

Brain Functional Alternations of the Pain-related Emotional and Cognitive Regions in Patients with Chronic Shoulder Pain

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Objective: Chronic shoulder pain (CSP) is a common health problem associated with shoulder dysfunction and persistent pain for many different reasons. However, the studies of pain-related functional brain regions in CSP have been poorly investigated. The main purpose of our study was to observe whether there are abnormal functional changes in brain regions in patients with CSP by using functional magnetic resonance imaging (fMRI).

Patients and Methods: We compared the differences of brain regions between 37 patients with CSP and 24 healthy controls (HC) using regional homogeneity (ReHo) method. The patients with chronic shoulder pain and healthy controls were matched for age and gender. Brain regions which had abnormal ReHo values were defined as seed region of interests. The approach of seed-based functional connectivity (FC) was further performed to analyze the connectivity between the seeds and whole brain regions. The relationship between abnormal regions and current clinical pain was also evaluated.

Results: Compared to healthy controls, the patients with CSP showed increased ReHo values in the left middle temporal gyrus and decreased ReHo values in right orbitofrontal cortex (OFC). The seed-based analyses demonstrated decreased connectivity between the right OFC and right rectus, superior frontal gyrus in patients with chronic shoulder pain. However, a correlation between ReHo values and clinical characteristics in CSP patients was not found.

Conclusion: The observed results indicate that there are abnormal ReHo values in brain regions of patients with CSP, especially in the OFC and middle temporal gyrus. Our findings demonstrate that the experience of CSP patients may be mainly associated with cognitive-affective pain processing, rather than nociception.

Keywords: functional magnetic resonance imaging, chronic shoulder pain, cognition, emotion

Introduction

Chronic shoulder pain (CSP) is a common musculoskeletal disorder associated with shoulder stiffness, a limited range of motion and persistent pain.¹ In the general population, the prevalence and incidence of CSP were about 66.7%² and 2.5%,³ respectively. Patients with CSP need cost about € 4139 per year⁴ and CSP causes about 4.5 million visits to physicians in the United States.⁵ CSP can lower the quality of life,⁶ reduce the ability to work, cause emotional disorders and has substantial socio-economic impact.⁷ For these reasons, it is appropriate to explore the neural mechanisms of CSP, which are associated with clinical treatment.

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Pain is an essentially subjective experience, associated with emotion and cognition which can be experienced differently by each individual and their personality.⁸ One systematic review had an interesting finding that our brain reserves certain activity for pain-related factors even in the resting state.⁹ The pain-related brain regions primarily included the thalamus, insula and anterior cingulate, while other brain regions were likely to be stimulus-specific.¹⁰ In recent years, many studies have valued the underlying neurophysiological mechanism of brain functional changes in low back pain,¹¹ trigeminal neuralgia,¹² chronic migraine,^{13,14} fibromyalgia,¹⁵ knee osteoarthritis,¹⁶ visceral pain,¹⁷ but literature focused on abnormal pattern of cerebral networks for pain processing in patients with shoulder pain is insufficient. In the brain, the functional interaction effects of pain, cognitive as well as negative affect have been widely reported^{18,19} and multiple mechanisms are needed to fully explain the emotional and cognitive brain alternations associated with pain.²⁰ It is uncertain whether CSP patients have any changes in brain.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a useful technique which can determine alternations of brain structure and function in patients with chronic pain. The blood-oxygen-level-dependent (BOLD) signals can measure the spontaneous and intrinsic neuronal activity as a better indicator of processing within an area, and also can be used to glean robust information about functional localization within the brain.^{21,22} Many studies use fMRI to reveal central pain processing mechanisms and provide an evidence for a musculoskeletal or neurologic disease. Chronic pain could impact brain function and behavior by altering the flow and integration of information between cerebral regions.²³ Regional homogeneity (ReHo) is applied to demonstrate the regional consistency of spontaneous neuronal activity characteristics of each voxel within the whole brain.²⁴ Moreover, among all kinds of rs-fMRI data analysis methods, the ReHo shows high test-retest reliability²⁵ and superior sensitivity in detecting complex spontaneous hemodynamic responses in brain function. The alterations of ReHo can be used as neural markers to reveal the mechanisms of some diseases.²⁶ Central system may play an important role in CSP, although the main pathophysiology changes of chronic shoulder pain remain unclear.

Overall, many neuroimaging studies have demonstrated that patients with pain-related symptoms have abnormal neuronal activity and structural function,^{11–17} few have focused on chronic shoulder pain. Therefore, the main objective of our study is to investigate how

chronic shoulder pain affects brain function. In view of the insufficient studies on the brain mechanisms of CSP, we preliminarily made a hypothesis that patients with CSP would exhibit abnormal ReHo values in certain functional regions compared with healthy controls.

Materials and Methods

Subjects

A total of 39 patients with CSP were recruited from department of acupuncture at Beijing Hospital Traditional Chinese Medicine Affiliated to Capital Medical University from December 2016 to July 2017. The study was conducted in accordance with the Declaration of Helsinki. All the participants were informed about the entire study procedures and provided written informed consent.

The inclusion criteria of CSP patients were: 1) age from 45 to 65 years; 2) right-handed;^{27,28} 3) shoulder pain duration of at least 6 weeks, and not more than 24 months; 4) visual analogue scale (VAS) score between 50 and 100mm (VAS score of 0–100mm, 0 mm means “no pain” and 100 mm means “worst pain”) in the past week. The exclusion criteria were: 1) other chronic pain conditions or shoulder trauma, such as headache, back pain, rheumatoid arthritis; 2) current therapy involving analgesics for the pain; 3) obvious abnormalities of brain structures on conventional MRI scan, such as tumors; 4) a history of neuropsychiatric disorders, such as depressive disorder, bipolar disorder, schizophrenias, stroke, or multiple sclerosis; 5) a history of alcohol or substance abuse; 6) had contraindications to have an MRI.

Healthy controls (HC) were recruited by using advertisements and they were age -and gender-matched to patients. The inclusion criteria for HC were as follows: 1) were right-handed; 2) no history of any chronic pain; 3) no organic lesion or altered brain structures on MRI; 4) no history of alcohol or medications abuse; 5) no neurological or psychiatric disorders; 6) no contraindications to have an MRI.

In our study, thirty-nine patients with chronic shoulder pain and twenty-six healthy controls fulfilled the inclusion criteria. Rs-fMRI data were collected from all participants and each participant had fully finished MRI scan. There were two CSP patients and two healthy controls who were excluded because of excessive head motion (head motion > 2mm and >2.0 degree) during MRI scanning. Before MRI scanning, all CSP patients need to complete a VAS score and a Constant-Murley score (CMS) to evaluate the degree of their pain.

MRI Data Acquisition

Functional MRI was carried out using a Siemens 3.0 Tesla scanner (Skyra, Siemens, Erlangen, Germany) equipped with a standard head coil. All participants underwent functional MRI scanning at the Department of Radiology for Beijing Hospital of Traditional Chinese Medicine Affiliated to Capital Medical University. Foam pads were used to minimize head motion and earplugs were used to reduce noise interference. During the rs-fMRI acquisition, participants were in a supine position with their eyes closed, and were instructed to remain awake, avoid thinking and keep still.

Rs-fMRI data were obtained using a gradient echo planar imaging (EPI) sequence with the following parameters: whole brain, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, field of view (FOV) = 220 mm × 220 mm, flip angle (FA) = 90°, slice thickness/gap = 3.5/0.6 mm, axial slices = 33, in-plane resolution = 64 × 64, and 240 volumes. All participants reported that they remained awake during the entire scanning time.

Imaging Data Preprocessing

The functional data were preprocessed using statistical parameter mapping SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8>) for MATLAB and the Data Processing Assistant and Resting-State fMRI (DPARSF) toolbox.²⁹ In order to get optimal and balanced rs-fMRI data, the first 10 volumes were removed from each participant. The remaining volumes were corrected using slice timing, spatially realigned and head motion. A participant was to be removed from the analysis if head motion was more than 2 mm in any direction. The corrected data were spatially normalized to fit a standard brain template in the Montreal Neurological Institute (MNI) coordinate space and then re-sampled to 3×3×3 mm³. The linear trend of the signals was removed over each run, and the nuisance signals (white matter signals, cerebral spinal fluid signal, and Friston 24 head motion) parameters were regressed. Subsequently, a band pass filter with a frequency range of 0.01–0.08Hz was applied, and these images were smoothed with an 8 mm full-width half-maximum Gaussian kernel.

ReHo Analysis

ReHo was computed using the Kendall concordance coefficient with the DPARSF toolbox. Kendall harmony coefficient is used to demonstrate the brain function regions to

be at a different time sequence consistency of voxel. The whole brain ReHo maps were acquired by computing the consistency of the time series between each voxel and its adjacent 26 voxel in brain.¹² The cluster-level corrected for Gaussian Random Field theory correction (GRF) (voxel level $p < 0.001$ and cluster level $p < 0.05$, Two-Tailed) was applied for the between-groups analysis.

Functional Connectivity Analysis

A seed-based analysis was applied to measure functional connectivity by extracting time series from the region of interest (ROI). The seed region was defined as a specific area which was identified by ReHo analysis between the CSP patients and healthy controls using a temporal correlation.³⁰ Seed-based correlation was calculated between the seed and whole-brain voxels by Pearson's correlation analysis. The obtained FC maps were converted to z values using Fisher's r -to- z transformation to normalized connectivity map of each individual. The cluster level corrected for Gaussian Random Field theory correction (GRF) (voxel level $p < 0.01$ and cluster level $p < 0.05$, Two-Tailed) was applied for the between-groups analysis.

Statistical Analysis

Demographic and clinical data obtained from participants were analyzed by the SPSS 22 software. Shapiro–Wilk test was used to detect the normal distribution. Two-sample independent t -test and Chi-square test were used to assess the differences in baseline age and gender. A two-sample t -test was performed to analyzed ReHo maps and FC maps comparing CSP patients and healthy controls using the DPARSF software. Cluster level corrected for multiple comparisons (GRF) was applied to the ReHo and FC analysis. Pearson's correlation coefficient was implemented to verify the relationships between abnormal ReHo values or seed-based FC values and clinical characteristics in patients, including VSA, CMS and shoulder pain duration.

Results

Demographic and Clinical Characteristics

Table 1 shows details about demographic and clinical characteristics of participants. Thirty-seven patients (mean age: 53.65±5.45 years, 17 females) and 24 matched HCs (mean age: 55.83±4.72 years, 14 females) completed the entire study. And the mean duration of CSP was 6.38 ±6.05 months, the mean pain score on the visual analogue

Table 1 Demographic and Clinical Characteristics of CSP Patients and Healthy Controls

Parameter	CSP Patients	Healthy Controls	P-value
Age(year)	53.65±5.45	55.83±4.72	0.113
Sex			
Male	20	10	0.344
Female	17	14	
Pain duration(month)	6.38±6.05	N/A	
Pain degree (VAS)	66.35±13.32	N/A	
Shoulder function (CMS)	53.24±13.84	N/A	

Note: Data are mean ± standard deviation for age, pain duration, pain degree and shoulder function.

Abbreviation: N/A, not applicable.

scale (VAS) was 66.35±13.32, and the mean shoulder function score on CMS was 53.24±13.84 in patients.

ReHo Differences Between Groups

After correction for GRF, the ReHo values in the CSP group were significantly increased in left middle temporal gyrus and decreased in right orbitofrontal cortex (OFC) compared with healthy controls (Figure 1 and Table 2). No correlation was found between ReHo values in abnormal brain regions and clinical characteristics.

Seed-Based Functional Connectivity Between Groups

Due to the significantly different ReHo maps in left middle temporal gyrus and right orbitofrontal cortex between CSP and HC, we chose the left middle temporal gyrus and right orbitofrontal cortex as seed regions and performed a whole brain FC analysis. Compared to HC, the results of seed-based resting-state functional connectivity analysis shown decreased FC between OFC and right rectus, superior frontal gyrus in patients (Figure 2 and Table 2). However, no brain regions with connectivity were found in left middle temporal gyrus.

Discussion

Our study aimed to explore the abnormal functional brain regions that are associated with pain during the resting state in patients with CSP. The primary findings showed that patients with CSP had significant increased ReHo values in middle temporal gyrus and decreased ReHo values in orbitofrontal cortex (OFC), compared to healthy controls. Two specific brain regions are both involved in

pain regulation, related with emotion, memory and cognition.^{31–33} Further seed-based FC analysis revealed decreased FC between OFC and right rectus as well as superior frontal gyrus, which are important regions related to cognition and the experience of pain.³⁴

Pain causes physical discomfort and psychological affective reactions³² and is perceived during consciousness.³⁵ OFC plays an important role in the cognitive processing of pain perception, for example, it can ease pain through adjusting and controlling endogenous opioid release.³⁶ Multivariate models are used to analyze brain responses to pain in fMRI studies, and OFC has been found to be a crucial region which could precisely distinguish pain and non-pain experience.³¹ The OFC has the capacity for pain and emotional regulation. Negative affectivity is associated with pain-related cognitions and OFC mediates automatic emotion regulation.³² Spontaneous magnetoencephalography (MEG) suggested that patients with fibromyalgia (FM) had abnormal spectral powers in OFC related to emotional and cognitive modulation of pain.³⁷ Another study indicated that deactivation of OFC was associated with nociceptive stimulation and sympathetic activation,³⁸ and the similar deactivated OFC was also observed in our study. Chronic pain may modify the functional patterns of OFC, and the deactivation of OFC also contributes to pain perception. Comparing CSP patients to healthy controls, our findings of altered ReHo values in OFC may be one reason for pain persistence in chronic shoulder pain.

During our study, hypoactive OFC was observed in chronic shoulder pain, and inhibitory compensation can be used to explain this finding, to balance the over-excitation input in pain modulation for long-term pain condition.³⁹ Chronic pain is a complex mechanism that affects our emotions and cognition; it also could distort our judgment and prediction based on emotional guide.⁴⁰ OFC is an important subdivision of prefrontal cortex (PFC) critically involved in subjective decision-making.^{41,42} Behavioral decision-making in adolescents can be adversely affected due to deactivation in OFC⁴³ and animal experiment further confirmed that the synchronous expression of inactive OFC and active NAC (Nucleus accumbens) can undermine behavioral control.⁴⁴ Our study reveals obvious difference in OFC, and also provide additional evidence for decision-making impairment in chronic pain conditions.

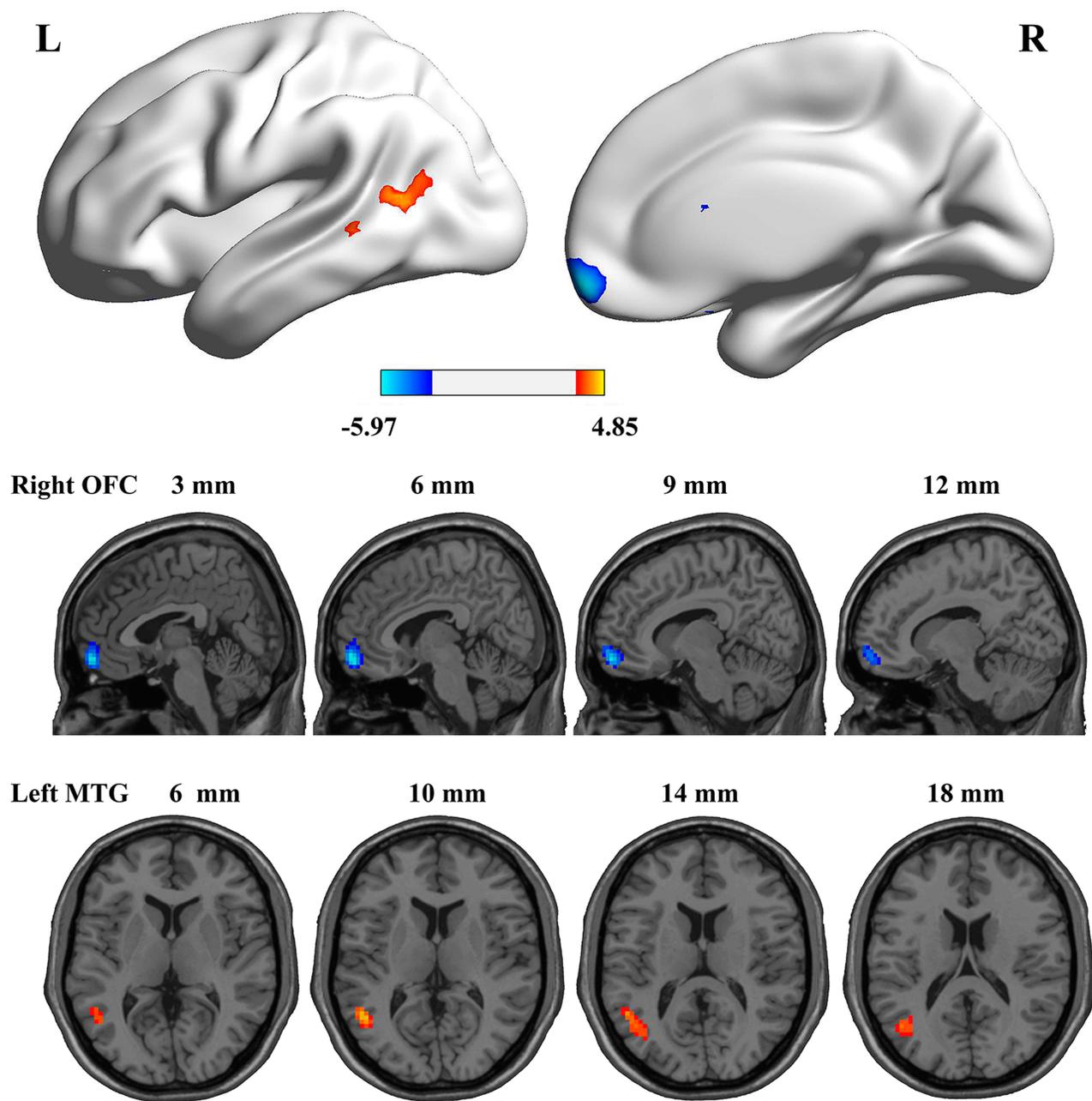


Figure 1 Medial views and axial medial views of significant changes in ReHo between chronic shoulder pain (CSP) group and healthy controls (HC) group. The hot color indicates that chronic shoulder pain (CSP) group had increased ReHo compared with healthy controls (HC) group. The cool color indicates that chronic shoulder pain (CSP) group had decreased ReHo compared with healthy controls (HC) group. Gaussian Random Field theory correction (GRF) correction with significant voxel level $p < 0.01$ and cluster level $p < 0.05$, Two-Tailed.

In this study, seed-based FC approach showed decreased connectivity between OFC and right rectus gyrus and superior frontal gyrus in patients. Based on current studies, the rectus gyrus is considered to be linked with the recovery of consciousness^{45,46} and dynamical emotion processing.⁴⁷ Superior frontal gyrus has similar functions as OFC and middle temporal gyrus,

which also is an important region related to cognition, social learning and painful experience.³⁴ A meta-analysis demonstrated that patients with Alzheimer's disease and mid-cognitive impairment had compensatory activity in superior frontal gyrus and medial temporal gyrus.⁴⁸ One study demonstrated that the worsening pain symptoms may attribute to the thinner cortex in

Table 2 Brain Regions Showing ReHo and Seed-Based Functional Connectivity Differences Between Two Groups

Brain Regions	Side	MNI Coordinates			Cluster Size (mm ³)	Peak t value
		x	y	z		
ReHo differences, CSP patient<healthy controls						
Orbitofrontal Cortex	Right	6	60	-12	150	-5.97
ReHo differences, CSP patient>healthy controls						
Middle Temporal Gyrus	Left	-51	-57	12	85	4.73
Seed-based functional connectivity: the right OFC, CSP patients<healthy controls						
Rectus Superior Frontal Gyrus	Right Right	9	12	-12	327	-5.30

superior frontal gyrus and anterior cingulate in cervical spondylosis patients.⁴⁹ And pain could lead to lower connectivity between precentral gyrus and superior frontal gyrus which participate in the processing of pain-related emotional and cognition in classical trigeminal neuralgia.⁵⁰ It is similar to our findings.

Another important finding in our study was the hyperactive middle temporal gyrus in CSP patients compared to healthy controls. Since many functional regions are shared for pain processing and cognitive processing, patients with chronic pain often complain cognitive impairment and inattention.^{51,52} Pain-related attention and emotion are closely associated with medial temporal cortex, which is considered to be linked with pain integration and pain perception.³³ Increased grey matter volume (GMV) in the middle temporal lobes was found in postherpetic neuralgia⁵³ and low-back pain altered several functional brain regions including middle temporal lobes,^{54,55} and a similar result was reported in burning mouth syndrome patients.⁵⁴ Our finding also demonstrated that the middle temporal gyrus engages in pain regulation. A study of fibromyalgia reported that dampened deactivation in the medial temporal lobe may contribute to the prolongation of pain sensation.⁵⁶ A Hyperactive medial temporal lobe, especially the anterior temporal pole was considered as a biomarker for migraine attacks.⁵⁷ A similar, activated

middle temporal lobe was observed in our study, which indicates the middle temporal lobe is associated with pain perception in CSP. Kucyi et al found enhanced functional coupling between PAG and default mode network regions (involved medial temporal lobe, mPFC and PCC) linked with attention on pain and considered the pain-related cognitive processing as a dynamic and continuous procedure.⁵⁸ In our study, the activated middle temporal lobe may be responsible for more attention to pain in CSP patients.

There are some limitations in this study. First, there are many distinctions between sub-categories of shoulder pain due to ageing, somatization tendency, mental health and occupation. We did not distinguish the functional changes between different shoulder pain categories.⁵⁹ Second, left and right shoulder pain have not been discussed separately, we will perform additional analyses to compare whether there is any differences between left and right shoulder pain in cerebral regions in future studies. Third, patients with CSP generally have anxiety or depression,⁶⁰ but emotion-related scales were not investigated in this study. We should assess patients' emotion condition to verify what role pain-related anxiety or depression plays in shoulder pain. Fourth, participants with age range between 45 and 65 years old were recruited which may restrict the generalization of the present results to other populations. Future studies with a wider age range are needed to increase external validity.

Conclusion

In summary, our findings illustrate CSP patients display abnormal ReHo values in OFC and middle temporal cortex compared with healthy controls, and decreased FC between the OFC and rectus gyrus as well as superior frontal gyrus. Given the impact of pain on emotion, cognitive and attention abilities, the current study provides evidence for cognitive-affective pain modulation and perception processing associated with chronic shoulder pain. The results also support that the abnormal ReHo values in the OFC and middle temporal cortex are involved in the mechanism of chronic shoulder pain.

Ethics and Consent Statement

The study was approved by the Research Ethical Committee of Beijing Hospital Traditional Chinese Medicine Affiliated

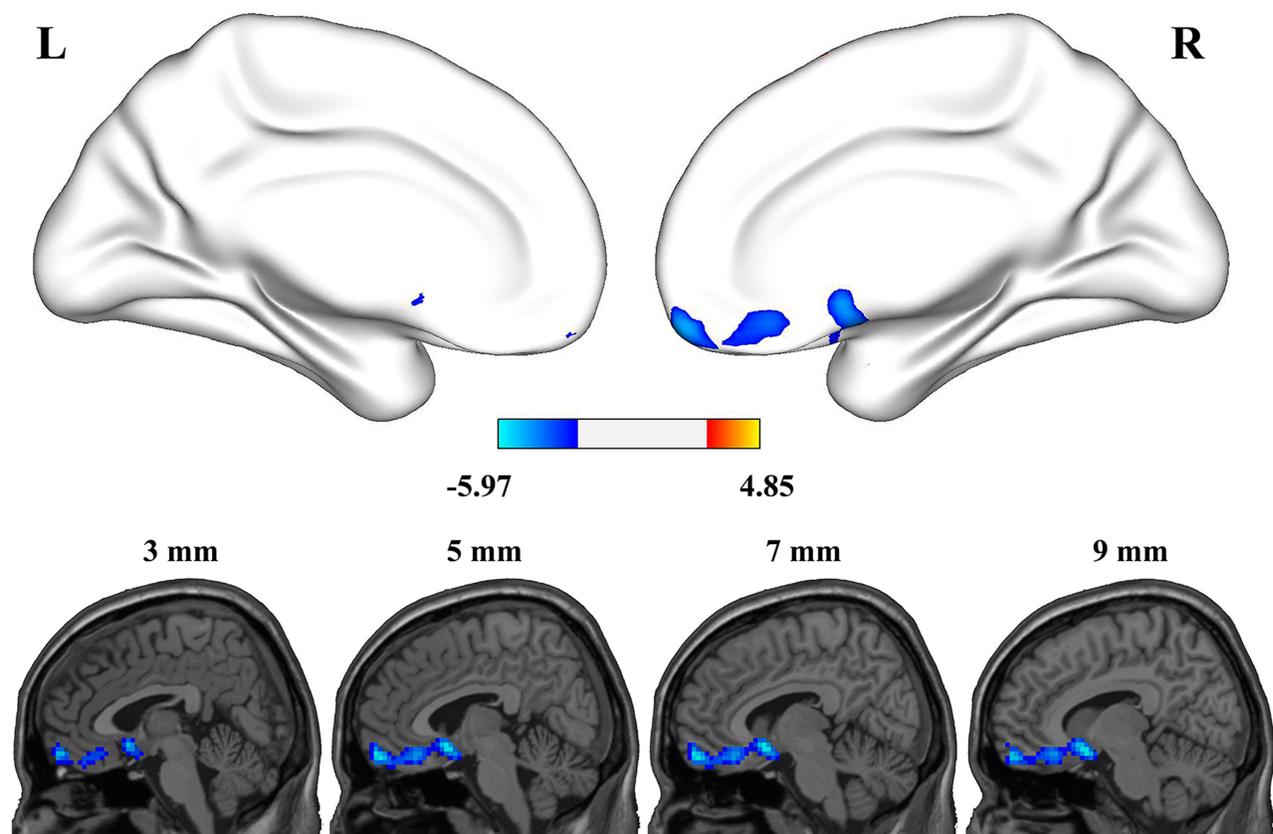


Figure 2 Group differences in seed-based functional connectivity. The seed was defined as the right orbitofrontal cortex. The cool color indicated decreased functional connectivity in the chronic shoulder pain (CSP) group compared with healthy controls (HC) group. Gaussian Random Field theory correction (GRF) correction with significant voxel level $p < 0.01$ and cluster level $p < 0.05$, Two-Tailed.

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Author Contributions

Cun-Zhi Liu conceived and directed the study design, Shuai Zhang, Chao-Qun Yan, Shang-Qing Hu participated in study design and performed the experiments, Na Zhang, Jin-Ling Li and Xu Wang analyzed and interpreted the data, Jin-Ling Li, Chao-Qun Yan, Na Zhang, Shuai Zhang and Shang-Qing Hu drafted the manuscript. Xu Wang, Li-Qiong Wang and Cun-Zhi Liu revised the manuscript. Chao-Qun Yan and Li-Qiong Wang assisted in imaging analysis. All authors contributed to data analysis, drafting or revising the article, gave final approval

of the version to be published, and agree to be accountable for all aspects of the work. And if you need the original data, please contact Cun-Zhi Liu, email: lcz_tg@126.com.

Disclosure

All authors declare no conflicts of interest in this work.

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