

Neurobiological features of fibromyalgia are also present among rheumatoid arthritis patients

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ABSTRACT:

Objectives: Many rheumatoid arthritis (RA) patients report pain despite excellent control of inflammation with immunotherapies. Variable degrees of co-existing fibromyalgia (FM) may explain this disparity. FM has been characterised by aberrant brain functional connectivity, especially between the Default Mode Network (DMN) and insula. We hypothesised that RA patients reporting the highest 2011 ACR FM survey criteria scores- a continuous measure of FM degree also known as fibromyalgians (FMness)- would demonstrate functional connectivity abnormalities similar to FM.

Methods: RA patients underwent an 11 min functional connectivity MRI brain scan (fcMRI) and a clinical evaluation which included a measure of FMness. Brain networks were isolated from FcMRI data. Individual patient network to whole brain connectivity analyses were then conducted followed by group level regression which correlated the connectivity of each network with FMness. Results were significant on the cluster level with a family wise error (FWE) rate p-value <0.05 derived from an uncorrected voxel level p-value <0.001.

Results: 54 patients participated (mean age 54.9years; 75.9% female; mean FMness score 13.3 [range 1-29]). From the whole brain analyses, a single significant positive correlation between DMN connectivity to the left mid/posterior insula and FMness ($r=0.58$, $p=0.001$ FWE) was demonstrated.

Conclusions: RA patients who have increased levels of FMness appear to share neurobiological features consistently observed in FM patients. This study is the first to provide neuroimaging evidence that RA is a mixed pain state, with many patients' symptoms being related to CNS rather than classic inflammatory mechanisms.

INTRODUCTION:

Rheumatoid arthritis (RA) is an archetypal chronic inflammatory disorder which is principally characterised by peripheral joint pain, stiffness and swelling. In recent times, management has been revolutionised by the early and aggressive application of anti-inflammatory therapies. These advances have led to tremendous average improvements in objective outcomes and even disability, but as many as 50% of patients continue to report clinically significant levels of pain despite excellent control of their peripheral inflammation^{1,2}.

This disconnect between improvements in inflammation and improvements in pain suggests that there is a likely contribution of pain mechanisms which are in addition to and distinct from peripheral inflammation. Central sensitisation - a consequence of dysfunctional central nervous system pain processing which defines the primary chronic pain syndrome of fibromyalgia (FM) - may represent one such mechanism³. This possibility is supported by clinical epidemiological research which has evidenced co-existing FM in 13-25% of RA patients⁴. This compares to a prevalence of 1-5% in the general population⁵. A further 7-15% of RA patients have hallmark features of FM (which include somatic symptoms such as fatigue as well as chronic pain) without meeting formal classification criteria⁴. Wolfe and colleagues derived a continuous scale from the ACR FM survey criteria and found it to predict pain and disability in RA even among patients who did not fully satisfy the FM criteria. The term fibromyalgians (FMness) was subsequently introduced to reflect this wide phenotypic range⁶.

There are very few studies that examine whether the prevalent FMness phenotype in RA is underpinned by the same central sensitisation pathways as demonstrated in 'primary' FM. If true, it would greatly enhance the argument for 'primary' FM therapeutic approaches (which are quite distinct to current peripherally directed anti-inflammatory RA therapies) benefitting RA patients who have clinical features of FMness.

Advanced neuroimaging techniques have been crucial in delineating the neurobiological features of central sensitisation in 'primary' FM, but have not previously been applied to concomitant FM in RA. Recent studies have employed functional connectivity MRI (fcMRI) - an adaptation of functional MRI data that examines temporal correlations in the MRI signal across various brain networks and regions. These connections are thought to be important for the maintenance of synaptic connectivity and as such modulates the efficiency and extent of neuronal transmission in the brain. Among FM patients, the dorsal attention (DAN), sensori-motor (SMN) and salience (SLN) brain networks have been implicated with increased connectivity to pro-nociceptive brain areas and decreased connectivity to anti-nociceptive brain areas⁷⁻⁹. However, currently the most convincing and reproducible fcMRI evidence relates to the association between the default mode network (DMN) and insular cortex – otherwise implicated with self-referential¹⁰ and multimodal sensory processing respectively¹¹. This specific connection is cross-sectionally associated with FM and pain intensity¹² and longitudinally associated with change of FM pain following both efficacious pharmacological (pregabalin) and non-pharmacological treatments (acupuncture)^{13,14}. The robustness of this finding is further corroborated by magnetoencephalography (a more direct measure of brain connectivity)¹⁵⁻¹⁷. These same patterns have been noted in other conditions known to be accompanied by central sensitization, such as irritable bowel syndrome and low back pain^{16,17}. Together this data indicates that functional connectivity – and specifically DMN-Insular hyperconnectivity – may be a key biological marker of both the presence and severity of FM related pain, and central sensitisation.

As yet, no studies have investigated whether fcMRI features of FM are observed in RA patients with co-occurring FM. Specifically we hypothesised that that RA patients reporting the highest levels of FMness would demonstrate fcMRI features of FM.

PATIENTS & METHODS:

Patients:

335 RA Patients were approached through a UK regional rheumatology service. Of those, 193 indicated interest in the study. Participants were considered eligible if they met the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria¹⁸, and had a clinically significant level of fatigue for at least 3 months (defined as a score > 3 on the Chalder fatigue binary scale (CFS)¹⁹. Exclusion criteria were contra-indications to MRI and left-handedness. 73 patients fulfilled these criteria and ultimately, 54 RA patients completed the study.

All consenting participants underwent a clinical evaluation. This included a measure of FMness using the ACR FM survey criteria which combines a measure of widespread pain (number of painful sites 0-19) with a symptom severity scale (e.g., fatigue, subjective cognitive problems, headache, poor mood, scores range 0-12)²⁰. In addition their levels of systemic inflammation (C reactive protein, CRP), disease activity (DAS28), current levels of overall fatigue and pain severity (0-10 numerical

rating scale), sleep disturbance (Jenkin's sleep scale²¹ and depression (Hospital Anxiety and Depression Scale²²) were recorded. Participants then undertook a fMRI brain scan.

Data Acquisition:

Each participant completed an 11-minute functional scan while performing the Paced Auditory Serial Attention Test (PASAT), a validated measure of cognitive function (auditory processing, calculation, working memory, attention) which has been previously used in an fMRI context²³. The PASAT was given in a block design with 3x3 minute 'on' periods, interspersed with 4x30 second rest periods. The functional images were acquired by a 3 Tesla (Achieva X-series, Philips Medical, Best, The Netherlands) 8 channel phased array head coil using a T2*-weighted gradient-echo single-shot echo-planar imaging pulse sequence with the following parameters: TR = 3000 ms, TE = 30 ms, flip angle (FA) = 90°, in-plane SENSE acceleration 2, matrix size 128 × 128 with 30 slices, field of view (FOV) = 240 mm, 1.88 mm × 1.88 mm × 5 mm voxels and 226 volumes. The first four volumes were discarded to avoid equilibration effects. A high-resolution structural T1-weighted fast-field echo 3D structural scan was collected for normalization (TR = 8.2 ms, TE = 3.8 ms, TI = 1018 ms FA = 8°, FOV = 240 mm, matrix size 240 × 240 matrix with 160 slices and 0.94 mm × 0.94 mm × 1 mm voxels).

Preprocessing:

All data were checked for motion greater than 3.76mm and 5° rotation and visually inspected for artifacts. No participants were excluded for these reasons. fMRI data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) running on MATLAB R2014a (Mathworks, Sherborn, MA, USA), as previously described²³. Briefly, the functional images were realigned, and the structural image was co-registered to mean functional image and then segmented. The structural and functional scans were normalized to the standard SPM Montreal Neurological Institute template grey prior probability map via the individuals segmented grey matter image. Functional scans were smoothed with an 8-mm FWHM Gaussian kernel.

Independent Component Analysis (ICA):

We performed Group ICA using the Group ICA of fMRI Toolbox (GIFT) to create group specific network masks²⁴. Component estimates were validated using ICASSO software²⁵ over 20 iterations to ensure the accuracy and reliability of results. Subject specific spatial maps and time courses were generated using the GICA3 back-reconstruction method. The networks of interest were the: DMN, SMN, SLN and DAN. These components were verified by spatial correlation between the component maps and previously identified templates²⁶. Spatial masks of the mean component map for each network were created using the Marsbar toolbox for seed-based connectivity analyses.

Network to whole brain connectivity analysis:

The preprocessed functional data were entered into the Functional Connectivity Toolbox (CONN; Cognitive and affective neuroscience laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA; www.nitrc.org/projects/conn) v15 in SPM8²⁷. A nuisance regression using the CompCor method²⁸ was performed with six subject-specific motion parameters, the signal from white matter and CSF, and their first order derivatives included as confounds. A band pass filter (0.01-0.1 Hz) was applied to remove linear drifts and high frequency noise in the data. The mean component maps generated from ICA were used as seeds. Beta maps for each individual representing connectivity between the network of interest and the rest of the brain were generated. The task beta maps were then passed onto second-level group analyses in SPM8. Using a multiple regression model, we

assessed the association between network-whole brain connectivity and FMness with age and sex originally included as covariates of no interest, followed by additional corrections for the putative confounders of CRP and amitriptyline use. The resulting maps were thresholded at an uncorrected voxelwise $p > 0.001$, and significance was set at $p < 0.05$ family wise error (FWE) cluster corrected for multiple comparisons. The average fisher transformed r values of significant clusters were extracted from the first level beta maps for each subject using Marsbar. These values were brought into STATA 12.1 (Stata, College Station, TX, USA) to enable sensitivity analyses and test post-hoc correlations analyses with disease and symptom measures.

RESULTS:

Clinical Characteristics:

In total, 54 patients completed the study. The mean age was 54.9 ± 11.41 years, $n = 41$ female and the mean disease duration was 11.49 ± 8.64 years. The mean FMness score was 13.20 ± 6.21 [range 1-29] and $n=5$ were receiving pharmacological treatment for FM (all low dose amitriptyline). Other patient characteristics are displayed in Table 1 and FMness correlations with these characteristics in the supplementary table.

[Insert table 1]

DMN-Insula functional connectivity is associated with FMness in RA:

There was a significant positive correlation between DMN connectivity to the left mid/posterior insula and FMness ($r=0.572$, $p = 0.001$ FWE corrected) in RA patients. The association remained significant after controlling for age and sex ($r = 0.577$, $p = 0.001$ FWE corrected, see Figure 1). Further, analyses correcting for the putative confounding factors of inflammation (CRP) and amitriptyline usage did not alter this observation ($r = 0.568$, $p = 0.001$ FWE corrected and $r = 0.556$, $p = 0.009$ FWE corrected, respectively). No other significant correlations were identified to any of the other networks of interest. Further, a sensitivity analysis of only those patients ($n=27$) who did not fulfil ACR preliminary criteria for FM (total score <13) observed the correlation between DMN-insula and FMness to remain highly significant ($p=0.006$, $r=0.51$).

[Insert figure 1]

We then examined correlations with phenotypic features (table 2). First, the individual components of the FMness score were examined, the widespread pain index and the symptom severity scale, in order to establish if the DMN-Insula connectivity relationship was directed by one or both components. Both the widespread index ($r=0.50$, $p<0.0001$) and symptom severity scale ($r=0.41$, $p=0.002$) were significantly associated indicating important contributions for both. This was further corroborated by significant associations with chronic fatigue ($p=0.002$) and sleep disturbance ($p=0.02$), although interestingly no association existed between DMN-insula and pain reported at the time of the scan ($p=0.52$). We next explored correlations between the identified functional connection and RA disease features. Overall disease activity (DAS28) was significantly correlated ($p=0.002$), although CRP was not ($p=0.19$).

[Insert table 2]

DISCUSSION:

To our knowledge, this study is the first to provide objective neuroimaging evidence that RA is a mixed pain state displaying characteristics of central sensitisation. RA patients who reported high levels of FMness demonstrated significantly higher functional connectivity between the DMN and insula - a recognised neurobiological feature of 'primary' FM. Further, the ACR FM survey appears to be a strong surrogate for this neurobiological marker of central sensitisation and, in the future, could be a useful tool to support clinicians' evaluation of pain and inform subsequent management.

Our group and others have previously identified significant alterations in DMN-insula connectivity in FM. The insula is a highly connected region of the brain with multiple functional features which routinely involve the integration and conversion of physiological inputs into higher level outputs²⁹. Numerous studies have implicated the insula with different disorders and dimensions of pain, including FM³⁰. Its purported role as a key relay station in pain processing has been supported by direct electric stimulation studies of the region which have effected painful sensations in some patients³¹. The DMN comprises synchronously functioning regions - including the posterior cingulate cortex, medial prefrontal cortex and lateral parietal lobes - which are commonly associated with activities of introspection and are also found to be disrupted in chronic pain³². It is unknown whether this network is a modulator of pain (potentially via descending inhibitory pathways³³) and/or related somatic features, or exclusively a consequence of chronic pain exposure³². Given these possible complementary roles in pain processing, it is plausible to speculate that DMN and insula may be functionally connected in FM¹²⁻¹⁵.

In this current study we expand on these findings by identifying a significant alteration of the very same functional connection in relation to phenotypic features of FM co-existing in another chronic pain disorder (with a distinct primary pathophysiology relating to inflammation). Presence of this connection despite the apparent absence of an association with significant concurrent peripheral inflammation or overall levels of pain further supports the apparent specificity of the DMN-insula connection as a marker of a distinct pain sub-type. It is however interesting to consider the significant correlation with the DAS28 which appears to be principally driven by tender and not swollen joint counts. This aligns with studies which have observed a conflation of DAS28 in the context of FM which in turn leads to greater biological therapies^{34,35}. That said, we cannot discount the possibility that inflammation may have some role in driving central sensitisation.

Although no other study has applied neuroimaging to characterise FM in a co-existing disorder, dysfunctional DMN-insula functional connectivity has been observed in irritable bowel syndrome¹⁶, chronic back pain¹⁷, and migraine³⁶ - all pain conditions where central sensitisation has been implicated³⁷. Of interest, these conditions are also associated with somatic symptoms^{38,39} which aligns with our post-hoc analysis indicating that the DMN-insula functional connection relates not only to pain but to symptoms such as fatigue and cognitive dysfunction also (as measured by the Symptom Severity Index). One noticeable discrepancy with previous non-RA studies is the absent correlation with current pain severity (which we have further confirmed with a voxelwise search of the insula). We speculate that RA has more ongoing nociceptive input due to inflammation compared to other studied clinical populations where central sensitisation is a greater contributor to current pain. A final point to note is that this connection remains significant even among those RA patients who do not fulfil ACR criteria, further evidencing that FM is a continuous rather than discrete construct.

Our findings indicate that centralised pain pathways co-exist with more established peripheral inflammatory driven pathways in RA. This is corroborated by QST studies which allude to

dysfunctional CNS pain pathways in RA by consistently evidencing hyperalgesia and allodynia⁴⁰. Specifically, lower pain-pressure thresholds have been measured across both diseased joints and non-joint sites in RA patients with concomitant FM in comparison to RA patients without⁴¹.

Our study builds on the few functional neuroimaging studies to have been conducted in RA. Although previous studies have been small and limited to provoked acute experimental pain at the site of joints (rather than non-diseased sites). They have provided evidence supporting a role of mixed CNS mechanisms in RA related pain. Jones et al originally reported differential cortical responses to acute pain using PET between RA (n=6) and a chronic pain population characterised by depression and dysfunctional coping. They subsequently speculated that the CNS mechanisms of inflammatory pain were distinct to other pain types⁴². More recently, Rech and colleagues undertook evoked pain fMRI pre and post anti-TNF therapy in n=10 RA patient and observed differences in brain activations between responders and non-responders⁴³. This again infers the possible existence of different neural signatures for different types of pain since responders are more likely to be characterised by pain of inflammatory origin in comparison to non-responders.

This present study is strengthened by its large sample study (n=54) – to our knowledge the largest neuroimaging investigation of any inflammatory rheumatic disease, thus reducing the risk of the false positive results which are endemic in neuroscience. The robustness of these results are further enhanced by our conservative analytical methodology. Despite employing a data driven global scan approach, only the key DMN-insula functional connection was identified. Furthermore, this data was acquired using a scanner in a centre which has previously not contributed to the literature evidencing the importance of this connection. Finally, replication of this specific pattern of co-activation in the context of a task (rather than resting state – as with previous studies) not only strengthens validity but also enhances existing views that fMRI largely reflects intrinsic communication networks which are unrelated to conscious activities⁴⁴.

Certain limitations to this study should also be considered. Firstly, although the study population includes a demographically representative cohort of RA patients with a mixture of disease activity states, there was a bias towards selecting patients with significant fatigue levels. This sample enrichment however enabled greater power to detect the mechanistic associations inherent to the research question. It also cannot be assumed that these findings may generalise to other rheumatic conditions, and this intriguing possibility should be the subject of future experiments. Secondly, due to the cross-sectional design, no assumption can be made regarding whether DMN-insula functional connectivity has causal role in FMness. This data does, however, re-inforce previous studies which propose this connection at least as a biological marker of the FM construct and so adequate to address our primary research question. Thirdly, despite being the largest study of its kind, the sample size cannot confidently exclude the existence of other relevant network to region connections (which most likely exist) and still lacks sufficient power to fully and independently correct for the multiple putative confounding variables which are implicated with FM. That said, our results remained significant following individual adjustments of age and sex. The latter is of particular interest because previous studies of functional connectivity in ‘primary’ FM have consisted almost entirely of females. Since numerous sex differences in FM biology have been reported⁴⁵, the generalisability observed here serves to enhance the usefulness of the DMN-insula marker further.

We have shown that central sensitisation is not confined to individuals with ‘primary’ FM and co-exists in patients with the biologically distinct disorder of RA. Such evidence for shared mechanisms could inform future clinical decision making. It is challenging for physicians to distinguish different pain states in patients, particularly those with a pre-existing chronic pain disorder. This is especially true since the centralised pain state of FMness is not only common but also artificially inflates

routinely used measures of peripherally based inflammatory pain states (e.g. DAS28)⁶ which are pivotal in guiding clinicians prescriptions of anti-inflammatory treatment. In consequence inappropriate prescribing of anti-inflammatory therapies for pain which is actually not inflammatory in origin is likely common and probably a principal factor for why many RA patients continue to report pain following anti-inflammatory therapy despite apparent resolution of inflammation¹. RA patients reporting significant pain and who have evidence of high levels of functional connectivity between the insula and DMN are more likely to benefit from centrally acting therapies which are effective for FM instead of or in addition to anti-inflammatory therapies. These currently include both pharmacological (e.g. neuroleptics) and non-pharmacological (e.g. CBT) agents⁴⁶. Unfortunately limited access, expense and specialised analysis requirements will likely prohibit implementation of fMRI into routine practice, however this technology may not be essential given the demonstrated relationship with the FM ACR Survey score. Instead application of this measure as a point of care tool may enable clinicians to quantify the contribution of central sensitisation to their patient's pain and subsequently inform management choices. Future refinements and abbreviations to this tool will hasten translation. Moreover since co-existing FM is a common issue among many diseases (musculoskeletal and beyond)⁴⁷⁻⁵¹, such a tool may be generically applicable and so testing across the spectrum of chronic pain disorders may finally move the pain field into the era of personalised medicine.

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CONTRIBUTORS:

NB, CK, EI, TL, GW, AM, RH and DC were involved in designing the study and interpreting the data, drafting the article and revising it critically for important intellectual content. All authors approved the final version to be published. NB and CK analysed the data and wrote the first draft. EI, TL and GW contributed to the data analysis. NB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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Table 1: Clinical characteristics

Clinical features	
RA disease activity ^a	3.62±1.30
CRP (mg/L)	7.78±8.54
Fatigue ^b	4.59±2.19
Depression ^c	6.89±3.92
Sleep disturbance ^e	15.67±5.46
Current overall pain ^f	3.81±2.38

^aDisease activity score 28; ^bCurrent fatigue 0-10 numerical rating scale (NRS); ^cHospital anxiety & depression scale; ^eJenkin's sleep scale; ^f Current pain NRS

Table 2: Disease and symptom correlations with DMN-Insula

Phenotypic features	Correlation^g	P value
FM widespread index	0.50	0.0001
FM symptom severity scale	0.41	0.002
Disease duration	0.03	0.83
RA Disease activity ^a	0.41	0.002
Swollen joint count	0.25	0.07
Tender joint count	0.32	0.02
CRP	0.18	0.19
Current overall pain ^b	0.09	0.52
Current Fatigue ^c	0.26	0.06
Chronic fatigue ^d	0.40	0.002
Depression ^e	0.10	0.46
Sleep disturbance ^f	0.31	0.02

^aDisease activity score 28; ^b Current pain NRS; ^cCurrent fatigue 0-10 numerical rating scale (NRS); ^dChalder Fatigue Scale; ^eHospital anxiety & depression scale; ^fJenkin's sleep scale; ^gpearson correlation r all except CRP which is spearman correlation rho due to distribution

Supplementary table: Phenotypic correlations with FMness

Phenotypic features	Correlation ^g	P value
Disease duration	0.04	0.76
RA Disease activity ^a	0.56	<0.0001
Swollen joint count	0.31	0.02
Tender joint count	0.46	0.0004
CRP	0.13	0.36
Current overall pain ^b	0.61	<0.0001
Current Fatigue ^c	0.41	0.002
Chronic fatigue ^d	0.52	0.0001
Depression ^e	0.49	0.0002
Sleep disturbance ^f	0.50	0.0001

^aDisease activity score 28; ^b Current pain NRS; ^cCurrent fatigue 0-10 numerical rating scale (NRS);

^dChalder Fatigue Scale; ^eHospital anxiety & depression scale; ^fJenkin's sleep scale; ^gpearson correlation r all except CRP which is spearman correlation rho due to distribution