Investigating the relationship between central and peripheral pathophysiology in fibromyalgia syndrome – a pilot neuroimaging study

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Background: Fibromyalgia syndrome is a chronic pain disorder which affects around 1 in 20 adults in the United Kingdom. It causes widespread pain, sleep problems and fatigue and it is often seen in tandem with other pain syndromes. Fibromyalgia often leads to a severe impact on patients' quality of life but the causes are not fully understood. Our previous research used brain imaging and revealed how differences in brain structure and function are associated with pain in fibromyalgia. A crucial role for the brain in fibromyalgia has been part of the prevailing opinion for the past two decades. However, newer evidence from our team and others indicates that nerves located throughout the body (peripheral nerves) are also likely to play an important part in generating the pain that patients endure. We now believe that it is highly likely that both of these mechanisms, brain and bodily nerves, work together to shape the pain that patients experience. Interestingly, most pharmacological treatments for fibromyalgia only exert their effects in the brain. However, current treatments are frequently found to be unsatisfactory for many patients. Improved understanding of how other, non-brain, mechanisms are involved in fibromyalgia could be very important for development of better treatments or diagnostic tests.

Aims: This project aims to investigate whether brain and peripheral mechanisms are related to each other in fibromyalgia syndrome patients. As a pilot study, this represents the first research to measure relevant brain and bodily nerve activity in the same group of fibromyalgia patients, it provides us with a unique insight so that we can consider the two mechanisms in tandem. As it is the first time anyone has attempted this, our research is classed as a pilot feasibility study. This means that one of our primary interests is to check that it is even possible to collect this battery of exciting data from a patient. Our second goal is to perform a first evaluation of known brain and non-brain mechanisms in a single patient group, to see if they are correlated with one another.

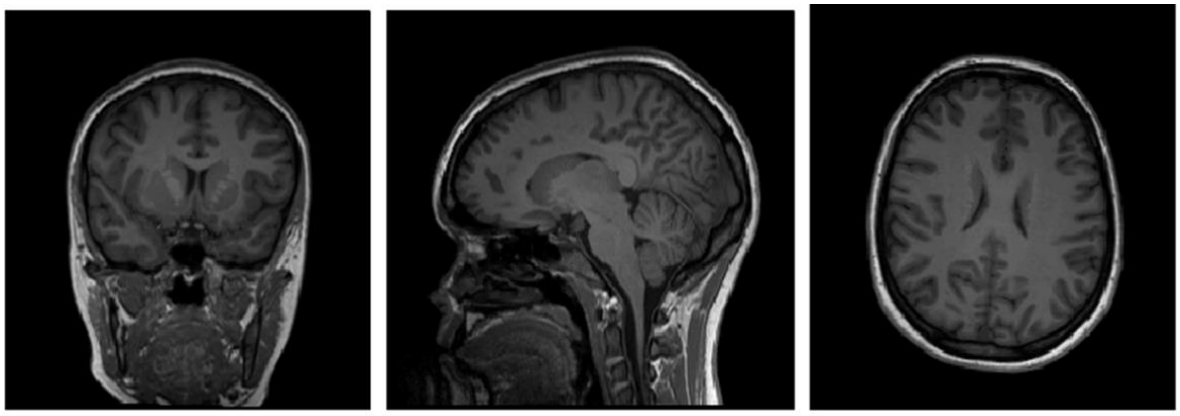
What do we do: The project team is comprised of experts in both brain imaging and the peripheral nervous system. We have unique access to a suitable group of 77 people with fibromyalgia syndrome who are participating in a project to investigate their peripheral nerve function. In our study, a sub-group comprising 18 of these patients will attend an additional brain scanning session at the Liverpool Magnetic Resonance Imaging Centre (LiMRIC) in the University of Liverpool. During this session the patients undergo 5 MRI brain scan procedures which quantify important aspects of the brain, including anatomical structure and how it is functioning. Some of the scans focus on the brains grey matter (the outer mantle of the brain), and the sub-cortical structures (primal brain systems in the centre of our brain which are involved in things like processing of emotions and motivations). Other scans are specialised to consider the white matter bundles that hardwire our brain so that it can function well. Finally, we are also recording two interesting scans that measure patients brain function. The first considers brain activity when the patients are at rest,

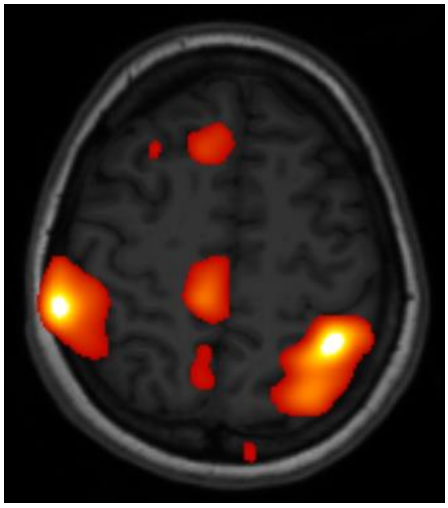
the second one is a ‘task scan’ which evaluates brain activity as the patients undergone some heat stimulation to their foot which can cause them some mild pain experience so that we can observe how their brains process the pain. In total the patients are in the scanner for 1 hour. We talk to the patients frequently via an intercom and the heat pain intensity is individually tailored so that it is acceptable to every patient.

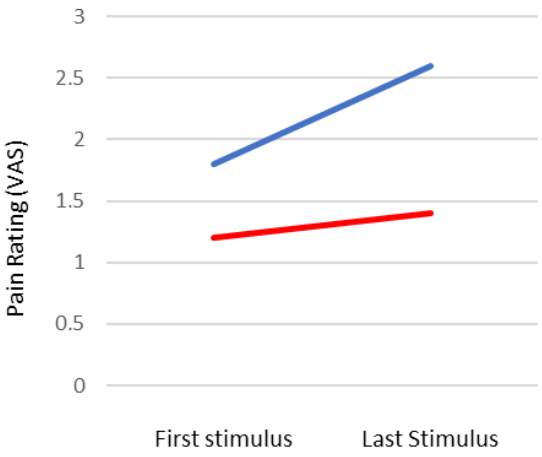
Progress: The project was originally planned to begin in October 2020, but unfortunately our start date was delayed by one year due to the COVID pandemic. We began testing of our equipment in October 2021. Our first patients completed their required peripheral nerve measurements in December 2021 and we commenced brain scanning in February 2022. So far, we have scanned 4 of the required 18 patients. We have already recruited a further 6 patients who are scheduled to be scanned in coming weeks. We anticipate completion of recruitment by Autumn 2022. This means that the project (whilst having a delayed start date) is progressing at a rate that is in line with our original estimates.

Anticipated result: From our experience so far, we can begin to consider some of the original aims of the study. Firstly, it seems that the patients generally find our approach to be acceptable. So far, one patient who attended our scanning facility has decided against going through with the study – this was due to claustrophobia which is a common cause of drop-out in brain scanning studies. We try to avoid this by explaining the procedure to patients in advance, and also often recruit patients who have experienced brain scans previously. Verbal feedback from all patients who have taken part so far has been positive, with no major issues identified with the study approach.

In terms of considering the mechanisms of fibromyalgia, processing of both brain imaging and peripheral nervous system measurements is now ongoing. We do not yet have sufficient data to perform any statistical comparison on brain and bodily measurements. However, even at this early stage we can produce high-resolution images which illustrate important aspects of patient brain structure and function. These images contain the data that will be extracted and compared in the final report for the study. A high-resolution image of one patient showing anatomical brain structure can be seen in figure 1 (*upper panel).* The heat blobs *(lower left panel)* illustrate the location of a famous network of connected brain regions which are active during rest (and which may be disrupted by chronic pain) known as the *default mode network*.







Moreover, we can also see behavioural responses from our example patient during heat pain (*lower right panel).* The ratings demonstrate an increase in perceived pain from first to last stimuli when heat pulses are delivered in quick succession (*blue line)*, compared to those delivered with larger gaps (*red line)*. This is an important measure of 'central sensitisation' something that was previously considered to be a core mechanism of fibromyalgia pain. In coming months, we will receive the data on peripheral nervous anatomy and activity from our patients, namely skin biopsy results, data from retinal scans and nerve function tests. We will correlate these measures with the brain and behavioural results shown above in an attempt to understand how different mechanisms may interact with one another.

Anticipated outcomes: As described, a principle aim of this research is to consider the feasibility and acceptability of the approach for patients. This information, combined with feedback from patients, will be essential to justify this type of multi-session research approach in future. The other principle aim of this investigation is to improve our understanding of the relationship between brain and body mechanisms in fibromyalgia. In the medium term, the pilot data will contribute towards development of a research program that will help to establish Liverpool at the forefront of fibromyalgia research. In the longer term, we hope that knowledge accrued will lead to studies which will aim to develop improved treatment approaches based on a better understanding of the multiple mechanisms contributing to each individual fibromyalgia experience.