A Multidimensional Approach to Pain in Rheumatoid Arthritis to understand sex differences using Functional Brain Imaging and Joint Ultrasound

Project Team Description

Name	Role	Affiliation
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Lara Russo	Collaborator	Patient Research Partner

Abstract:

Background:
Rheumatoid Arthritis (RA) treatment guidelines suggest treating the disease to a target of remission according to composite clinical indices which use weighted combinations of variables, including tender and swollen joint counts, patient assessment of pain, patient global assessment of disease activity, and laboratory measure of acute phase response. Pain is a subjective experience that is of utmost importance to patients, yet nearly 40% of patients have residual pain, which can remain debilitating despite improved inflammatory synovitis. Women tend to have a more significant reported burden of pain, which can be more resistant to therapy. It is not entirely clear whether this is driven by local synovitis, central pain processing, or alternative psychosocial or societal influences. With the help of technology, we can ascend beyond composite clinical indices to investigate this problem further. With the use of bedside Musculoskeletal Ultrasound (MSUS), we can identify the presence or absence, as well as the severity of synovitis in the reported painful joint which is a first step in understanding whether ongoing synovial inflammation and secondary nociceptive pain signalling is playing an ongoing role in the pain experience. We can also use functional magnetic resonance imaging (fMRI) scanning to visualize real-time changes in cerebral activity between resting and post-pain stimulus states. We hope to determine whether there is a difference in cerebral activity following pain stimulus between male and female patients with RA and stratify based on whether the stimulus was applied to an inflamed or non-inflamed joint and understand the effect of fibromyalgia, an ordinary, widespread, centralized pain condition, has on this.
Hypothesis: We hypothesize that there will be sex-dependent differences in fMRI brain activity responses to painful stimuli between sexes and that these differences will remain across synovitis and fibromyalgia subgroups.
Primary Objective: To compare fMRI features in female vs male RA patients with similar disease activities, on 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 during resting state and after pain induction. To compare fMRI features in female vs male RA patients with or without fibromyalgia on resting state and after pain induction.

Exploratory objectives: 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.
Design: Prospective observational study with cross-sectional analysis of the primary and secondary objectives and a three-month follow-up analysis for the exploratory analysis.
Groups: Male and female patients with rheumatoid arthritis. Subgroups will be based on the presence or absence of at least one joint with at least moderate MSUS-detected synovitis in the right 2^{nd}-5^{th} Metacarpal Phalangeal (MCP) joints and the presence or absence of fibromyalgia according to the widespread pain index score.
Measurements:
Sex will be determined as "sex assigned at birth" and will be either male or female. *Gender* will be determined by patient-reported gender and will either be man, woman, or gender diverse. *Disease activity* will be measured using standard components of the Disease Activity Score – 28 joints (DAS28) and treatment response will be measured using the European League Against Rheumatism (EULAR) response (swollen joint count, tender joint count, physician global assessment visual analogue scale (VAS), HAQ, PGA VAS, pain (100 mm VAS). *Pain* will be assessed using the following questionnaires: 100 mm VAS with "no pain" and "pain as bad as it could be" as anchors, McGill Pain Questionnaire, Widespread Pain Index, Symptom Severity Scale, and Polysymptomatic Distress (PSD) Score. A single-blinded ultrasonographer will obtain MSUS images and will be scored for Grayscale synovitis and Power Doppler synovitis using The Global OMERACT-EULAR Synovitis Score (GLOESS) score by a second blinded sonographer. fMRI Regional homogeneity (ReHo) and fractional amplitude of low-frequency fluctuation (fALFF) change in resting state and after non-painful/pain stimuli will be recorded and blinded to the clinical features.

Research Proposal

1-) Background:

Rheumatoid Arthritis and Disease Activity Assessment:

Rheumatoid arthritis (RA) is the most common type of inflammatory arthritis and has many physical, mental, and social consequences (1). The composite clinical indices used to assess disease activity in RA are calculated through the weighted combinations of variables, including tender and swollen joint counts, patient assessment of pain, patient global assessment of disease activity, and laboratory measures of acute phase response. However, there are major limitations of the composite indices: a) Some of the patients' symptoms are independent of synovitis but affect clinical indices such as pain and fatigue, b) Tender joint counts are subjective and depend on patients' pain threshold, with comorbid fibromyalgia and/or osteoarthritis acting as confounders, c) Swollen joint counts may not show active synovitis in patients with longstanding inactive chronic synovitis. The limitations of the physical exam and clinical tools to accurately measure the inflammatory disease activity leave approximately half of the patients with moderate/high disease activity without treatment changes during the clinical encounter (2, 3).

Pain in Rheumatoid Arthritis:

Pain is the universal symptom of RA and impacts the patients' daily function and quality of life (4). Unfortunately, despite many advances, around 30-38% of RA patients describe residual pain even after the inflammatory pathways are well controlled (4, 5). As an "invisible symptom," pain is one of the leading causes of the discrepancies between patients' and physicians' global assessments of disease activity, ranging between 25-76% (6). Pain in RA is linked to multiple mechanisms. Inflammatory cytokines and mediators within the joints trigger peripheral pain through direct stimulation of the peripheral nociceptors and sensitization of the neurons within the nociceptive pathway. Sensitization also impacts the central nervous system, reducing inhibitory signaling and amplifying the response. Post-inflammatory joint damage can also cause pain even without ongoing inflammation (7). Determining the cause of the pain can be difficult with clinical examination alone, creating significant challenges in practice as the treatment approaches differ depending on the pain mechanism (8).

Sex differences in Rheumatoid arthritis

Sex differences in RA are significant and impact both the prevalence and progression of the disease. Women are about two to three times more likely than men to develop RA (9). Men, though less commonly affected, are more likely to have severe joint damage by the time of diagnosis (10). Symptoms also tend to manifest differently between sexes; women often experience more severe pain, fatigue, and disability, which can affect their quality of life and response to treatments (11). Women are reported to have higher pain intensity and lower pressure pain detection thresholds than men despite controlling for peripheral inflammation (assessed by swollen joint counts) and systemic inflammation (measured by C-reactive protein levels) (12). This sex-based variability suggests the need for more personalized approaches to RA management, considering biological, hormonal, and social factors that influence disease outcomes in men and women. This sex-based variability suggests that there is a need for better understanding and individualizing approaches to pain evaluation and management in RA.

Musculoskeletal Ultrasound to Understand Joint Inflammation:

Musculoskeletal Ultrasound (MSUS) is a non-invasive bedside imaging technique enabling the visualization of the joints and delineating active inflammatory synovitis from other processes. It is superior to physical examination in detecting the progression and risk of flares. Given its predictive and prognostic value, as a radiation-free patient-friendly modality, MSUS is an excellent supplement to clinical indices to assess disease activity (13, 14).

Functional magnetic resonance imaging to understand pain mechanisms:

Functional magnetic resonance imaging (fMRI) measures the changes in cerebral blood flow, allowing the understanding of how the brain responds to different triggers. It is increasingly used in experimental pain studies. In pain syndromes, fMRI studies are based on comparing activities of other brain regions in response to painful and non-painful stimuli and resting states. Some studies on the cerebral processing of pain in rheumatic diseases use fMRI as the primary outcome (15, 16). Sandstorm et al., demonstrated that

cerebral processing of pain with stimuli applied to unaffected joints in RA patients resembled healthy controls.
In contrast, differences in cerebral flow could be shown if the same stimuli are applied to the painful joints in RA. The same study also showed that the cerebral processing of pain depends on the pressure applied (16). In another prospective study, Rech et al. showed a relationship between basal fMRI images and response to treatment. Interestingly, in responders, fMRI response was detected well before responses were observed with clinical indices or hand MRI (15).

Our Preliminary Work:

The **O**ttawa **R**heumatology **C**ompre**HE**n**S**ive **TR**eatment and **A**ssessment (ORCHESTRA) clinic is an initiative we established in February 2022 within the Division of Rheumatology. It serves patients with inflammatory arthritis who are about to start a new biologic therapy. The ORCHESTRA clinic was built to recognize, treat, and prevent comorbidities, improve the disease activity assessment using the best standard care, enhance patient education, and increase treatment adherence. Within two years, the initiative allowed us to make the following observations:

1) Patients with the difficult-to-treat disease have similar disease burdens clinically, whereas their inflammation levels in the US are higher before starting a new biologic therapy (17).
2) Patients with Doppler positivity at baseline, compared to those who are Doppler negative, give a better improvement in their disease activity scores (measured by the percentage of people who achieve Minimally Important Clinical difference in their Disease Activity Score – 28 joints scores) (18).
3) The response and flare rates in Doppler-positive joints differ from Doppler damaging joints, suggesting a different phenotype that can be determined based on the presence of Doppler signals (19).

In the current proposal, we would like to add the information that can be gained from fMRI of the brain to better understand the pain mechanisms in males and females.
Pain processing in Psoriatic Arthritis: Enthesitis, the inflammation of the tendon insertions, is a key process of Psoriatic Arthritis (PsA), and yet difficult to assess clinically due to the subjectivity of the physical exam. Our group performed a proof-of-concept study to compare fMRIs of PsA patients with enthesealgia, with or without US inflammation on the same entheses. Despite a small sample size of 19, our group demonstrated that patients with entheseal Doppler inflammation process pain differently with more neural connectivity than patients without (20). The trainee (UG) that presented this collaborative work between the division of Rheumatology and the Royal Hospital received the best presentation award at the 2023 international GRAPPA congress.

2-) Aim:

In this project, our aim is a) to better understand the pain mechanisms that impact RA patients according to their sex and b) to understand how the US can be used to differentiate the pain mechanisms as a surrogate to the fMRI.

3-) 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.

3-) Research Approach/methodology and Rationale:

Study Design: Prospective observational study with cross-sectional analysis for the primary and secondary objectives and three-month follow-up analysis for the exploratory analysis.
Setting: The study will be conducted at the Arthritis Center at The Ottawa Hospital. RA patients with moderate-high disease activity, according to the Disease Activity Score–28 joints with erythrocyte sedimentation rate (DAS28ESR) will be a candidate. Patients who consent will get an fMRI of the brain in the Royal Hospital within two weeks of the clinical and MSUS assessment.

4-) Patient profile:

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

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.

5-) Clinical Assessment and Outcomes:

Descriptive and demographic variables:

At the first visit, the demographic of patients, as well as baseline disease characteristics, including age, disease duration, joint deformation, smoking status, presence and medical and psychiatric comorbidities, current and previous medications (for RA and comorbidities) and widespread pain syndrome, will be noted. Sex will be recorded based on the biological attributes and categorized as female or male. Gender will be based on how the patient self-describes the socially constructed roles, behaviours and expressions and will be categorized as woman, man and gender diverse.

Assessment of disease activity and response (24):

The composite index, DAS28ESR, will assess the disease activity. The response will be assessed using the EULAR response. The components of these disease activity and response criteria will be collected at recruitment for all patients and at follow-up for the subgroup in 3 months if they start a new therapy: swollen joint count, tender joint count, physician global assessment visual analogue scale (VAS), Health Assessment Questionnaire (HAQ), Patient Global Assessment (PGA) VAS, pain (100 mm VAS). New biologic therapies include tumor necrosis factor (TNF) inhibitors, interleukin-6 (IL-6) receptor antagonists, B-cell–depleting agents (e.g., rituximab), Janus kinase (JAK) inhibitors, and T-cell co-stimulation modulators (e.g., abatacept).

Pain assessment

Pain will be assessed using the following questionnaires: 100 mm VAS with "no pain" and "pain as bad as it could be" as anchors (25), McGill Pain Questionnaire (26), Widespread Pain Index (27), Symptom Severity Scale (23), and Polysymptomatic Distress (PSD) Score (23).

Laboratory assessment

Rheumatoid factor and anti-cyclic-citrullinated peptide (CCP) antibody results will be collected from the charts if available or will be collected at recruitment if missing. ESR and C-reactive protein will be performed within 2 weeks of the baseline and follow-up visits (for the subgroup)

Radiologic assessment

We will obtain the radiographs of the hands and feet at the baseline visit, if not available within the last 12 months, to understand the disease phenotype (erosive vs non-erosive).

Musculoskeletal Ultrasound

a) Standardization of the Ultrasound scanning

The image acquisition will be performed by one sonographer with at least five years of experience.
Machine settings: All scans will be performed in a darkened room, using a high-end US machine equipped (GE LogicE10) with a high-frequency linear probe (20 MHz). Power Doppler settings will be standardized with a pulse repetition frequency of 500 Hz and a low wall filter.

b) Anatomical sites to be scanned by 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 (2^{nd}-5^{th}) from the dorsal view.

c) MSUS-interpretation of the findings:

Within a week of recruitment, blinded to patients' clinical data, a central reader with 15 years of MSUS experience will score the MSUS images and determine the group (SZA). Gray-scale synovitis and Doppler findings will be defined and scored according to the definitions developed by the Outcome Measures in Rheumatoid Arthritis in Clinical Trials (OMERACT) US task force on a scale between 0-3 for each joint (28).

Classification of patients:

For the primary outcome, the biological sex of the patients will be used to categorize them as males and females.
For the secondary outcomes:

a) Fibromyalgia diagnosis will be based on the Widespread Pain Index (score ≥4 categorized as fibromyalgia).
b) The US positivity will be based on the cut-off of grade≥2 synovitis and Doppler signals (29):
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 2^{nd} MCP joint will be used.
We selected swelling and tenderness in the right hand for inclusion to ensure consistency in study assessment. Given that different body sites may elicit distinct effects on brain activity and pain processing, we restricted inclusion and intervention to the hand and maintained consistency by focusing on the same anatomical site.

fMRI

a) Determination of pain threshold before fMRI

Patients' pain thresholds will be individually determined for painful (VAS=50 mm) and non-painful (VAS=0 mm) stimuli, following a standardized protocol. Pain assessment will be conducted on the day of the fMRI session, immediately prior to scanning. A single research assistant, consistent across all participants, will administer the pain stimuli. A standardized, pre-prepared protocol will be employed, consisting of distinct phases: anticipation, pain induction, and relaxation. The research assistant will document individual pain thresholds as well as any additional observations for each participant. The pressures required to induce pain of VAS=0 (only by light touch) and VAS=50 in the most affected MCP joint and unaffected area of the patient's right hand will be determined at the baseline visit. A velcro-adjusted vascular cuff will be used to determine these values. This vascular cuff will be secured to the right hand's most affected PIP joint and thumbnail. The cuff will be inflated with a pressure of 5-10 mmHg every 2 seconds to determine the pressure that produces the light touch sensation. The initial pressure at which the light touch sensation occurs will be recorded as the pressure required for non-painful stimulation. The cuff will then be inflated in 20-30 mmHg increments every 2 seconds until the pain of VAS=70 mm is achieved. After reaching VAS=70 mm of pain, the pressure of the cuff will be reduced by 20-30 mmHg

every 15 seconds until the patient feels no pain, during which time the pressure required to produce VAS=50 mm of pain (painful stimuli) will be determined. This procedure will be repeated two times, and the average pressure needed to produce a VAS=50 mm pain will be used to induce pain during fMRI.

No changes to pain medication will be introduced as part of the study protocol. Participants' current analgesic use, along with any modifications made by their primary physician, will be documented at each visit. Because pain threshold determination and pain induction occur on the same day as the fMRI assessment, variations in pain management are not expected to confound the analysis

b) Brain fMRI acquisition

The fMRI will be done within two weeks after the clinical and MSUS assessment. The fMRI procedure will take approximately 45-60 minutes to complete and will take place at the Royal Ottawa Mental Health Center's Brain Imaging Center. Two different pressure stimuli will be used during functional scanning: non-painful stimuli (VAS=0 mm) and painful stimuli (VAS=50 mm), using patients' pre-calibrated individual pain thresholds. Each pressure trial will last a variable time (seconds), preventing the patient's prediction of time and onset of pressure. Before fMRI, each subject will be instructed to focus on the stimulus applied and not use any coping or distraction techniques. Regional homogeneity (ReHo) and fractional amplitude of low-frequency fluctuation (fALFF) change in resting state and after non-painful/pain stimuli will be recorded and blinded to the clinical features.

6-) Analysis:

Statistical Parametric Mapping 12 (SPM12) will be used to post-process the fMRI data and to perform the statistical analyses. The functional images will be reconstructed, realigned, spatially normalized, and smoothed. First-level analyses will be performed for each participant using these images to represent the different conditions of the fMRI task. Whole brain and region of interest (ROI) investigations will be conducted. ROIs will be selected according to the appropriate areas previously observed engaged during the task, such as the somatosensory cortex. Significant results will be adjusted for multiple comparisons. The whole brain between group investigations will include flexible factorial analyses (second-level analyses) conducted at a set threshold of $p= 0.05$ corrected, with a cluster-wise correction at $pFWE = 0.05$.

For the primary objective, fMRI features at resting state and after pain induction will be compared between male and female patients. For the secondary objectives, fMRI features at resting state and after pain induction will be compared between male and female patients, according to US subgrops. Additional analysis will be performed in patients with or without fibromyalgia. For the exploratory analysis, resting state and after pain induction fMRIs will be compared among patients who give a EULAR good response at month three vs not.

Our group has used the GLOESS scoring method in previous studies (30) and a single reader will perform the central reading. The interobserver reliability of the reader has been tested in previous studies, and excellent agreement was reached. Therefore, we will not perform another reliability test for the current project.

7-) Sample size:

With percent signal changes of approximately 0.5% and spatial smoothing at FWHM of 5 mm, a minimum of 12 subjects for each group are needed to ensure 80% power at (α) =0.05 at the single voxel level (31). Therefore, we will be including 12 patients in each group.

Our primary hypothesis is that male and female patients will demonstrate distinct patterns of fMRI brain activity in response to painful stimuli, and that these sex-dependent differences will be preserved across both the synovitis and fibromyalgia subgroups. Based on stratification by sex, fibromyalgia status, and the presence of Doppler signals in the MCP joints, the study requires a total sample size of 96 participants. Based on our previous experience, approximately 5% of the patients cannot complete the fMRI for several reasons. Therefore, we plan to recruit 100 patients. Treatment response is only intended as an exploratory analysis and, thus, is not included in the sample size.

8-) Roles:

Dr. Aydin, the PI, is a Professor at the University of Ottawa, Associate Scientist at the OHRI and Tier 2 Chair in inflammatory arthritis. She is an expert in MSUS. She has over 160 manuscripts published in inflammatory arthritis. She will be the central reader for the US, oversee all the study, data collection, analysis and manuscript preparation.

Dr. Hepworth is an early career investigator in Rheumatology. He is the clinical lead in the ORCHESTRA clinic and provides co-management to all patients receiving a new biologic therapy in the division. Dr. Hepworth will be doing the blinded US scans. He will also help with the study design, analysis, and manuscript preparation. Drs. Hepworth and Aydin will have the co-shared last authorship in the presentations and manuscript.

Dr. Smith has a Ph.D. in Neuroscience and is an expert in functional brain MRI, performing analyses using fMRI.

Dr. Gazel is a second-year Rheumatology resident planning to have her Master's in Epidemiology and chose an academic pathway. This project will be a part of her master's project. She will be doing the ethics applications, blinded clinical assessment on the day of recruitment and determining the pain threshold on the day of the fMRI. She will have the first authorship in the presentations and the final manuscript.

Drs Sabido-Sauri and Tsechelidis are the clinical/research fellows who will perform the screening, patient de-identification, applying inclusion/exclusion criteria, consenting, data collection and data entry.

9-) Feasibility:

RA is the most common type of inflammatory arthritis, with a prevalence of 1-2% of the population and is the most common disease treated in our unit. Ten rheumatologists are practicing at the Ottawa Hospital, and screening will be performed in all clinics. In addition, the ORCHESTRA clinic, which will be another source for patient recruitment, serves more than 100 RA patients per year with moderate/high disease activity, and the research team already receives consent from these patients to use their data in future projects with >70% success rate. Therefore, by extending the study recruitment to two years, we do not have any concerns about being able to reach the target of 100 patients. Our group has previously successfully collaborated with the Royal Ottawa Mental Health Center in another study. The design of this current project includes similar study procedures that ensure success.

10-) Limitations:

We do not know the gender disparities in our patient population. Although gender may play a role in pain processing and deserves research, we do not know how many patients would be needed to reach the required sample size. Therefore, we will be collecting the gender data; however, gender is not included in the primary or secondary objectives. Future research is planned based on the observations that will be gained from this study.

11-) Timelines

Protocol writing	Oct-Nov 2024
REB application (TOH and Royal) and contracts	Dec2024-Jan 2025
Patient recruitment	Feb 2025-Oct 2026
Analysis	Nov-Dec 2026
Abstract submission to EULAR 2026 congress	Jan 2027
Manuscript writing and submission	Feb-April 2027

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