Functional MRI in Rheumatic diseases – with a Focus on Fibromyalgia

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Abstract

Pain is the most common symptom in rheumatic diseases. However, the severity of pain does not correlate with pathology. The lack of an objective test for pain results in clinicians consider pain in patients with fibromyalgia as psychological. Research over the last two decade using functional neuroimaging especially functional MRI scan have demonstrated objectively that patients with fibromyalgia were not malingering. Pain processing is complex and multiple regions of the brain are involved. One consistent finding is decrease activity in regions of the brain involved in pain inhibitory pathways suggesting this is one of the fundamental pathophysiology processes in fibromyalgia.

Introduction

Pain is a common and dominant symptom in rheumatic diseases[1]. Patients with rheumatoid arthritis (RA) rank pain as the most important and disabling symptom, with a major impact on quality of life[2,3]. In many patients, the severity of pain does not correlate with disease activity or underlying pathology[4,5]. In RA, pain may be present in patients in clinical remission. In osteoarthritis (OA), many people with severe radiographic abnormalities report no joint pain and joint replacement does not always alleviate pain[6]. A disconnect between symptoms of pain and anatomical abnormalities is particularly evident in the patients with fibromyalgia, in whom local tender points are seen in the absence of local pathology. The absence of an objective test for pain leads many clinicians to consider pain in such cases as psychological and patients are malingering[7].

The advent of the functional neuroimaging has allowed researchers to study processing of pain in the brain objectively over the last two decades in fibromyalgia and other rheumatic diseases. Results from these studies have indicated that processing of pain is complex, involving different regions of the brain. Pain is more than a "sensation". This review will discuss principles of functional neuroimaging and key findings in rheumatic diseases, particularly in fibromyalgia.

Functional neuroimaging

Several methods are available to assess cerebral function, including electroencephalography (EEG), functional Magnetic Resonance Imaging (fMRI) by blood oxygenation level dependent (BOLD) or arterial spin labelling (ASL), and radio-isotope imaging by Single-photon emission computed tomography (SPECT) or positron emission tomography (PET).

Neuroimaging of Pain

The strength of neuroimaging of pain lays mainly in its objectivity. Initially, studies have focussed on acute evoked pain in healthy volunteers with experimental stimuli to analyze effects of analgesic medications[8]. These studies indicated that many regions in the brain are involved in the processing of pain, which has led to the concept of a 'pain matrix'. These regions include the anterior cingulate cortex, primary somatosensory cortex, secondary somatosensory cortex, prefrontal cortex, insular cortex, hypothalamus, thalamus, amygdala and brainstem. The notion that there is a unique and fixed cerebral signature for pain perception has proven to be too simplistic. Recent studies have shown that the response to pain is affected by the type of painful stimulus, chronicity of symptoms, disease condition, and imaging method[9,10]. Indeed, similar brain networks can be activated by the anticipation of pain[11], and may be involved in processing the saliency of sensory events[12]. Current

thought is that the network of brain areas which are associated with pain processing is dynamic[9,10]. In patients with chronic pain conditions, more involvement is seen of affective-cognitive regions such as the insula cortex than the sensory discriminatory region (somatosensory cortex), highlighting differences between chronic pain and acute pain[8]. This has influenced study design and development of new technology in neuroimaging.

Electroencepalography (EEG) Studies

EEG records the electrical neuronal activity. It can be used to monitor the activity of different brain region over time. When combined with painful stimuli, EEG has been used to study cerebral response to pain which has been used in rheumatic diseases[13]. However, it can only be used to study only superficial brain regions, and has not proven of substantial value to understand chronic pain.

Functional Neuroimaging using Radio-isotopes

SPECT and PET use radio-isotope tracers to assess regional cerebral blood flow. Using specific tracer, PET can also assess cerebral metabolism.

Single Photon Emission Computed Tomography (SPECT)

SPECT was the first functional neuroimaging tool used for research in patients with fibromyalgia. A small study in 10 patients found lower activity in the thalamus and caudate nucleus when compared to 7 controls[14]. A subsequent SPECT study with a larger sample of fibromyalgia patients and healthy controls found decreased regional cerebral blood flow in the thalamus and pontine tegmentum[15]. Reduced regional cerebral blood flow in the thalamus and caudate nucleus were replicated in a third SPECT study of FM patients[16]. However, SPECT images are of low resolution are prone to artefact, and therefore has been replaced by PET and fMRI.

Positron Emission Tomography (PET)

Unlike SPECT which uses gamma rays emitting radio-isotopes, PET uses radio-isotopes which emit positrons. The latter leads to higher sensitivity and resolution. In fibromyalgia, a small study of 8 patients using PET reported higher regional cerebral blood flow in the retrosplenial cortex but reduced regional cerebral blood flow in the frontal, temporal, parietal, and occipital cortices[17]. Using 18F-fluorodeoxyglucose as a tracer, PET can assess glucose metabolism so can assess metabolic activity as well as regional cerebral blood flow. However, Yunus et al. using a PET with 18F-fluorodeoxyglucose tracer found no difference in resting state between the patient and control groups[18]. Harris et al used 11C-carfentanil to evaluate μ-opioid receptor binding in patients with fibromyalgia. The binding potential of μ-opioid receptors was reduced in several areas of the brain in patients with fibromyalgia compared with healthy individuals, including the rostral anterior cingular cortex, nucleus accumbens and amygdala, which are correlated significantly with pain and depression[19]. Endogenous opioids and opioid receptors are important for pain inhibition. The results from this study suggest pain modulation is impaired in patients with fibromyalgia and may explain the limited efficacy of opioids in fibromyalgia[20].

fMRI Studies

Blood Oxygenation Level Dependent (BOLD) fMRI of Evoked Pain

Increased neuronal activity leads to increased local blood flow and conversion of oxygenated haemoglobin to deoxyhaemoglobin. Oxyhaemoglobin and deoxyhaemoglobin have different magnetic characteristics. fMRI scan can detect these changes to provide a measure of neuronal activity.

BOLD fMRI studies are based on comparing activities of different brain regions in response to painful and non-painful stimuli. The BOLD fMRI studies have been used extensively in experimental studies of acute pain using various experimental pain stimuli from electric to pressure induced pain[8]. It has also been used in many rheumatic diseases including RA[21,13,22], OA[5] and fibromyalgia. In OA, BOLD fMRI, has identified regions of the brain involved in processing evoked pain and spontaneous pain[23]. In RA, activation of brain region correlated with tender-swollen joint ratio and depression, suggesting depression is related to pain processing[21].

In fibromyalgia, Gracely et al first demonstrated objectively using BOLD fMRI that cerebral activities matched with patient-reported pain[24]. At the time, many clinicians regard fibromyalgia as a "functional/psychological disorder" since the severity of pain does not correspond with pathology. Using a device which applied a varying degree of pressure on the thumbnail ranging from non-painful to painful. Cerebral activity in patients with fibromyalgia was compared to healthy control subjects. Importantly, painful and non-painful stimuli were applied randomly during BOLD fMRI so that subjects could not anticipate whether the stimuli should be painful or non-painful. BOLD fMRI imaging documented that activities in the brain are similar in patients with fibromyalgia and control subjects, but occurred at lower pressure-pain stimuli in fibromyalgia patients. For the first time, it provided objective evidence that patients with fibromyalgia are not malingering, but rather they are more sensitive to pain provocation than normal individuals.

A subsequent study using the same method found that patients with fibromyalgia had reduced activity in the rostral anterior cingulate cortex when compared to controls[25]. This region of the brain has been linked to the descending pain inhibitory pathways. The attenuated response to pain in this brain region is the first demonstration of a specific brain region in which the impairment of pain inhibition is seen. This observation was supported by a study using PET imaging assessing μ-opioid receptor binding discussed earlier in this review[19]. Further analysis from this study found that the rostral anterior cingulate cortex displayed significantly reduced connectivity to the amygdala, hippocampus, and brainstem in patients with fibromyalgia compared with healthy controls[26].

Reduced connectivity of the pain inhibitory network suggested that the dysfunction of the descending pain modulatory network plays an important role in the pathophysiology of fibromyalgia. These findings were further supported by structural MRI analyses in patients with fibromyalgia, indicating decreased cortical thickness, decreased brain volumes, and decreased functional regional coherence in the rostral anterior cingulate cortex[27]. The morphometric changes were more pronounced with longer exposure to FM pain.

fMRI has also been used to assess cerebral pain processing in response to anti-depressant. A double-blind, placebo-controlled clinical trial was conducted with milnacipran, a serotonin-norepinephrine reuptake inhibitor. fMRI scans were performed before and after treatment

in 92 patients with fibromyalgia[28]. Following treatment, responders to milnacipran exhibited significantly higher activity in the posterior cingulate cortex compared with responders to placebo as well as non-responders to milnacipran. Changes in activity in the posterior cingulate cortex were correlated significantly with reduction in patient-reported pain. This observation suggested that milnacipran improved pain in fibromyalgia by increasing the activity of the posterior cingulate cortex, which is a part of the brain regions implicated in pain inhibition.

Despite being objective, one of the weaknesses of BOLD fMRI imaging is its reliance on "experimental" pain stimuli. In fibromyalgia, in which "allodynia" or "tenderness" is a classical feature, assessing evoked pain and pressure pain threshold is logical. However, in many rheumatic diseases, including fibromyalgia, patients report "spontaneous" pain in the absence of noxious stimuli. The relevance of observations made through BOLD fMRI imaging to "spontaneous" pain reported by patients has been questioned[29]. One way of addressing this possible weakness is to utilise resting state BOLD fMRI or arterial spin labelling.

Resting state BOLD fMRI
Resting state BOLD fMRI monitors changes in brain activity over time without painful stimuli. It was used to identify the default mode network (DMN), a network of brain regions that is active 'at rest'. DMN is thought to be involved in self-referential orientation and monitoring. In many chronic pain conditions, spontaneous pain was associated with aberrant connectivity in the DMN[30,31]. In fibromyalgia, decreased connectivity DMN has been localized to the pain inhibitory network[26,32] supported the findings from evoked pain study[25].

Arterial Spin Labeling (ASL)
ASL measures regional cerebral blood flow by magnetically labelling water. ASL is suitable for studying spontaneous pain[33], both acute[34] and chronic including recently in thumb OA[35], in which patient-reported pain was associated with increased activity in the somatosensory cortex, insular cortex, cingulate cortex, thalamus, amygdala, and hippocampus. In fibromyalgia, regional cerebral blood flow in the basal ganglion is correlated significantly with physical disability[36]. regional cerebral blood flow in the right putamen and right lateral globus pallidus was? reduced in patients compared with control subjects.

Summary
Functional neuroimaging has provided an objective assessment of pain processing in the brain. A network of brain regions is involved. In fibromyalgia, different neuroimaging tools have demonstrated dysfunction in the connectivity of DMN suggesting the key pathophysiological feature in fibromyalgia is a dysfunctional inhibitory pain network.

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