Journal of Clinical Neuroscience 38 (2017) 13–22

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

Alterations of brain activity in fibromyalgia patients

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A R T I C L E I N F O

Article history:
Received 25 September 2016
Accepted 26 December 2016

Keywords:
Fibromyalgia
Brain activity
Brain morphology
Functional Magnetic Resonance Imaging
Anterior cingulate cortex
Insula

A B S T R A C T

Fibromyalgia is a chronic pain syndrome, characterized by widespread musculoskeletal pain with diffuse tenderness at multiple tender points. Despite intense investigations, the pathophysiology of fibromyalgia remains elusive. Evidence shows that it could be due to changes in either the peripheral or central nervous system (CNS). For the CNS changes, alterations in the high brain area of fibromyalgia patients have been investigated but the definite mechanisms are still unclear. Magnetic Resonance Imaging (MRI) and Functional Magnetic Resonance (fMRI) have been used to gather evidence regarding the changes of brain morphologies and activities in fibromyalgia patients. Nevertheless, due to few studies, limited knowledge for alterations in brain activities in fibromyalgia is currently available. In this review, the changes in brain activity in various brain areas obtained from reports in fibromyalgia patients are comprehensively summarized. Changes of the grey matter in multiple regions such as the superior temporal gyrus, posterior thalamus, amygdala, basal ganglia, cerebellum, cingulate cortex, SII, caudate and putamen from the MRI as well as the increase of brain activities in the cerebellum, prefrontal cortex, anterior cingulate cortex, thalamus, somatosensory cortex, insula in fMRI studies are presented and discussed. Moreover, evidence from pharmacological interventions offering benefits for fibromyalgia patients by reducing brain activity is presented. Because of limited knowledge regarding the roles of brain activity alterations in fibromyalgia, this summarized review will encourage more future studies to elucidate the underlying mechanisms involved in the brains of these patients.

1. Introduction

Fibromyalgia syndrome (FMS) is chronic widespread musculoskeletal pain, with diffuse tenderness at multiple tender points [1]. FMS is a common pain disorder which affects 2–4% of the population, with 80% of those suffering being women [2]. Patients with fibromyalgia reported a lower pain threshold and higher pain rating in response to noxious or non-noxious stimuli, when compared with healthy controls [3–5]. The pathophysiology of fibromyalgia remains elusive. Several studies demonstrated that the peripheral sensitization together with changes in the central nervous system may play an important role in fibromyalgia development and progression [6–9]. For example, impaired anti-nociception and altered central processing of nociceptive input, such as pathological wind-up mechanisms [9], have been proposed as the potential neurobiological basis [10] of the chronic pain experienced in fibromyalgia. Moreover, vanilloid receptor, purino-receptors, and acid-sensing ion channel receptors, which are important nociceptive systems in the muscles and skin, seem to have some changes in fibromyalgia patients through unknown mechanisms [11]. Furthermore, the mediators of inflammation and nerve growth factors have been shown to stimulate these receptors and cause alterations in pain sensitivity, without any inflammatory lesions [11]. These findings suggest that the underlying mechanisms of fibromyalgia could be due to changes in the central nervous system without peripheral causes. The possible underlying mechanisms have been proposed including an impaired mechanism for descending pain inhibition, and the inhibition and diminished activation of the rostral anterior cingulate cortex and the brainstem, known as brain regions for pain modulation [2,12].

Despite these potential roles of the central nervous system (CNS) in fibromyalgia, limited knowledge is available at this time.

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http://dx.doi.org/10.1016/j.jocn.2016.12.014
0967-5868/

In this review, the changes in brain activity in various brain areas obtained from reports in fibromyalgia patients are comprehensively summarized. Evidence from the Magnetic Resonance Imaging (MRI) as well as the Functional Magnetic Resonance Imaging (fMRI) studies in fibromyalgia patients are presented and discussed. Moreover, evidence from non-pharmacological and pharmacological interventions offering benefits for fibromyalgia patients by reducing brain activities is presented. By using fMRI, those findings observed the correlation of elicited changes on the behavioral level and brain physiology [13–19]. In addition, fMRI during experimental pain of fibromyalgia patients showed an increase in pain sensitivity together with enhancement of brain activation, when compared with that of healthy controls [20]. Although peripheral nervous changes were widely investigated in *in vitro* and *in vivo* studies, several studies found the alterations of CNS, including the spinal cord and brainstem of fibromyalgia patients [2,9,12,13,16–20]. These findings emphasize the important roles of the high brain in the pathogenesis of fibromyalgia. However, the alterations of brain morphology and brain activity in fibromyalgia patients remain unclear. Therefore, the aim of the present review was to summarize possible alterations of brain morphology and brain activity in fibromyalgia patients and to provide the potential brain regions, which could play an important role in maintaining pain of fibromyalgia patients.

2. Evidence of the morphological changes in brain of fibromyalgia patients

Fibromyalgia has been proposed as one of the central nervous system disorders with an abnormal level of augmented sensory processing and an inability to modulate pain effectively [21]. Previous reports have used MRI and fMRI to investigate changes in the brain activity of fibromyalgia patients [2,21–23]. Changes have been found in both brain morphology and activity [23]. For brain morphology, changes in both white and grey matter have been found in fibromyalgia patients.

The white matter of the brain is composed of nerve fibers and myelin which are responsible for insulation and acceleration of impulse conduction [21]. White matter of the anterior cingulate cortex appears to be a functionally and morphologically conspicuous site in fibromyalgia patients [12,21,23]. Jensen and colleagues found a significantly lower volume of cortical white matter (the left rostral anterior cingulate cortex and the left lateral orbitofrontal cortex) of fibromyalgia patients, compared to healthy controls [23]. When the white matter reduces the conduction of impulses along nerve fibers slows down or completely fails, leading to impair brain function. These findings suggest that decreased white matter in those brain regions could be linked to a dysregulation of the inhibitory pain mechanism in fibromyalgia patients.

Grey matter consists of cell bodies and many synapses. Several studies showed a decrease in grey matters of some brain areas, but an increase in grey matter in other brain regions in fibromyalgia patients [14–16]. Increasing grey matter was found in the orbitofrontal cortex, cerebellum, basal ganglia, cingulate cortex, insula, SII and caudate, whereas the superior temporal gyrus, thalamus, amygdala, periaqueductal grey, insula and putamen were found to have a reduction in grey matter [21–24]. The orbitofrontal cortex (OFC) plays a role in the antinociceptive system, particularly to cognitive modulation of pain whereas the cerebellum shows an activation in response to nociceptive stimuli and is thus regarded as part of the pain processing network [25]. Activation in the cerebellum of fibromyalgia patients was highly

Table 1
Evidence of the brain morphological changes in the brain of fibromyalgia patients.

Study model	Sample size	Modality	Changes in brain morphology			References
			White matter	Grey matter		
			↓	↑	↓	
Case Controlled Study	20 FM Patients22 Healthy Controls	MRI, Voxel-Based Morphometry		• Lt. Orbitofrontal Cortex • Lt. Cerebellum • Bilat. Striatum	• Rt. Superior Temporal Gyrus • Lt. Posterior Thalamus	[21]
Cross Sectional Study	29 FM patients with affective disorders (AD), 29 FM patients without AD and 29 healthy controls	MRI, Voxel-Based Morphometry			• Lt. anterior insula (FM patients with AD)	[24]
Cross Sectional Study	9 FM Patients11 Healthy Controls	MRI		• Anterior Cingulate Cortex • Insula • Basal Ganglia • SII • Caudate	• Amygdala • Thalamus • Periaqueductal Grey • Putamen	[22]
Cross Sectional Study	26 FM Patients13 Healthy Controls	MRI	• Cortical White Matter • Lt. Rostral Anterior Cingulate Cortex • Lt. Lateral Orbitofrontal Cortex		• Cortical Grey Matter • Subcortical Grey Matter • Rostral Anterior Cingulate Cortex • Lt. Lateral Orbitofrontal Cortex	[23]
Observational Study	46 Premenopausal Women (23 FM Patients, 23 Age-Matched Healthy Controls)	MRI, Voxel-Based Morphometry		• Superior Frontal-Gyrus • Cerebellum • Medial • Orbitofrontal Cortex • Frontal Superior Medial Cortex	• Medial Orbitofrontal Cortex	[26]

FM = fibromyalgia; MRI = magnetic resonance imaging; Lt = left; Bilat = bilateral; SII = secondary somatosensory cortex.