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ORIGINAL RESEARCH

The Duration of Chronic Pain Can Affect Brain Functional Changes of the Pain Matrix in Patients with Chronic Back Pain: A Resting-State fMRI Study

Yingxuan Hu[1,*], Junqin Ma[1,*], Bingmei Chen[2], Jiahui Pang[1], Wen Liang[2], Wen Wu[1]

[1]Department of Rehabilitation Medicine, Zhujiang Hospital, Southern Medical University, Guangzhou, People's Republic of China; [2]Department of Radiology, Zhujiang Hospital, Southern Medical University, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wen Wu; Wen Liang, Email wuwen66@163.com; liangwendoc@163.com

Purpose: This study was conducted to explore the differences in functional changes in the pain matrix in patients with chronic back pain (CBP) at different stages and identify whether these brain changes were related to the pain duration.

Patients and Methods: In this study, 29 healthy individuals and 54 patients with CBP were recruited. According to the pain duration, 25 patients (3 to 12 months) were divided into the CBP-S group and 29 patients (≥ 24 months) were divided into the CBP-L group. All subjects completed clinical pain-related measurement and functional magnetic resonance imaging (fMRI) scans. Moreover, the amplitude of low-frequency fluctuation (ALFF), functional connectivity (FC), and correlation analysis were conducted in this study.

Results: Compared with healthy controls, patients in the CBP-L group showed significantly decreased ALFF in the left precuneus. In the FC analysis, patients in the CBP-S and CBP-L groups showed significantly decreased FC in several regions in the bilateral orbitofrontal cortices (OFC) and the left ventral posterior insula. Moreover, there were significant differences in the FC between the left hyper granular insula and the probabilistic area in OFC in pairwise group comparisons. The correlation analysis results demonstrated that pain duration was correlated with these functional brain changes, and the ANCOVA results revealed that pain intensity and pain interference scores did not affect the FC analysis results.

Conclusion: There are different changes in the pain neural matrix in patients with chronic pain at different stages. Furthermore, the pain duration is related to brain functional changes.

Keywords: chronic back pain, pain duration, fMRI, resting-state, pain matrix

Introduction

Chronic pain is a prevalent condition with a substantial disease burden that affects a large population worldwide. Around the globe, more than 30% of individuals suffer from chronic pain,[1] which has become a leading cause for individuals to seek medical care.[2] Prolonged pain duration not only increases the economic burden on patients but also leads to emotional distress, sleep disturbance, and impaired social functioning.[1,3] Therefore, investigating the progression and chronicity of pain holds significant value.

In the research on the mechanism of pain chronicity, brain and peripheral nerve abnormalities in patients with chronic pain were revealed in some neuroimaging studies based on healthy individuals and patients with acute pain and chronic pain. In contrast to healthy individuals, patients with chronic pain showed abnormally increased activity in multiple brain regions and a decrease in the gray matter volume.[4–6] Besides, these patients also exhibited altered brain activity in comparison with those experiencing acute pain. Most patients with acute pain presented with atypical activation in the sensory processing region, while those with chronic pain displayed heightened activity in areas associated with emotion, cognition, and reward.[7–9] A study based on functional magnetic resonance imaging (fMRI) demonstrated that the interaction between the dorsal attention network and the default network can be utilized to predict the development of chronic pain

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during the progression from acute to chronic pain.[5] There have been many studies on brain activity and structure alterations in patients with acute or chronic pain. However, there are fewer studies on the persistence of pain in individuals with chronic conditions, as well as the variations and relevant characteristics in brain networks among patients with chronic pain at different stages. Conducting pertinent research may provide a more profound insight into the mechanisms that contribute to the enduring nature of chronic pain, thus providing additional theoretical foundations for the prevention and treatment of this disease. Furthermore, these findings are expected to further clarify the brain mechanisms related to the persistence and chronicity of pain and identify possible neuroimaging markers for chronic pain.

To identify the brain networks related to chronic pain, different methods were employed in some neuroimaging studies based on patients with chronic pain. It was found that a series of brain regions played an important role in pain responsiveness, which can be summarized as the pain neural matrix.[10,11] The pain matrix included key regions of prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula cortex (IC), somatosensory cortex, thalamus, amygdala (AMG) and the periaqueductal gray (PAG). Previous studies have provided strong evidence that the interaction of these brain regions had a significance in the initiation and maintenance of pain.[12] In some fMRI-based studies, it was found that acute pain and chronic pain exerted different effects on the changes of the pain matrix. Linnette et al found that acute pain induced increased excitability of the pain matrix, while chronic pain caused decreased excitability.[7] However, it remains unclear about the changes in the pain neural matrix in patients with chronic pain at different stages. Therefore, this study was conducted to explore the impact and change of different pain stages on the pain neural matrix and investigate the differences and similarities between them, thus clarifying underlying mechanisms.

More specifically, this study was performed to identify whether patients with chronic pain at different stages exhibited different changes in the pain neural matrix compared with healthy individuals and further investigate the potential correlation of these changes with pain duration. The fMRI technology was employed to conduct resting-state brain function scans on patients with chronic pain at different stages and healthy controls. Besides, the differences in brain regional activity, functional connectivity, and network features between both groups were also analyzed. To avoid the influence of pain types, only patients with chronic back pain (CBP) were included in this study.

Materials and Methods

Participants

All subjects in this study were recruited from Zhujiang Hospital of Southern Medical University. All patients were diagnosed with CBP for more than 3 months. A total of 89 participants were recruited in this study, including 30 healthy individuals (the healthy control [HC] group) and 59 patients with CBP. These patients were divided into the short-duration (CBP-S, 3–12 months) group and the long-duration (CBP-L, ≥24 months) group. However, 6 subjects were excluded due to image quality and head motion (1 in the HC group, 2 in the CBP-S group, and 2 in the CBP-L group) (Figure 1). Finally, there were 29 participants in the HC group, 25 patients in the CBP-S group, and 29 in the CBP-L

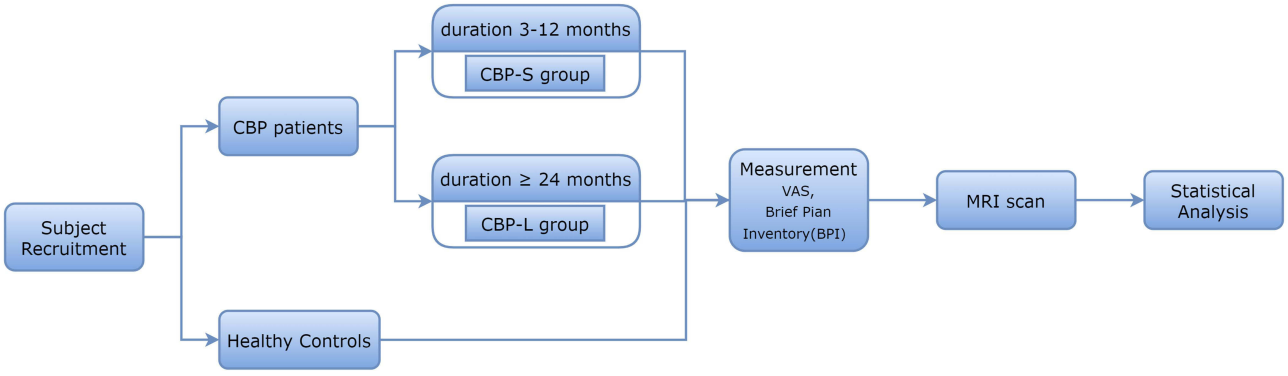

Figure 1 Procedures of this study.

group. The inclusion criteria included (1) subjects aged 18–75 years; (2) subjects with a score of visual analogue scale (VAS) equal to or larger than 3 points; (3) subjects with no fMRI contradiction; (4) subjects who could understand all terms and items in BPI and complete the questionnaire; (5) subjects with no cerebral lesions. The exclusion criteria included (1) subjects with life-threatening diseases in the cardio-cerebrovascular, hematopoietic, hepatic, or renal system; (2) pregnant subjects; (3) subjects with spinal fracture; (4) subjects with magnetic component objects in their bodies. This study was approved by the ethics committee of Zhujiang Hospital of Southern Medical University. All participants understood the procedures of this study, possible risks, and discomforts.

Data Acquisition

These subjects received scanning in a standard radiofrequency head coil. All image data were acquired by a Philips 3.0 T Ingenia magnetic resonance imager in Zhujiang Hospital of Southern Medical University. The structure data were acquired with a high-resolution 3D T1-weighted sequence: repetition time (TR)/echo time (TE) = 7.2/3.3 ms; flip angle = 7°; field of view (FOV) = 256 mm × 256 mm; matrix size = 256 × 256; 1 mm × 1 mm in-plane resolution; slice thickness = 1 mm; 176 slices; slice gap = 0 mm. The functional MRI data were acquired using a T2*-weighted, single-shot, gradient-recalled echo planar imaging sequence: TR/TE = 2000/30 ms; field of view (FOV) = 224 mm × 224 mm; matrix size = 64 × 63; flip angle = 90◦; 3.5 mm × 3.5 mm in-plane resolution; slice thickness = 3.5 mm; 33 slices; slice gap = 0.7 mm; number of signal averages (NSA) = 1.

Clinical Characteristic Measurement

The VAS was adopted to assess the pain severity of subjects. The Brief Pain Inventory (BPI) is a measure to assess pain severity and its influence on social and daily functioning.[13] In this study, the short form was used in consideration of brevity and the convenience of use for subjects. Each item was rated from 0 to 10, with 0 indicating no pain-related functional handicap while 10 representing a major disruption of everyday life by pain. The average of the scores for the 4 questions was determined as the assessment result of the scale.

Statistical Analysis

The Kruskal–Wallis test and the Mann–Whitney *U*-test were performed to analyze the differences in demographic data between groups. The Kruskal–Wallis test was used to compare the age, gender, and BPI scores among three groups, and the Mann–Whitney *U*-test was used to compare pain duration and VAS scores between two CBP groups. The Shapiro–Wilk test was used to assess the distribution normality of the data. All statistical assessments were two-tailed, and the significance threshold was $p = 0.05$.

Data Preprocessing

The resting-state fMRI image was preprocessed by a data processing assistant REST plus toolbox based on Statistical Parametric Mapping (SPM12).[14] The preprocessing procedures included data format conversion, deletion of the first 10 data points, slice timing, realignment, linear detrending, smoothing, and filtering. The first 10 time points were deleted to reduce the non-equilibrium effects of magnetization and the maladjustment of patients. In addition to adding 24 head movement factors as covariates to the linear regression, other techniques were also adopted to limit the impact of head movement on the data: censoring and scrubbing. In addition, a 3 mm translation and 3° rotation threshold were also added for excessive head movement. The images of each subject were resampled at a resolution of 3 mm × 3 mm × 3 mm. The normalized functional images were smoothed spatially using a 6 mm full width at half maximum (FWHM) Gaussian kernel. Finally, linear detrending was conducted to reduce the influence of low-frequency drift and filtering to keep the low-frequency band (0.01–0.08 Hz).

ALFF Analysis

ALFF is a measure to assess the intensity of spontaneous brain activity in the resting state based on the frequency spectrum of fMRI signals. It focuses on the low-frequency range of 0.01–0.08 Hz, where most neural fluctuations occur and where the effects of noise sources such as drift, respiration, and cardiac signals are minimized. In this study, to clarify individual differences in the brain structure, the ALFF value of each voxel was normalized by dividing it by the average

ALFF value of the whole brain. In addition, a 6 mm FWHM isotropic Gaussian kernel was employed to smooth the preprocessed data and calculate the ALFF value.

Functional Connectivity Analysis

As reported in previous studies, the pain matrix is a term describing the brain regions that are affected by either acute or chronic pain. These regions consist of cortical and subcortical areas that are involved in pain perception, modulation, and processing.[15] In this study, a mask of the pain matrix was generated with the Human Brainnetome Atlas,[16] which consisted of multiple brain areas involving pain processing. This mask was applied to the seeds picked based on the objectives of this study. Besides, the average time series of these brain regions were extracted (Table 1). Additionally, resting-state functional connectivity analysis were performed with the voxel-wise method, and the time series of these brain regions were compared with those of every voxel in the whole brain. Further, the correlation coefficients were transformed from FC into z values by Fisher z-transformation. Moreover, multiple comparison correction was performed based on the Gaussian random field theory (GRF) (voxel-level forming statistical threshold of $z = 2.58$, cluster-level $p < 0.05$). Finally, the one-way ANOVA and two-sample *t*-test were performed to compare the differences in the z-value among three groups.

Analysis of Covariance

Based on the functional connectivity study of these three groups, the analysis of covariance was conducted to identify whether the pain severity and interference could influence the results of the function connection of these brain regions. The VAS and BPI of these subjects in three groups were added as covariates. The analysis was performed using SPSS22.0 (SPSS, Chicago, IL, United States).

Table 1 Brain Regions Extracted in the Pain Matrix as ROIs in Functional Connectivity

Label ID	Regions	Brodmann Area and Modified Cyto-Architectonic	MNI		
			X	Y	Z
155	"Postcentral Gyrus"	"Area 1/2/3"	−50	−16	43
156	"Postcentral Gyrus"	"Area 1/2/3"	50	−14	44
157	"Postcentral Gyrus"	"Area 1/2/3"	−56	−14	16
158	"Postcentral Gyrus"	"Area 1/2/3"	56	−10	15
159	"Postcentral Gyrus"	"Area 2"	−46	−30	50
160	"Postcentral Gyrus"	"Area 2"	48	−24	48
161	"Postcentral Gyrus"	"Area1/2/3 (trunk region)"	−21	−35	68
162	"Postcentral Gyrus"	"Area1/2/3 (trunk region)"	20	−33	69
163	"Caudodorsal Posterior Insula"	"Hypergranular insula"	−36	−20	10
164	"Caudodorsal Posterior Insula"	"Hypergranular insula"	37	−18	8
169	"Ventral Posterior Insula"	"Ventral granular insula"	−38	−4	−9
170	"Ventral Posterior Insula"	"Ventral granular insula"	39	−2	−9
171	"Rostrodorsal Posterior Insula"	"Dorsal granular insula"	−38	−8	8
172	"Rostrodorsal Posterior Insula"	"Dorsal granular insula"	39	−7	8
179	"Cingulate Gyrus"	"Pregenual area 32"	−6	34	21
180	"Cingulate Gyrus"	"Pregenual area 32"	5	28	27
183	"Cingulate Gyrus"	"Caudodorsal area 24"	−5	7	37
184	"Cingulate Gyrus"	"Caudodorsal area 24"	4	6	38
187	"Cingulate Gyrus"	"Subgenual area 32"	−4	39	−2
188	"Cingulate Gyrus"	"Subgenual area 32"	5	41	6
235	"Thalamus"	"Sensory thalamus"	−18	−23	4
236	"Thalamus"	"Sensory thalamus"	18	−22	3

Correlation Analysis

After the voxel-wise FC analysis and GRF correction, the significant seeds were recruited in the subsequent correlation analysis. Spearman correlation analyses were conducted to calculate the neuroimaging data and clinical characteristics. Pearson correlation analyses were used for normally distributed data. The boxplot method was used to identify and eliminate outliers of clinical characteristics.

Results

Demographic Data and Clinical Characteristics

The demographic data and clinical characteristics of patients in the three groups are summarized in Table 2. There was no significant difference in age and gender among three groups, while BPI scores exhibited significant differences among these groups. As for the two CBP groups, no significant difference was observed in pain intensity and BPI scores.

ALFF Analysis Based on Rs-fMRI

In this study, the ANOVA analysis was performed among three groups. The z value of ALFF showed significant differences in the left precuneus (Figure 2A). Then, pairwise comparisons were conducted among these groups. Compared with the HC group, patients in the CBP-L group showed significantly lower ALFF in the left precuneus (Figure 2B), but no significant difference was observed in the comparison between the CBP-L and CBB-S groups. Moreover, no significant differences were observed between the CBP-S group and the HC group.

Functional Connectivity Analysis

After the voxel-wise analysis, one-way ANOVA was conducted on the three groups. The results revealed that a series of brain regions showed decreased function connectivity, including bilateral orbitofrontal cortices and the right ventral posterior insula (Table 3). To further clarify the differences, the z-values of these brain regions were extracted to conduct two-independent sample *t*-tests for pairwise comparisons between groups. Compared with the HC group, both the CBP-S and CBP-L groups showed decreased functional connectivity between the 1) bilateral postcentral gyri and bilateral orbitofrontal cortices (PoCG1 to OFC1, PoCG2 to OFC1/2), 2) the left insula (INS1) and bilateral orbitofrontal cortices (OFC2), and 3) the right subgenual cingulate cortex (sgACC) and the left orbitofrontal cortex (OFC4). There was also decreased functional connectivity between the left and right ventral posterior insula (INS2 to INS3) (Figures 3 and 4). In addition, the FC between the right ventral posterior insula (INS1) and the probabilistic area of the orbital frontal cortex (OFC3) differed significantly among these three groups (Figure 5A). Moreover, the CBP-L group exhibited significantly lower functional connectivity than the HC group, while the CBP-S group showed significantly lower functional connectivity than both the HC group and the CBP-L group (Figure 5B).

Analysis of Covariance of ROIs

The ANCOVA results indicated that BPI and VAS scores did not affect the function connectivity of the listed brain regions.

Correlation Analysis Within ROI

The correlation analysis results suggested that pain duration was significantly negatively correlated with FC in PoCG1-OFC1 connectivity (r=−0.2532, p=0.0209), PoCG2-OFC1 connectivity (r=−0.3714, p=0.005), PoCG2-OFC2 connectivity

Table 2 Demographic Data and Clinical Characteristics of Subjects

	CPB-S	CBP-L	HC	P-value
Age	36.15±12.00	36.72±12.14	36.97±10.97	0.874
Sex ratio, female	16 (64%)	18 (62.07%)	19 (65.52%)	0.954
Pain duration, months	6.42±2.86	61.45±37.69	/	<0.001
Pain intensity, by VAS	4.86±1.44	4.48±1.12	/	<0.001
BPI scores	5.50±2.68	4.8±1.86	0.33±0.67	<0.001

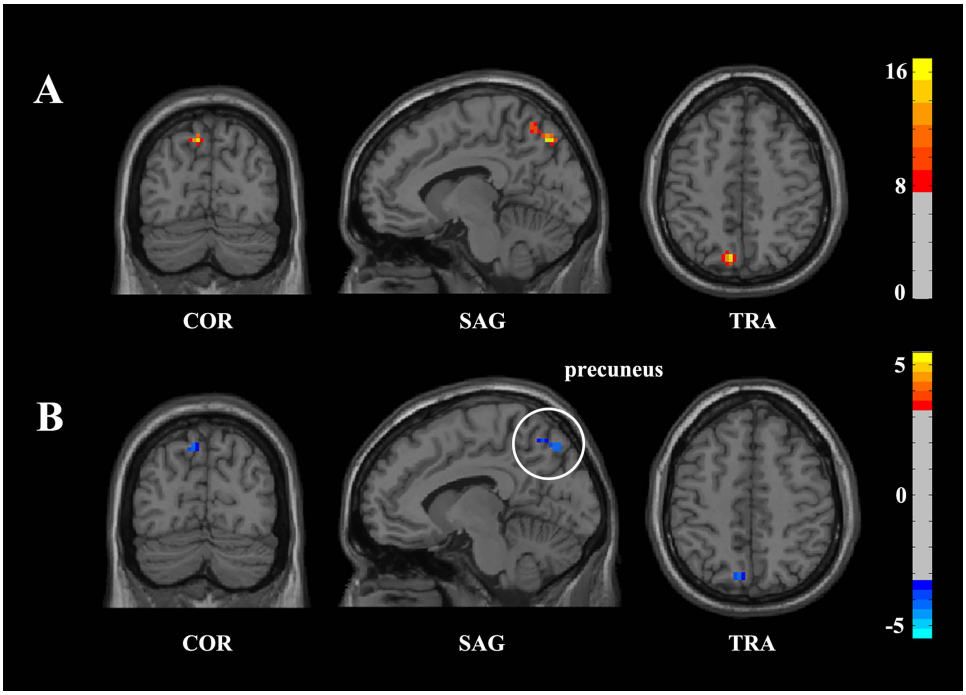

Figure 2 ALFF analysis results with significant differences among groups.
Notes: (**A**) ANOVA of three groups showed significant differences in the left precuneus. (**B**) Pairwise two-sample *t*-test showed decreased ALFF in the left precuneus between the CBP-L group and the HC group.

(r=−0.5179, p<0.001), INS1-OFC2 connectivity (r=−4266, p<0.001), INS1-OFC3 connectivity (r=−0.3490, p=0.0012), INS2-INS3 connectivity (r=−0.5466, p<0.001), and sgACC-OFC1 connectivity (r=−0.2503, p=0.0225) (Figure 6).

Discussion

There were four major findings in this study. 1) Patients in the CBP-L group showed decreased ALFF in the left precuneus compared with the HC group. 2) Compared with the HC group, patients in the CBP-L group showed decreased functional activity in the orbital frontal cortex and insula. 3) Compared with the HC group, patients in the CBP-S group showed reduced functional connectivity between the right ventral posterior insula and the left orbital frontal cortex; those in the CBP-L group also showed decreased FC compared with the CBP-S group and the HC group. 4) The FC in patients with CBP was negatively correlated with pain duration. These results indicated that individuals with longer pain duration exhibited impairments in pain sensitivity and perception.

In the ALFF analysis, it was observed that only patients in the CBP-L group showed decreased activation in the left precuneus compared with the HC group. The precuneus is located in the parietal lobe of the brain. In some previous studies on pain, it has been found that the precuneus is involved in continuous information collection and representation of the internal and external environments, as well as in the evaluation of self-relevant sensations.[17,18] Additionally, pain sensitivity and pain representation depend on separate neural sub-systems.[17] Fan et al observed that the activity of the

Table 3 The Brain Regions with Significant Functional Connectivity Among Groups

Regions	R/L	Cluster Size Voxels	MNI			z-values
			x-	y-	z-	
Orbital frontal cortex	L	71	−12	51	−24	20.7405
Orbital frontal cortex	R	31	12	33	−21	13.6179
Insula	L	53	−39	0	−9	47.8113

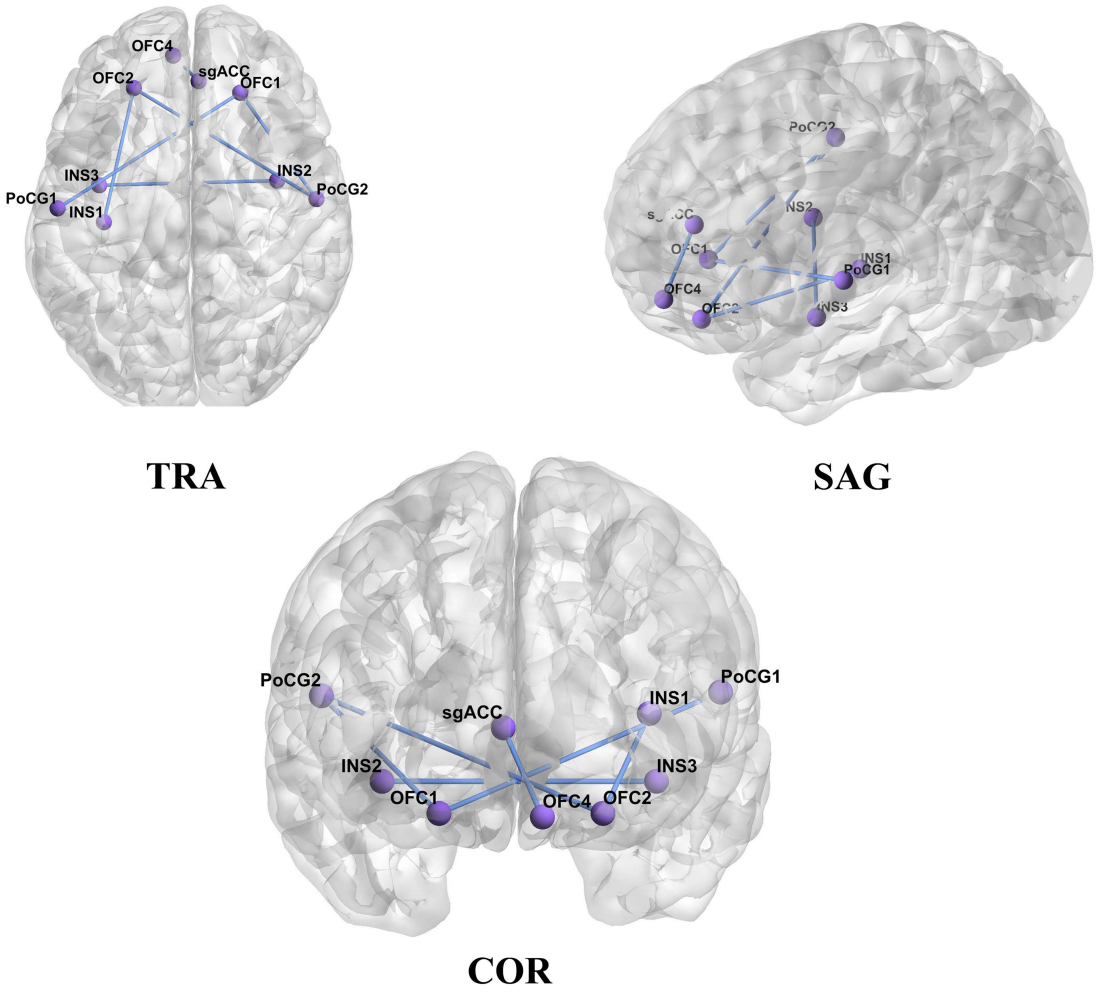

Figure 3 Functional connectivity results with significant differences between the HC group and the two CBP groups.
Abbreviations: OFC, orbital frontal cortex; PoCG, postcentral gyrus; sgACC, subgenual cingulate cortex; INS, insula.

precuneus in patients with CBP was negatively correlated with pain sensitivity,[19] which was consistent with our findings. In this study, the ALFF value of the CBP-L group was significantly lower than that of the HC group. However, there was no significant difference in patients with shorter pain duration. This may indicate that the sensitivity to pain stimuli was compromised with an increase in pain duration.

Compared with the HC group, both the CBP-L and CBP-S groups showed a decrease in the functional connectivity of the left and right ventral posterior insula, as well as the postcentral gyrus, hyper granular insula, subgenual cingulate cortex (sgACC), and orbitofrontal cortex (OFC). This indicated that patients with chronic pain had reduced pain perception and regulatory dysfunction. The postcentral gyrus is an important component of the primary somatosensory cortex that is involved in pain and sensory information processing and is responsible for encoding pain sensation information.[20,21] As a region located in the medial prefrontal cortex of the brain, the sgACC plays a crucial role in the descending pain modulation system and has been shown to participate in the processing and perception of pain-related information in patients with CBP.[22–24] Therefore, the central posterior gyrus and sgACC play an important role in the processing of pain information. The insula is also related to the coding and modulation of pain signals and the integration of pain with other sensations.[25–27] The OFC is a part of the prefrontal cortex and has strong connections with the sensory cortex SI, SII, insula, and cingulate cortex.[5,28,29] Based on these findings, it can be inferred that the reduced functional connectivity of the OFC in patients with chronic pain was related to the aberrant integration of pain perception information.

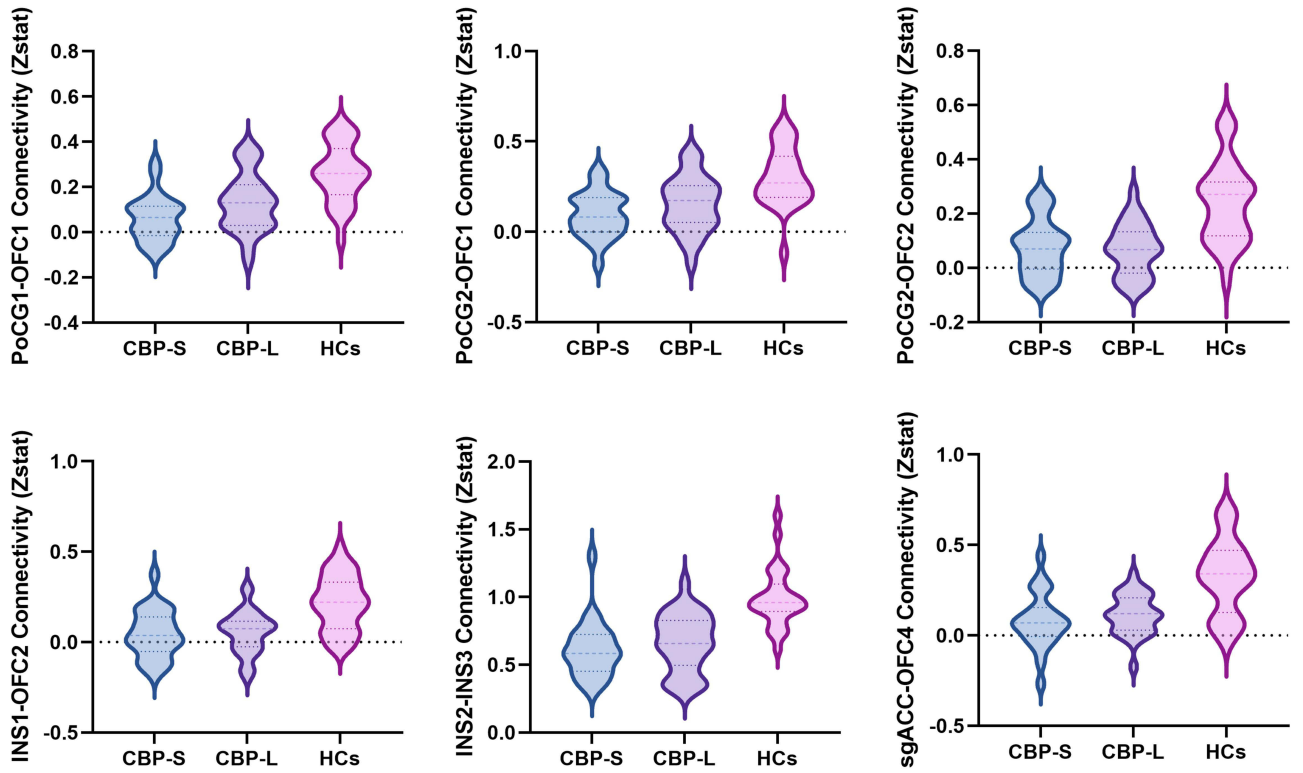

Figure 4 The z values of functional connectivity of the HC, CBP-S, and CBP-L groups.

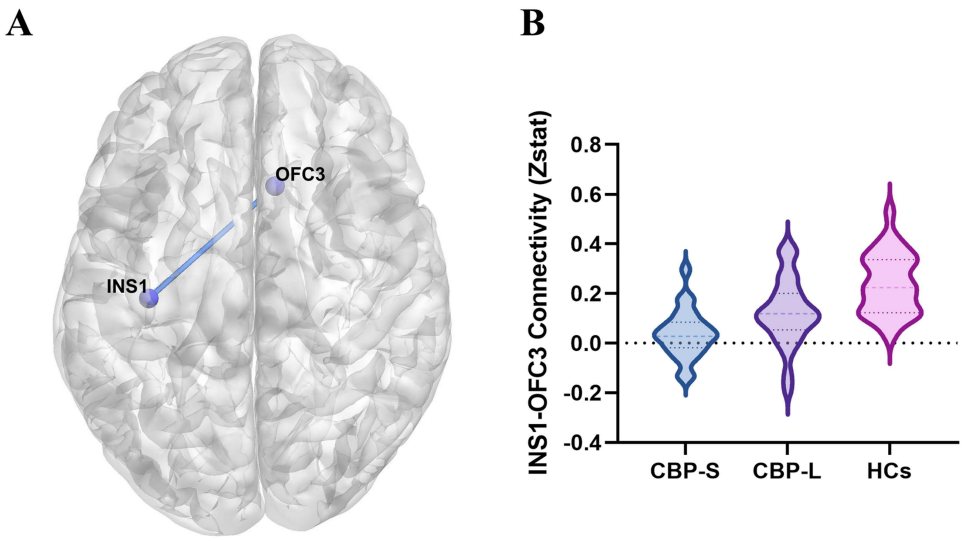

Figure 5 The functional connectivity of INS1-OFC3 of three groups.
Notes: (**A**) The FC of INS1-OFC3 showed significant differences among the three groups. (**B**) The z-values of the HC, CBP-S and CBP-L groups of the FC in INS1-OFC3.

As per previous studies, the insula participates in pain perception, and the activity of the insula is associated with pain perception.[30] Zhao et al mentioned that the FC between the posterior insula and the sensory motor cortex represents changes in the integration of visceral sensory and motor processing, and the extent of activity in the posterior insula cortical area was most indicative of the course of chronic pain.[31] This indicated that changes in insula activity were associated with the persistence and progression of pain. In another study, alterations in insula cortical connections were

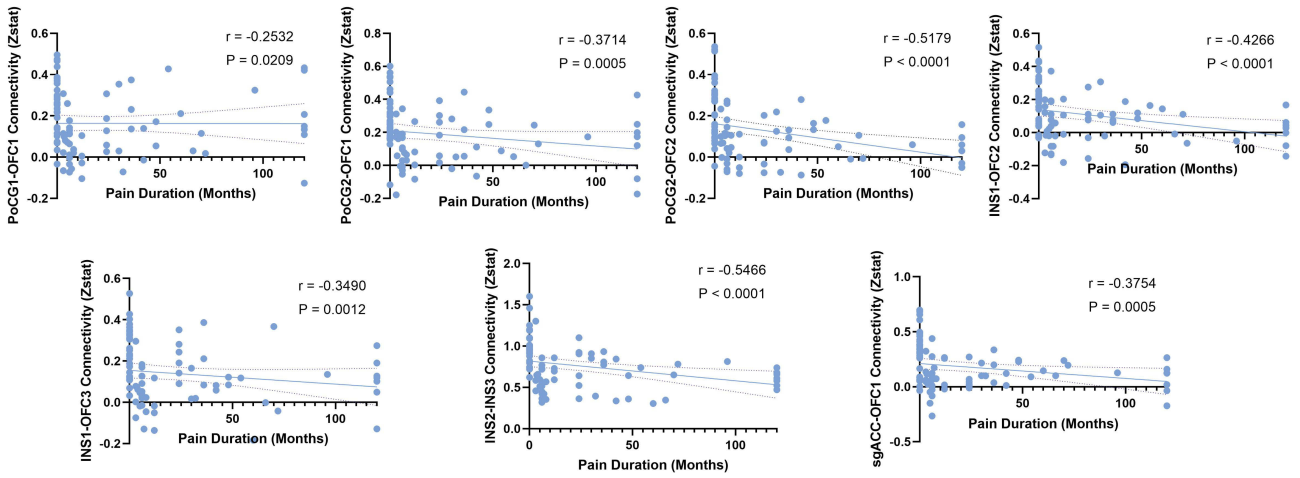

Figure 6 The correlation analysis between pain duration and functional connectivity.

observed in patients who received medication treatment to reverse chronic pain.[32] In this study, the results revealed that the functional connectivity of the insula was reduced in the CBP-S and CBP-L groups, which was consistent with the findings of previous studies. However, there was no significant difference between the CBP-S and CBP-L groups, which may imply that chronic pain reduced the abnormal sensitivity of patients to pain, and this change did not alter with an increase in pain duration.

It was also observed that the functional connectivity between the insula and OFC in patients with CBP was significantly reduced compared with healthy controls. The OFC has connection with the sensory cortex in chronic pain,[33,34] while the insula is related to the encoding of pain perception information.[30] There is a limited number of research investigating the functional connectivity between the insula and OFC in individuals with chronic pain, and there is currently no published data on the link between the ventral posterior insula and OFC. However, a study discovered a correlation between the anterior insula and OFC in the context of pain processing.[35] This suggested that abnormal insula activity may be related to pain duration. Moreover, it was speculated that the reduced connectivity between the insula and OFC may cause abnormal perception and integration of pain information in patients with chronic pain. However, contrary to our expectations, lower FC were observed in CBP-S group compared to CBP-L group. Since there is a lack of in-depth research on the population of patients with different stages of chronic pain, one possible explanation was that as the duration of pain prolongs, the brain may undergo further adaptations. The recovery of FC could represent compensatory mechanisms or maladaptive changes. Additionally, patients who have experienced pain for a longer period of time typically receive lengthier, more standardized therapies, which might be one of the factors affecting the recovery of patients' brain functional connections.

Conclusion

The results of this study suggest that compared with healthy controls, patients with chronic pain at different stages have different alterations in the pain neural matrix, and the pain duration is related to the changes in brain functions.

Innovation and Shortcomings

To our knowledge, this is the first clinical trial on the duration of chronic pain based on fMRI. The results of this study may provide novel insights and evidence for the early diagnosis and intervention of chronic pain. However, there are still some limitations in this study. Firstly, the sample size of all groups in this study is relatively small. Hence, it is necessary to perform explorations based on a larger sample size to confirm these findings and increase the dependability of the results. Secondly, in order to further investigate the specific reasons that may affect function impairment and life quality of patients with CBP, more assessments on both patients and HCs should be conducted, such as depression, anxiety, and

sleeping disorders. Finally, to further investigate the correlation between functional changes of the brain and underlying mechanisms, more subjects with more significant pain duration differences need to be added for more extensive grouping studies and follow-up.

Data Sharing Statement

The datasets generated during the current study are not publicly available due to the informed consent right of the subjects, but are available from the corresponding author on reasonable request.

Ethics Statement

Our study complies with the Declaration of Helsinki, and our research protocols involving human subjects underwent review and approval by Zhujiang Hospital of Southern Medical University and Guangdong Provincial Hospital of Chinese Medicine (Clinical registration number 2022-KY-257-01). Written informed consent was obtained from all patients/participants who agreed to participate in this study.

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Disclosure

The authors declared that there were no financial or commercial ties that might raise the possibility of a conflict of interest in the implementation of this study.

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