Altered whole brain functional activity in patients with fibromyalgia

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Abstract

Objective

Fibromyalgia (FM) is a chronic pain disorder that takes a severe physical and psychological toll on patients and severely reduces their quality of life. In recent years, an increasing number of studies have used functional magnetic resonance imaging (fMRI) to investigate its pathogenesis. However, a recent summary analysis of functional connectivity in patients with FM is lacking.

Methods

We searched bibliographic databases, including PubMed, Web of Science (from inception until September 1st, 2022). Two separate researchers assessed the bias and quality of the studies. In order to further explain the core mechanism for FM, the abnormal brain function of FM was investigated by Activation Likelihood Estimation (ALE) analysis.

Results

Twenty-six FM publications (1,056 subjects) were eligible to be included in an ALE analysis. We found that the anterior cingulate (ACC) and insula (Ins) were abnormally active in patients with FM. In particular, the peak coordinates of (8,46,4) and (-46, -4,10) correspond to brain regions that were less active than healthy individuals. Furthermore, the Z-values were 4.46 and 4.97, while the p-values were 4.06 and 3.38. Surprisingly, we found that the degree of pain was negatively correlated with the activation of Ins (SDM-Z = -2.714).

Conclusion

This study demonstrates abnormal brain activation which could lead to increased sensitivity of pain in patients with FM. The study sheds light on the central mechanisms of FM and provides the basis for further research.

Key words

fibromyalgia, functional magnetic resonance, anterior cingulate, insula, central mechanism

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Received on June 7, 2023; accepted in revised form on November 2, 2023.

Competing interests: none declared.

Introduction

Fibromyalgia (FM) is a disease with chronic widespread pain (1), characterised by fatigue, sleep disorders, anxiety, depression, cognitive impairment or fibro-fog (2). Noteworthy, the prevalence of FM in the general population is 2–8% (3). The main explanation for the pathophysiology of FM is central nervous system sensitisation, resulting in sensitivity to both painful and painless stimuli (4, 5). Furthermore, studies have demonstrated that FM is characterised by an unbalanced transfer of excitatory and inhibitory neurotransmission, such as increased glutamate/glutamine and decreased gamma-aminobutyric acid (GABA), resulting in increased pain (6). Many neuroimaging studies have supported the theory that FM is a disease in the central nervous system (7).

The brain's functional activity would be changed as a result of FM. According to Schmidt-Wilcke (8), this alteration of functional activity may reflect the prominent role of various central nervous system levels in maintaining pain (even in the absence of primitive nociceptive stimuli) rather than inputting persistent sense of pain from the peripheral, which leads to chronic stimulation of the central pain system. Furthermore, other signs of FM, such as anxiety and despair, are also related to changes in function (9, 10). Therefore, it is necessary to compare the differences in functional activity between patients with FM and healthy subjects. Functional magnetic resonance imaging (fMRI) has made it possible to non-invasively assess functional activity in the brain (11). Thus, it has improved our understanding of the neural networks responsible for pain perception. Recently, an increasing number of studies have used fMRI to research the central mechanisms of FM. However, a recent summary analysis of functional connectivity in patients with FM is lacking. We aimed to use the "activation likelihood estimation" (ALE) method to further describe the change of functional activity in patients with FM.

Methods

Search strategy

We searched the PubMed and Web of Science bibliographic databases through November 1, 2022. The search input was a combination of main keywords according to the disease terminology of FM and either one of the general neuroimaging techniques: ["Fibromyalgia" OR "Fibrositis"]AND["fMRI" OR "functional Magnetic Resonance Imaging"] AND ["resting state" OR "baseline"]. For additional references, all reviews and bibliographies of relevant publications were reviewed.

Inclusion and exclusion criteria

The inclusion criteria were: (1) the article must include the results of a brain imaging study; (2) whole brain analysis was used to obtain activation results; (3) results are reported in a standardised coordinate space at the Montreal Neurological Institute (MNI) or standard Talairach space; (4) participants are not currently taking psychotropic medication or receiving other types of psychotropic interventions.

The exclusion criteria were: (1) no brain imaging; (2) single case report; (3) no statistical comparison of groups; (4) studies only with restricted region of interest (ROI) or volume of interest (VOI) analysis, no whole brain analysis; (5) no standard stereotactic spatial coordinates (Talairach or MNI); (6) connection connectivity; (7) patients with a history of mental illness or taking psychotropic drugs or receiving other types of psychotropic interventions, such as opioid medication, anticonvulsant agent, antidepressant drug monoamine (tricyclic antidepressants, dual serotonin/norepinephrine reuptake inhibitors, benzodiazepine, selective serotonin reuptake inhibitor, etc.).

Data extraction and demographic characteristics

Two authors (A.H. and H.Y.) examined the titles and abstracts to identify eligible studies that met all the inclusion criteria and no exclusion criteria. The selection procedures for the studies are summarised in Figure 1.

ALE analysis

We used Ginger ALE (v. 3.0.2, http://brainmap.org) and performed an ALE analysis of coordinates in Montreal Neurological Institute (MNI) space

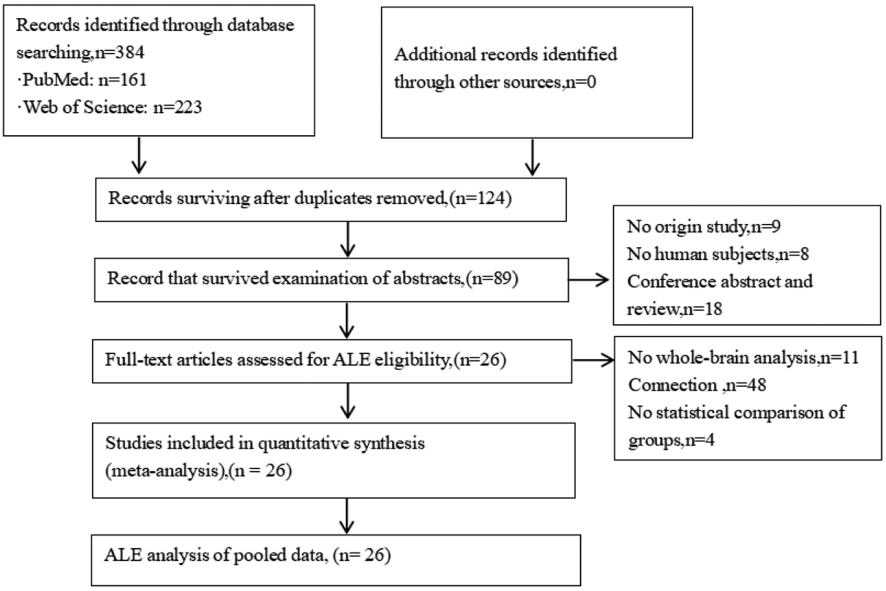

Fig. 1. PRISMA flow diagram of the identification of articles.

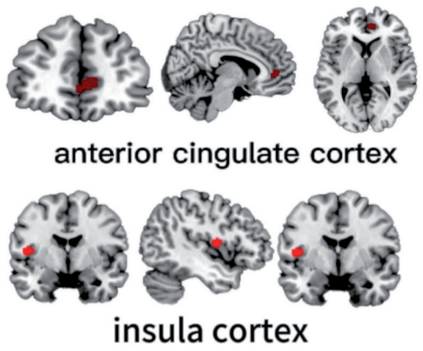

Fig. 2. Map of abnormal brain area activation in FM patients. The abnormal brain area activations are the anterior cingulate cortex and insula cortex. The peak coordinates of (8,46,4) and (-46, -4,10) are lowlier activated than healthy controls. The *p*-values are 4.06 and 3.38; meanwhile, the Z-values are 4.46 and 4.97.

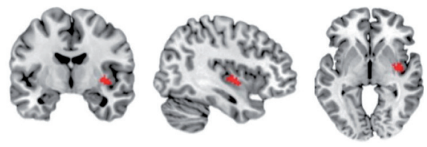

Fig. 3. Activation map of brain regions that correlate with pain levels. Increased pain degree was negatively correlated with the activation in the insula cortex (BAs 48; peak MNI coordinates: x = 40, y = -8, z = -2, voxels=111, p = 0.003322482, SDM-Z = -2.714).

(12). ALE analysis is a widely used coordinate-based analysis of neuroimaging data (13). The transformation tool (Talairach to MNI) implemented in Ginger ALE was used to convert all coordinates into MNI space in the Ginger ALE software. Then, the included coordinates were sorted based on whether they showed increased or decreased activation. Statistical ALE maps were corrected using the family-wise error rate (FWE), $p<0.05$. In order to set the null distribution, 1,000 permutation tests were performed. For illustration, the ALE maps were imported into Mango (rii.uthscsa.edu/mango) as an overlay on a standardised MNI-normalised template (Colin_27_T1).

Finally, we used the Seed-based *d* Mapping (SDM) software to explore possible relationships between local brain activation levels and patient anthropometric and clinical characteristics (age, sex, comorbidities, course of disease, and degree of pain) (14, 15). Statistical significance was determined using a stringent threshold of $p<0.025$ and a cluster extent = ten voxels.

Results

1,056 individuals from 26 studies were included in the analysis. The investigation discovered aberrant activation of the anterior cingulate cortex and insula. In particular, the peak coordinates of (8,46,4) and (-46,-4,10) correspond to brain areas that were more minimally active than healthy controls. Furthermore, the Z-values were 4.46 and 4.97, while the *p*-values were 4.06 and 3.38. The precise diagram is displayed in Figure 2 and Table I.

Regression analysis showed that increased pain degree was negatively correlated with the activation in the insula cortex (BAs 48; peak MNI coordinates: x=40, y= -8, z= -2, voxels=111, p=0.003322482, SDM-Z = -2.714; Fig. 3). We found that the age, sex, comorbidities, and course of diseases had no obvious correlation with brain activation.

Discussion

This ALE analysis was designed to evaluate brain activation changes in FM patients. In order to gain more detailed understanding of the underlying pathophysiology of chronic pain syndrome, we included brain areas with both increased and decreased activation in FM patients. Corrected by ALE multiple comparisons, our analysis revealed the differences between brain regions of FM and healthy controls, including the anterior cingulate cortex and insula.

The anterior cingulate cortex and the inferior pain modulation system

The anterior cingulate cortex (ACC) is a critical cortical area for pain perception, chronic pain and emotional disturbance (16). It can be subdivided into anterior-middle and posterior parts. The anterior part participates in attentional stimuli, while the posterior area participates in the sensory integration aspects of pain processing (17). Furthermore, the ACC is a very diverse cortical region in terms of intrinsic and extrinsic connectivity (18), which offers a physiological explanation for the relationship between pain and anxiety. Within the ACC, there is an abundance of neurons, pyramidal cells, projection fibres, etc. (16), contributing to the tight connectivity between the layers of cells. In addition, it transfers projections to other cortical regions, such as the cortex, subcortical regions and spinal cord (19).

The ACC with periaqueductal grey (PAG) and medial prefrontal cortex (mPFC) are key brain areas in the downstream pain modulation system. Together, they constitute a core network with the rostroventral medulla (RVM). They modulate pain through their inhibitory effects on pain (20). Surprisingly, many studies found reduced functional connectivity between ACC and mPFC (19-23) and PAG (20,

Table I. Results table. Cluster-forming value: *p* uncorr. <0.001; cluster-level inference: *p* corr. <0.05; N foci contrib.: the number of foci of the included studies which contributed to a resulting cluster.

Label	Cluster size	Coordinates (MNI)					
	mm3	X	Y	Z	P	Z	N foci contrib.
anterior cingulate cortex	912	8	46	4	4.066729E-6	4.46	5
Insula cortex	768	-46	-4	10	3.3807086E-7	4.97	4

23-25) in patients with FM. In the meantime, the functional connectivity between ACC and PAG was negatively correlated with depression (21). Consistently, improved ACC/PFC functional connectivity has been used as a benchmark for good results after exercise treatment in FMS patients (20).

As a whole, FM patients have considerably lower functional connectivity in the ACC, PAG, and mPFC, which shows that the downstream pain inhibitory circuit has lower functional connectivity and has been disrupted and aberrant in FM patients. This aberration weakens the body's natural ability to suppress pain, increasing the severity of pain perception and encouraging more unfavourable reactions to it.

Lateral effects of the insula

The insula (Ins) plays a crucial role in pain processing (27). On the one hand, the anterior Ins and ACC are essential to processing emotional pain and learning as a part of the medial pathway (28). On the other hand, the posterior Ins encodes pain as a part of the lateral pain pathway, together with the primary and secondary somatosensory cortex. There is increasing evidence that Ins flexibly connects attentional and emotional brain regions (29), and these connections are essential determinants in the experience of factual pain.

In Ins, there is a lateralised effect whose performance is hemispheric asymmetry (30). Interestingly, our study revealed that the functional connectivity tendency of left and right side Ins is the opposite. The functional connectivity of the left Ins to the PAG (26, 28, 33, 34) and PFC (21, 26, 31-33) appeared similarly reduced in the resting state. Meanwhile, subjective clinical pain levels were inversely linked with the connectivity between the left insula and the PAG (33), and patients with FM who had higher connectivity would experience better paroxysmal effects following treatment. On the contrary, there was an increase in the functional connection between the right insula and the PAG (34, 35). Minor functional connectivity produced more significant analgesia following treatment (36); higher functional connectivity between the right Ins and cuneate lobes (37) was associated with higher pain levels, and the same phenomenon occurred with the right Ins and the right intraparietal sulcus (38).

The structural laterality of Ins is linked to cognition and emotion, and it has been hypothesised that changes in autonomic input to the cortex physiologically underlie the lateralisation of emotional processing (39). The alteration in parasympathetic function, comprising safety, positive effects, and approach behaviours, is caused by direct stimulation of the left Ins (40). However, the right Ins controls the sympathetic nervous system, which is responsible for hunger, unfavourable emotions, and avoidance behaviours. However, further research is warranted to understand the mechanisms underlying functional connections between the left and right hemispheres.

Anterior cingulate cortex and insula
– Functional connectivity between the anterior cingulate cortex and insula

A close functional connectivity was also found between ACC and Ins, which was more potent at baseline in patients with FM than in the healthy group (23). Furthermore, it had also been found that functional connectivity between Ins and ACC was negatively correlated with pressure thresholds (37). Better post-treatment episodes were related to a lower connection at baseline (36). At the same time, therapeutic outcomes were predicted by the functional connection between ACC and Ins (40). Specifically, patients with lesser connection would experience more pain reduction following therapy. Additionally, it was discovered that the 'second pain' (TSSP) condition, which produced and sustained the state of central nociceptive hyperalgesia, activated both Ins and ACC (41). In this state, Ins and ACC become the pathways for integrating the sensory features of unpleasant and painful sensations (42).

In conclusion, we could summarise the findings that ACC and Ins have the presence of central sensitisation in patients with FM. They are closely related to pain and emotion in response to increasing stimuli, such as pain, which increases emotional factors in FM. This would contribute to the development of emotional factors in FM and further contribute to the chronicity of pain. These findings may enrich the central mechanisms of FM and improve further evidence for the relationship between emotional factors and chronic pain.

– Anterior cingulate cortex and insula with the network of brain regions

The ACC and Ins were closely related to the resting-state network (DMN) (43). The DMN has the functions of psychological activity, including autobiographical memory, self-monitoring, self-regulation and source monitoring, and social cognitive functions. In addition, severe psychopathology is associated with an overactive and overconnected DMN (45). Surprisingly, the connectivity of ACC and DMN networks could predict the effects after treatment with transcranial magnetic stimulation in patients with FM (37). Specifically, prior to treatment, the weaker the connection, the better the effect after treatment. Furthermore, the connection of the right Ins and the DMN network had significantly improved (43, 44). Mainly, mPFC, a central DMN hub and explicitly involved in self-reflection, had aberrant functional connectivity with both the ACC and Ins (26). Thus, the link between Ins ACC and DMN is closely associated with the central mechanism of FM.

Meanwhile, ACC and Ins form the core structures of the salience network (SN), which is related to identifying internal and external stimuli, evaluating emotion, and guiding behaviour (45). In addition, it is a part of the neural sign of physical pain, which plays a role in the processing of pain (47). The central, autonomic, and peripheral nervous systems are intricately linked to the core of SN structures. This enables them to participate in intricate brain and biological processes, including memory and emotion, as well as immunological, digestive, and cardiac functions (48, 49). Interestingly, studies have shown that FM is associated with the abnormality of SN (50). Specifically, SN showed more sensitivity to emotional stimuli (51) and a more extended pain response (52, 53). Consistently, SN had increasing connectivity with DMN (33, 54). Thus, ACC and Ins, the core structures of SN, also play an essential role in connectivity between various brain networks. Different brain network changes enrich the basis for structural and functional brain abnormalities in patients with FM.

Pain effects on the activation of the brain in fibromyalgia

A significant finding of our study was the correlation between increased pain in FM patients and reduced activation in the insula. This observation was consistent with research done by Sawaki *et al*. who noted that patients with insula lesions displayed abnormally heightened sensitivity to pain (55). The neurobiological basis indicated the critical role of synaptic plasticity in pain encoding, potentially altering the excitation/inhibition balance in the brain (56). As a significant cortical region, the insula boasted highly adaptable neuronal synapses and played a pivotal role in pain perception and chronic pain (57). We could speculate that aberrant insula activation can influence excitatory synaptic transmission and neuronal excitability. Moreover, as an integral component of the brain's pain processing network, the hypoactive insula may disrupt the network's pain regulation, ultimately leading to increased pain sensitivity.

Conclusions

In summary, our findings indicate abnormal activation of the anterior cingulate cortex (ACC) and insula (Ins) in patients with FM, and further analysis revealed a trend towards decreased functional connectivity between ACC and the downstream pain inhibitory pathway. In addition, there is an opposite trend in functional connectivity between the left and right Ins and other brain structures. Furthermore, ACC and Ins are found to have abnormal connectivity with DMN. At the same time, they are the part of SN. This study proves that the FM pain network's excitatory and inhibitory pathways are out of balance. It will be helpful for further studies of the underlying causes of persistent pain, anxiety and depression in FM patients. Meanwhile, we speculate that the hypoactive insula activation leads to abnormalities in the pain pathway's regulation of pain, resulting in increased sensitivity to pain in patients with FM. It consistently implies that brain structural activation and functional connectivity may serve as critical predictors for managing chronic pain in the future.

Limitations

This analysis concentrated on abnormal total brain activation in FM patients. Nevertheless, because we included only 26 studies and the heterogeneity in trial design and demographic baseline between studies, the results should be interpreted with caution. Further analyses by functional connection should be performed in the future.

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