medicine and Division of Rheumatology (Canada)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Study information

Scientific Title
A multidimensional approach to pain in rheumatoid arthritis to understand sex differences using functional brain imaging and joint ultrasound

Study objectives
Primary Objective: To compare fMRI features in female vs male RA patients with similar disease activities in resting state and after pain induction.

Secondary objectives: To compare fMRI features in female vs male RA patients with or without objective features of inflammation in the US on resting state and after pain induction. To compare fMRI features in female vs male RA patients with or without fibromyalgia in resting state and after pain induction.
Exploratory objective: To test whether baseline fMRI findings differentiate the good clinical response to a biologic therapy (subgroup analysis), To understand the prevalence of the sex and gender disparities in our patient population to inform future research.

Ethics approval required
Ethics approval required

Ethics approval(s)
submitted 28/10/2025, OHSN-REB (Ottawa Hospital, Civic Campus 725 Parkdale Avenue, LOEB Building, Civic Box 675, Ottawa, ON, K1Y 4E9, Canada; +1 6137378899; REBAdministration@ohri.ca), ref: 20250429-01H

Study design
Single-centre prospective interventional study

Primary study design
Interventional

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Rheumatoid arthritis

Interventions
Ultrasound: We will perform the MSUS on the same day of the clinical assessment, the sonographer being blinded to all the clinical data. The US will be performed for the metacarpophalangeal (MCP) joints (2nd-5th) from the dorsal view. This would take 15-20 minutes.

fMRI procedure of the brain and application of mild pressure using a vector-adjusted vascular cuff: The fMRI procedure will take approximately 45-60 minutes to complete

Questionnaires (HAQ, McGill Pain Questionnaire, Widespread Pain Index, Symptom Severity Scale, and Polysymptomatic Distress (PSD) Score): Completion would take about 10 mins

Follow-up: A 3-month follow-up would be conducted only if the participant starts a new biologic therapy.

Intervention Type
Other

Primary outcome(s)
Biological sex of the patients will be used to categorize them as males and females to compare fMRI features in female vs male RA patients with similar disease activities, on resting state and after pain induction.

Key secondary outcome(s))
1. Fibromyalgia diagnosis will be based on the Widespread Pain Index (score ≥4 categorized as fibromyalgia).
2.US positivity will be based on the cut-off of grade≥2 synovitis and Doppler signals:
-US positive if they have at least one MCP joint with grade≥2 synovitis and Doppler signals;
-The US is negative if they do not have any MCP joints with grade≥2 synovitis and Doppler signals.
-The joint that will be exposed to pain stimulation during the fMRI will be the joint that has the highest degree of US inflammation (for US-positive patients) or the most tender joint (US-negative patients). In the case of more than one MCP joint with similar features, the 2nd MCP joint will be used.

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Adult patients (≥18 years) having RA fulfilling the 2010 ACR/EULAR classification criteria (21)
2. Moderate-to-high disease activity according to DAS28ESR (22)
3. Tenderness and swelling in any metacarpophalangeal joint in the right hand

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
99 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Pregnancy (current or planned within the study period) or breastfeeding;
2. Inability to give informed consent,
3. Failure to communicate verbal or written responses to questionnaires;
4. >7.5 mg/day of prednisone (or equivalent) used two weeks before the baseline visit;
5. The presence of contraindications for MRI, such as magnetic prosthesis in the body;
6. Use of medications that can alter brain activity or known psychiatric diseases that can alter

brain activity (23).
7. Swelling in both hands will not constitute an exclusion criterion; however, patients with pain and swelling in the right hand will be included, and the most painful joint in the right hand will be selected for pain stimulation.

Date of first enrolment
01/03/2026

Date of final enrolment
31/12/2027

Locations

Countries of recruitment
Canada

Study participating centre
The Ottawa Hospital Research Institute
1967 Riverside Dr.
Room 6-25
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Sponsor information

Organisation
The Ottawa Hospital Research Institute

Funder(s)

Funder type
Not defined

Funder Name
The Ottawa Hospital

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		22/10/2025	03/12/2025	No	No