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Altered Functional Connectivity of The Amygdala in Postherpetic Neuralgia*

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Abstract Postherpetic neuralgia (PHN) is a common type of neuropathic pain, the central mechanism of which is still unclear. The amygdala has recently garnered increased attention in pain processing. The purpose of this study is to investigate the functional neural networks of the amygdala in PHN and explore the mechanism of chronic neuropathic pain. Conventional magnetic resonance imaging (MRI) and resting-state functional MRI (fMRI) were performed in eight PHN patients and eight healthy controls. The functional connectivity (FC) of each subregion of the amygdala with the whole brain was computed. Paired *t* tests of the FC data were performed between the two experimental groups. Correlation analysis was applied between disease duration, visual analog scale (VAS), and FC strength. We found increased FC between the laterobasal (LB) and superficial (SF) amygdala and several brain regions including the temporal lobe and frontal lobe. We observed decreased FC between the SF amygdala and the precentral cortex, as well as the SF amygdala and parietal lobe. Correlation analysis showed that FC strength of the LB amygdala with both the temporal lobe and frontal lobe changed with disease duration and VAS in PHN patients. This altered FC in PHN suggests that the amygdala and several other brain regions involved in emotion, recognition, and attention play an important role in the modulation of chronic neuropathic pain.

Key words postherpetic neuralgia, neuropathic pain, fMRI, functional connectivity
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Postherpetic neuralgia (PHN) is the most frequent complication of the herpes zoster and a common type of neuropathic pain [1]. PHN is defined by most clinicians as pain that lasts more than 90 days after the onset of the herpes zoster skin rash[2]. The frequency of developing PHN varies from 5% to more than 30%[3]. This pain has been described as a constant burning or stabbing pain, which when combined with allodynia, may persist for years and cause sleep disturbances, mood changes, depression, and anxiety [4]. PHN is refractory to most treatments[5] and its pathogenesis is still unclear. As a typical form of chronic neuropathic pain, PHN exhibits multiple signs of peripheral and central neuropathy. Research investigating changes in the central nervous system can help us understand the mechanism of PHN and facilitate the development of effective strategies towards prevention and treatment of this disease.

Functional magnetic resonance imaging (fMRI) provides a noninvasive method to explore the central mechanism of PHN. Several studies have investigated the changes of brain activity in PHN patients using fMRI in different ways[6–11]. These studies showed that not only the affective and sensory-discriminative brain regions but also the areas associated with emotion, hedonics, reward, and punishment such as the striatum, amygdala, and frontal cortex were activated by the spontaneous pain of PHN [6]. Liu *et al*. [12] found increased cerebral blood flow (CBF) in the primary somatosensory cortex (S1), striatum, insula, amygdala, and thalamus, and decreased CBF in the frontal cortex. They also found altered functional connectivity (FC) between several regions such as the striatum,

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prefrontal cortex, and amygdala[12]. Abnormal regional homogeneity (ReHo) and fractional aptitude of low-frequency fluctuation (ALFF) were also observed in the thalamus, limbic system, temporal lobe, prefrontal lobe, and cerebellum of PHN patients[6].

As a brain area critical to emotion processing[13], the amygdala has emerged as an important region in pain modulation in recent years [14]. The amygdala consists of a set of nuclei divided into three main groups: superficial (SF), laterobasal (LB), and centromedial (CM). The LB nucleus is the major sensory input region of the amygdala, and the CM nucleus plays a prominent role in efferent connections [14]. Jiang *et al*.[15] found that the FC of the amygdala with the central executive and default mode networks, were perturbed in chronic low back pain patients. Chen *et al*.[16] also found altered FC of the amygdala in migraine patients.

There has been no study investigating the FC of the amygdala in PHN. Based on current knowledge, we hypothesized that the FC of the amygdala in PHN patients will be altered. Therefore, the purpose of this study is to investigate the FC changes of each amygdala subdivision in PHN patients and to explore the mechanism of chronic neuropathic pain.

1 Materials and methods

1.1 Subjects

Eight PHN patients (4 males and 4 females), recruited from the Functional Neurosurgery department of Xuanwu Hospital Capital Medical University, were entered into this study. The diagnosis of PHN was based on the international association for the study of pain (IASP) criteria for postherpetic neuralgia[17]. All participants were less than 65 years old. The painful areas reported by all patients were the same areas as expected for herpes zoster on the back and chest. All participants reported persistent pain for more than six months (6 – 19 months) following the healing of the herpes zoster rash, with a pain intensity of at least 5 on a visual analog scale (VAS) of 10. None of the patients displayed MRI scans with obvious abnormalities such as infarction or atrophy. No participant had a history of psychiatric, neurological disorders or other severe diseases. The self-rating anxiety scale (SAS) and self-rating depression scale (SDS) tests were performed to exclude anxiety and depression disorder. Healthy controls (n = 8) were age-, gender-, education level-matched volunteers. None of these individuals suffered from any type of pain, chronic diseases, neuropsychiatric disorders, or brain structural abnormalities. This study was approved by the local ethics committee, and written informed consent was obtained from all participants.

1.2 Data acquisition

All fMRI experiments were performed on a 3.0 Tesla (T) Siemens Magnetom Verio Tim MRI at Xuanwu Hospital Capital Medical University. Patients were asked to stop taking all medication at least 24 h prior to the MRI scans. During the scans, subjects were instructed to stay awake with their eyes closed and not to think systematically about anything, and their heads were immobilized by foam padding. Resting-state fMRI data were acquired for 8 min using an echo planar imaging (EPI) sequence with the following parameters: repetition time (TR)/echo time (TE) = 2 000/30 ms, slice thickness = 3.5 mm, gap = 0.7 mm, flip angle = 90°, field of view (FOV) = 200 × 200 mm, matrix 64 × 64, 190 volume. In addition, 3D T1-weighted images were obtained by magnetization-prepared rapidly gradient echo (MP-RAGE) sequence with the following parameters: TR/TE = 2 000/2.2 ms, inversion time (TI) = 900 ms, FOV = 224 × 256 mm, matrix = 224 × 256, slice thickness = 1 mm, gap = 0.7 mm.

1.3 Data processing

Resting-state fMRI images were processed using Statistical Parametric Mapping 8 (SPM8), resting-state fMRI data analysis toolkit (REST V1.8)[18] and data processing assistant for resting-state fMRI(DPARSF)[19] running under MATLAB 2013a.

Data pre-processing carried out by DPARSF included the following steps: (1) elimination of the first ten volumes of each time series; (2) slice timing correction; (3) head motion correction (no subjects with more than 1.5° head rotation or 1.5 mm displacement were included); (4) spatial normalization to the montreal neurological institute (MNI) template; (5) spatial smoothing; (6) linear detrending; and (7) temporal band-pass filtering (0.01 – 0.08 Hz).

The FC analysis was performed as follows: (1) The seed regions of interest (ROIs) in the amygdala were the superficial (SF), laterobasal (LB), and centromedial (CM) nuclei that were determined using maps developed by Amunts *et al*.[20] and implemented in Julich Histological Atlas [21] (Figure 1);

(2) Computation was performed with the REST (v 1.8) toolkit. The time course of the bilateral amygdala was extracted, and Pearson correlations were used to calculate the FC between the extracted time courses and the averaged time courses of the whole brain in a voxel-wise manner. The white matter, cerebrospinal fluid, and six head-motion parameters were used as covariates.

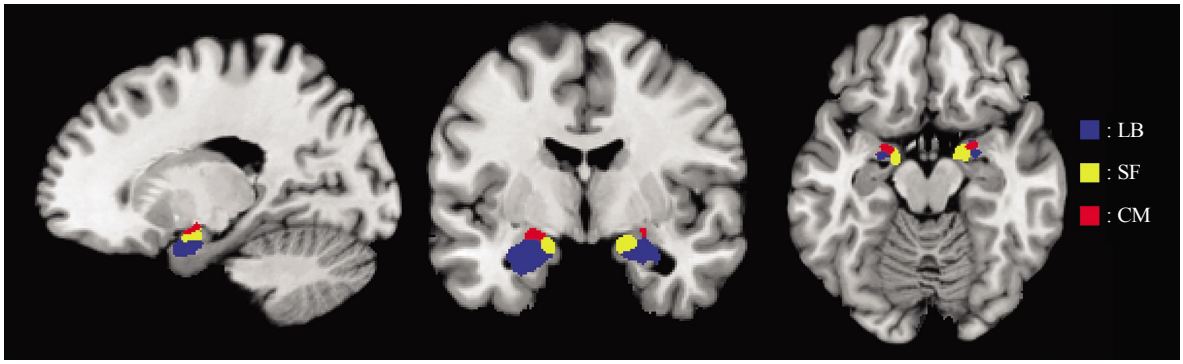

Fig. 1 The seed regions of interest in the amygdala

Seed ROIs in the amygdala's laterobasal nucleus (LB), superficial nucleus (SF), and centromedial nucleus (CM) are shown in blue, yellow, and red, respectively.

1.4 Statistical analysis

Demographic and clinical characteristics of the study subjects were compared using the two-sample *t* test. The FC differences between the two groups were also analyzed with two-sample *t* tests. The results were displayed using the Slice Viewer tool of the REST toolkit. Correlation analysis was performed between disease duration, VAS, and connectivity strength in PHN patients. Voxel-based multiple regression analysis was performed using SPM8, with FC strength as the dependent variable and VAS score and disease duration as covariates of interest. False discovery rate (FDR) corrections were applied.

Table 1 Clinical characteristics of the study subjects

	PHN	HC
Gender (F/M)	8 (4/4)	8 (4/4)
Age	60.00 ± 7.01	59.75 ± 6.86
DD (month)	10.42 ± 5.52	NA
VAS	5.88 ± 0.99	0.5 ± 0.53*
SDS	25.14 ± 3.02	10.00 ± 3.21*
SAS	31.24 ± 5.57	8.85 ± 3.91*

F/M: Female/male; DD: Disease duration; VAS: Visual analog scale; SDS: Self-rating depression scale; SAS: Self-rating anxiety scale
*$P < 0.001$.

2 Results

2.1 Demographic and clinical characteristics

Demographic and clinical characteristics of the study subjects are shown in Table 1. We found no significant difference between the two groups for age and gender. However, the VAS, SDS, SAS scores of the healthy control group were significantly lower than those of the PHN group.

2.2 Functional connectivity of amygdala nuclei in PHN

In this study, we examined the FC of three main subregions of the amygdala: the SF, LB, and CM nuclei. Our data demonstrated that there were no significant differences in FC of the CM nucleus between PHN patients and the control group. However, we detected increased FC of the LB nucleus with several brain regions, primarily the bilateral inferior temporal gyrus, middle temporal pole, orbitofrontal cortex, limbic lobe, and occipital lobe (Figure 2 and Table 2). We did not observe any decreased FC of LB.

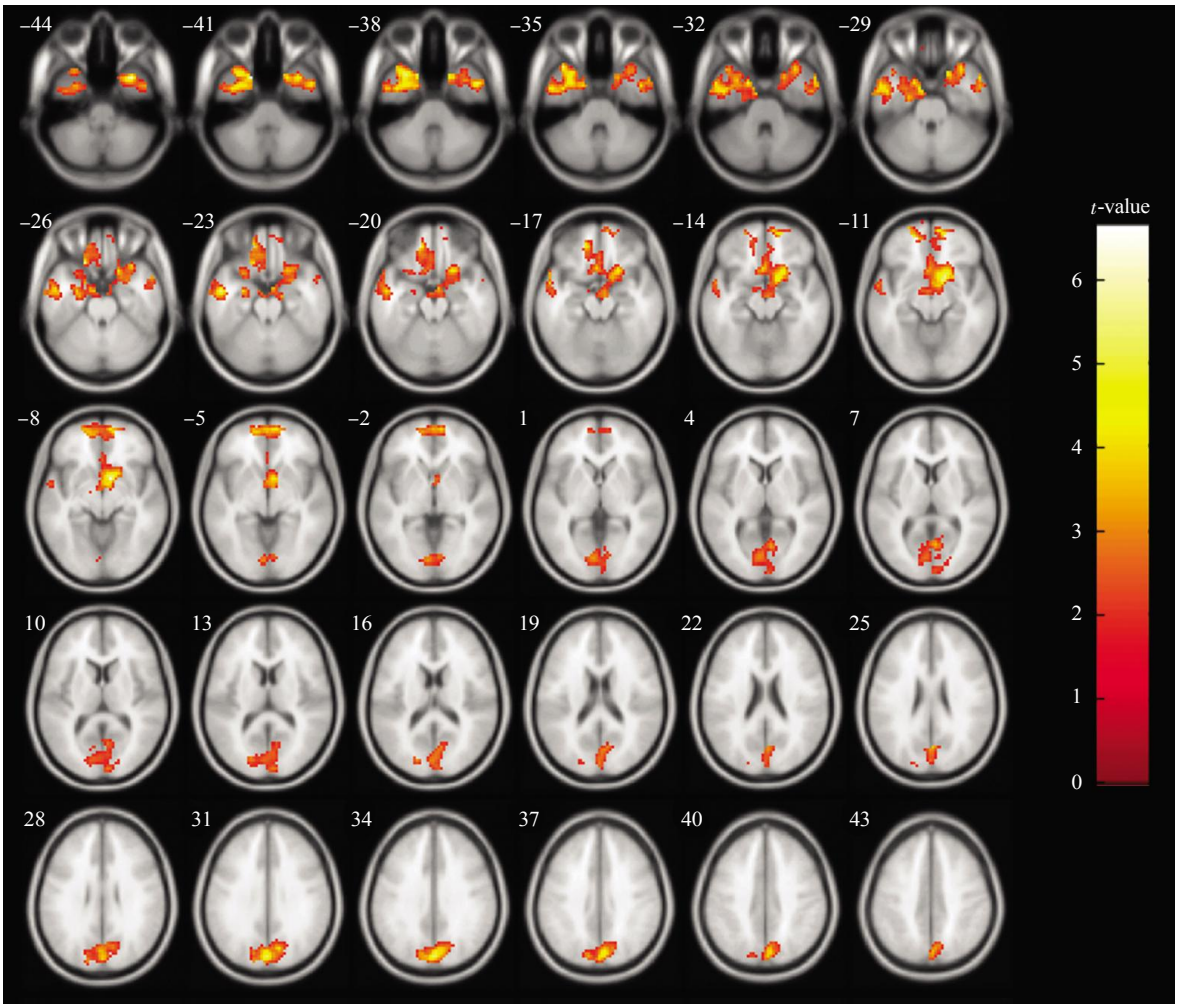

Fig. 2 Increased functional connectivity of the laterobasal amygdala

Table 2 Increased functional connectivity of the laterobasal amygdala

Anatomic region	MNI space			Cluster size	*t* value
	X	*Y*	*Z*		
Temporal_Inf_L	−33	12	−39	197	5.09
Temporal_Inf_R	33	9	45	133	6.14
Temporal_Pole_Mid_L	−18	9	−42	126	6.58
Temporal_Pole_Mid_R	33	9	−42	103	4.68
Frontal_Med_Orb_R	9	60	−12	100	4.40
Frontal_Sup_Orb_L	−15	42	−18	95	4.32
Calcarine_L	−9	−81	0	146	3.03
Calcarine_R	6	−72	18	116	2.94
Cuneus_L	0	−81	33	176	5.32
Cuneus_R	3	−81	33	148	5.06

MNI: Montreal Neurological Institute.

We found increased FC of the SF nucleus with the frontal lobe and temporal lobe. We also found decreased FC between the SF amygdala and the precentral gyrus, post central gyrus, frontal lobe, and occipital lobe (Figure 3 and Table 3).

Table 3　Altered functional connectivity of the superficial amygdala

Anatomic region	MNI space			Cluster size	*t* value
	X	*Y*	*Z*		
FC Increased					
Temporal_Inf_L	−33	12	−42	143	5.90
Temporal_Inf_R	33	9	−45	97	6.67
Temporal_Pole_Mid_L	−30	12	−42	86	7.46
Frontal_Med_Orb_R	12	57	−9	114	4.79
FC Decreased					
Frontal_Mid_R	39	36	15	189	−3.65
Frontal_Inf_Oper_R	51	12	15	148	−4.31
Precentral_R	60	3	18	138	−5.15
Parietal_Sup_R	33	−45	57	155	−3.34
Parietal_Inf_R	30	−48	54	82	−3.69
Postcentral_R	57	−21	51	139	−4.4
Postcentral_L	−54	−21	30	108	−3.11
SupraMarginal_R	51	−33	27	132	−3.57
Parietal_Sup_L	−24	−60	42	296	−5.15
Parietal_Inf_L	−24	−66	42	263	−4.18

FC: Functional connectivity; MNI: Montreal Neurological Institute.

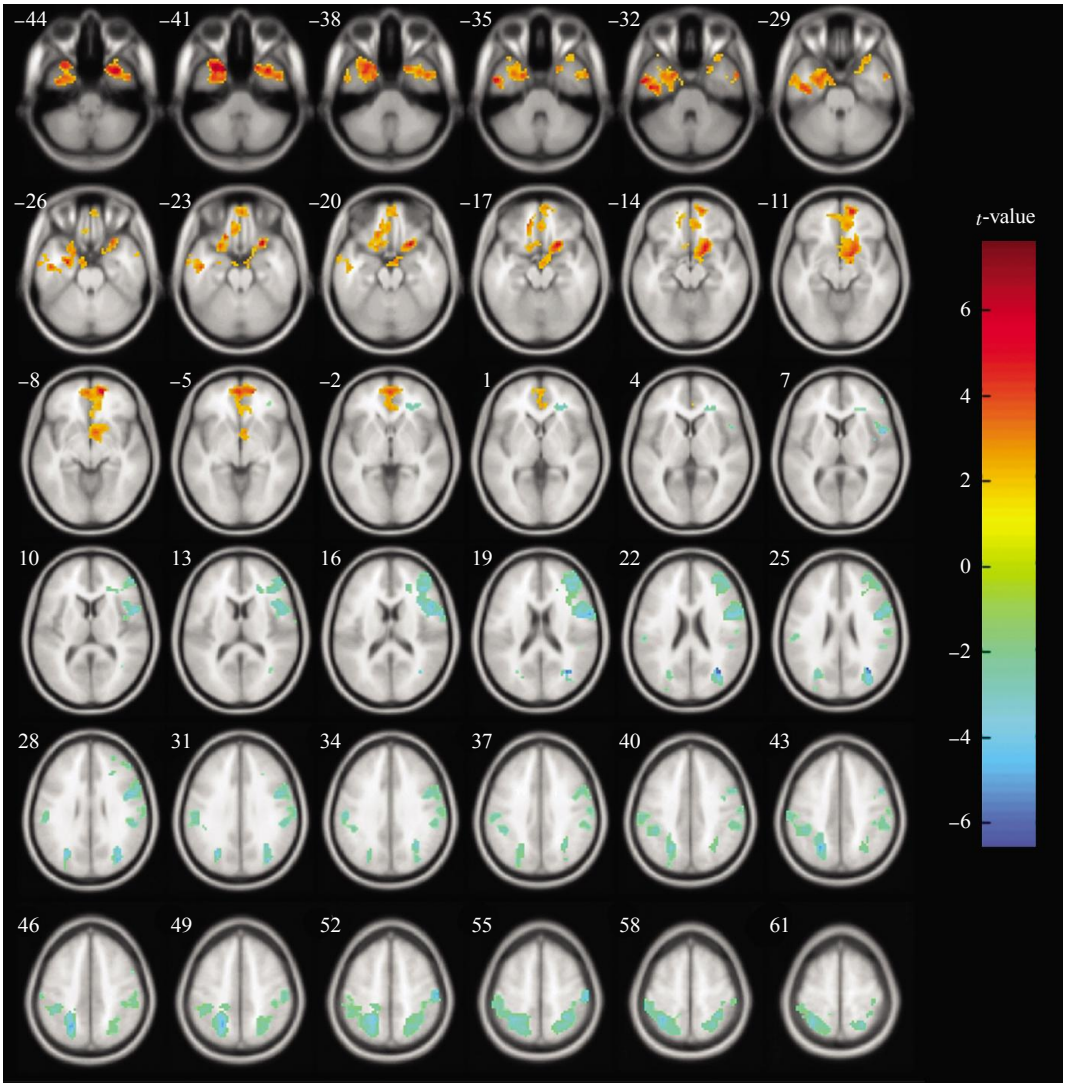

Fig. 3　Altered functional connectivity of the superficial amygdala

2.3 Correlation analysis of connectivity strength with disease duration and VAS

The brain regions with altered FC by VAS score are shown in Table 4 and Figure 4. We found positive correlations between the VAS score and FC of the LB amygdala in the frontal lobe and parietal lobe, and negative correlations mainly in the temporal lobe. In the SF nucleus, we found a positive correlation between FC and VAS in the parietal lobe.

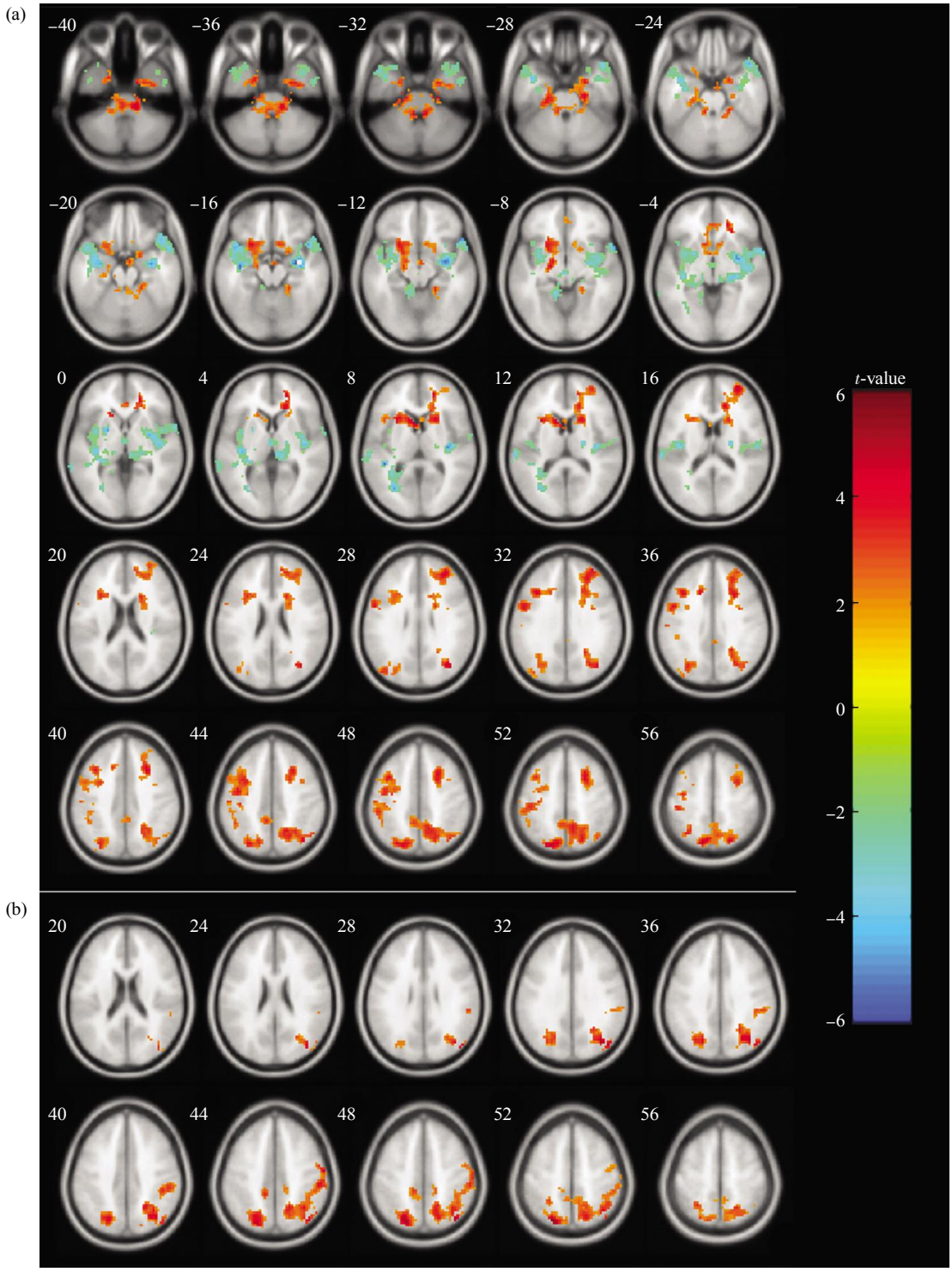

Fig. 4 Functional connectivity changes associated with VAS score

(a) FC strength in the LB amygdala. (b) FC strength in the SF amygdala.

Table 4 Correlation analysis of functional connectivity changes associated with VAS score

Anatomic region	MNI space			Cluster size	*t* value
	X	*Y*	*Z*		
Positive correlations in the LB					
Frontal_Mid_R	30	54	18	380	4.59
Frontal_Sup_R	30	57	15	153	4.13
Parietal_Sup_L	–18	–75	51	141	4.71
Parietal_Sup_R	21	–69	54	124	3.87
Precuneus_L	–12	–72	57	168	4.65
Precuneus_R	3	–57	63	203	3.78
Negative correlations in the LB					
Temporal_Pole_Sup_L	–45	12	–15	106	–4.45
Temporal_Pole_Sup_R	45	15	–18	187	–4.78
Positive correlations in the SF					
Parietal_Sup_L	–24	–72	51	184	5.76
Parietal_Sup_R	18	–69	51	146	3.64
Parietal_Inf_R	45	–54	54	119	3.72
Precuneus_R	18	–69	48	155	3.58

LB: Laterobasal amygdala; SF: Superficial amygdala; MNI: Montreal Neurological Institute.

The brain regions showing correlations between FC and disease duration are shown in Table 5 and Figure 5. In the LB amygdala, positive correlations were found in the frontal lobe and parietal lobe, and negative correlations were mainly found in the frontal lobe, occipital lobe, and temporal lobe. In the SF amygdala, FC negatively correlated with disease duration in the precuneus lobe and corpus callosum.

Table 5 Correlation analysis of functional connectivity changes associated with disease duration

Anatomic region	MNI space			Cluster size	*t* value
	X	*Y*	*Z*		
Positive correlations in the LB					
Frontal_Mid_R	21	9	48	423	6.77
Frontal_Sup_R	24	6	48	226	7.55
Parietal_Sup_L	–15	–66	63	233	6.72
Parietal_Sup_R	18	–66	51	163	5.48
Negative correlations in the LB					
Frontal_Inf_Orb_L	–42	18	–6	131	–3.99
Frontal_Mid_L	–39	57	0	196	–4.43
Calcarine_L	3	–90	–3	259	–3.80
Calcarine_R	15	–78	12	305	–6.02
Temporal_Pole_Mid_L	–48	15	–33	99	–4.42
Positive correlations in the SF					
Precuneus_R	15	–51	33	112	–4.14
Corpus Callosum	9	–24	24	108	–6.00

LB: Laterobasal amygdala; SF: Superficial amygdala; MNI: Montreal Neurological Institute.

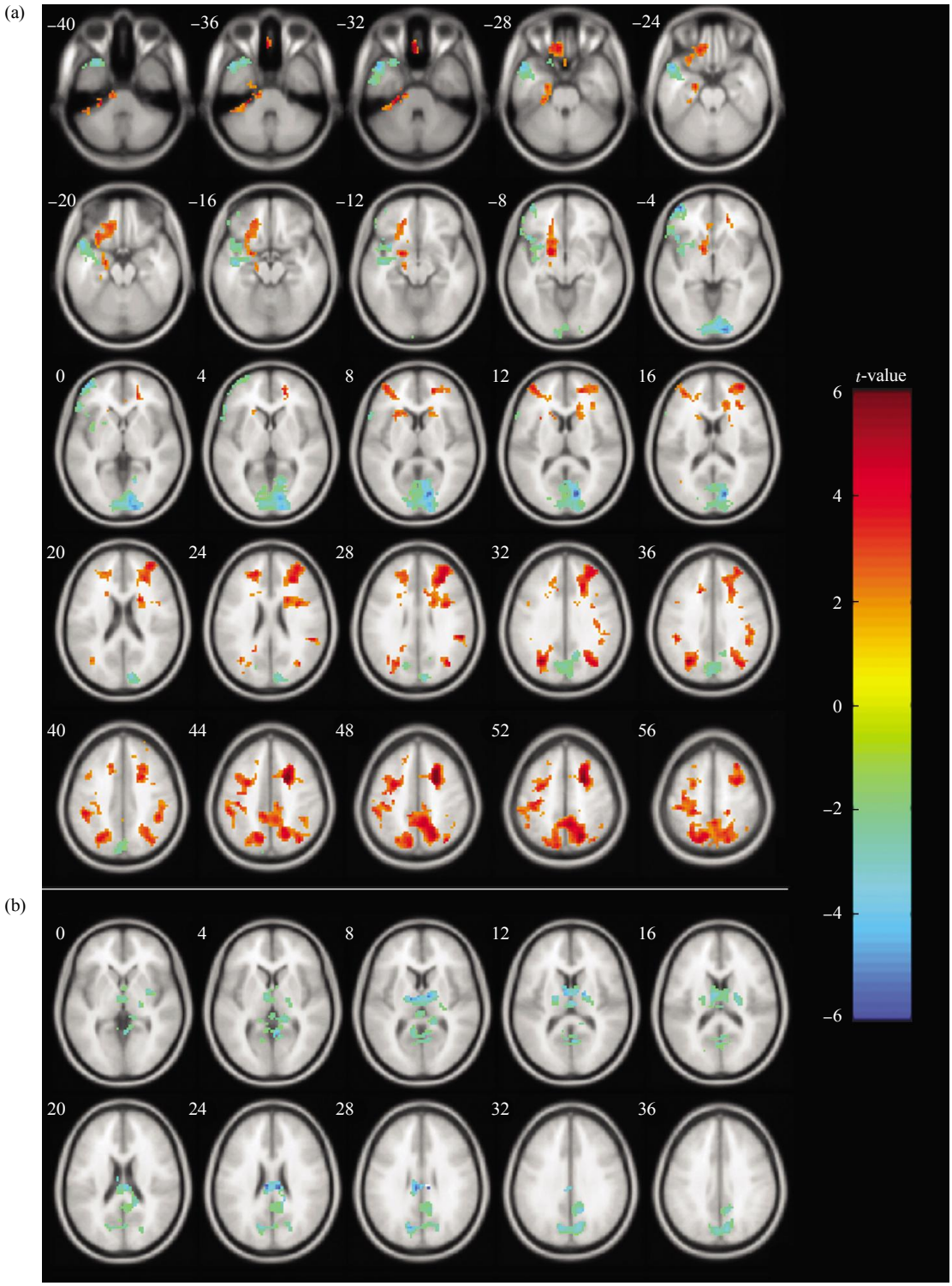

Fig. 5 Functional connectivity changes associated with disease duration

(a) FC strength in the LB amygdala. (b) FC strength in the FS amygdala.

3 Discussion

As a typical type of chronic neuropathic pain, the central mechanism of PHN is still unclear, and studies investigating this topic have been relatively few. Geha *et al.*[11] were the first to examine brain activity in PHN patients with spontaneous pain and since then, more related neuroimaging studies have appeared[6, 8-9, 12]. The

amygdala is well known for its important role in emotional processes such as fear conditioning and regulation[22–23]. The amygdala is also associated with a variety of psychiatric disorders including anxiety, depression, and post-traumatic stress disorder [24–26]. Neuropathic pain is a complex disorder with multi-dimensional aspects that encompass sensorimotor, emotional-affective, and cognitive components. As research in this field continues to expand, the role of the amygdala in the different dimensions of pain have been emerging[27–29].

In this study, we examined the FC of the amygdala in PHN patients. We set stricter inclusion criteria for our study cohort than many other studies. Previously, most PHN patients recruited were old and encephalatrophy is known to become more serious with age. In order to minimize the effects of encephalatrophy on the results of the fMRI data, all participants in our study cohort were under 65 years old. Additionally, the effect of PHN on brain activity increases with pain duration. Therefore, we maximized our effect size by recruiting patients who had experienced pain for more than six months. Despite these advantages, our study also has some limitations. First, the number of PHN patients was very small. The small sample size limits the reliability of the data and restricts more detailed fMRI analyses. Second, we did not conduct an exhaustive neuropsychological evaluation of the study subjects. The combination of fMRI and detailed neuropsychological evaluation could help further understand the mechanism of chronic pain. Furthermore, longitudinal observation of study subjects over the course of their disease would be critical to understand the evolution of the mechanisms of PHN pain.

In this study, we examined the FC of each subregion in the amygdala. We found no difference in FC of the CM nucleus of the amygdala between PHN patients and the healthy control group. The LB amygdala is the main area receiving inputs from multiple brain regions. This LB nucleus receives information from the thalamus, insula, anterior cingulate cortex, and prefrontal cortical areas [14]. Signals are then transmitted to the central nucleus from LB for higher information processing. We found that the main regions with enhanced FC with the LB amygdala were the temporal lobe, frontal lobe, limbic lobe, and occipital lobe. The FC we observed in PHN patients between the inferior temporal gyrus (ITG) and the amygdala was not unexpected, as changes in the temporal lobe have been found in several chronic pain studies [30–32]. In chronic migraine patients, grey matter volume was found to be decreased in the right ITG[33] and enhanced connectivity between the ITG and the amygdala was further confirmed in yet another study[16]. Since the ITG plays a key role in the processing of visual information and object recognition [34], its enhanced FC with the amygdala may provide a new clue to the neuromechanism of chronic pain.

The orbitofrontal gyrus (OFG) is another area showed obvious enhanced FC with the amygdala and our fMRI data confirmed this increased FC with the LB amygdala. The OFG is also called the ventromedial prefrontal cortex and has been extensively connected with the amygdala[35]. The OFG participates in sensory integration, decision-making, reward expectation, and emotion regulation[36]. The role of the prefrontal cortex in chronic pain has been revealed by many previous studies [37], as well as its enhanced FC with the amygdala in chronic migraine patients [16]. Future studies should pay more attention to the precise functional changes of the OFG in chronic pain.

The SF nucleus of the amygdala lies adjacent to the LB complex and participates in processes of the olfactory system[38]. Roy *et al*.[39] used fMRI to reveal FC between the limbic cortex and the SF amygdala, suggesting that this SF nucleus may play a role in the affective component of chronic pain. Few studies have investigated the FC of the SF amygdala in chronic pain patients. Our data showed decreased FC between the SF nucleus and the precentral gyrus (a primary motor area). The stimulation of the precentral gyrus can significantly relieve neuropathic pain [40–41], but the mechanism remains elusive. Lefaucheur *et al*. [42] believed that stimulation of the motor cortex can elicit the descending inhibitory system to relieve pain. We observed decreased FC between areas of the parietal lobe (superior parietal cortex, inferior parietal cortex, and postcentral cortex) and the SF nucleus and we conjecture that this finding could suggest the involvement of the SF amygdala in the mechanism by which the motor cortex mediates pain in PHN. The parietal lobe is the main sensory area of the brain and plays a key role in pain differentiation, location, and analysis processing, especially in acute pain processing [43–44]. The amygdala has been thought to participate in the descending pain modulatory system[27,45]. Human imaging studies revealed connections linking

the periaqueductal gray region (PAG) to the amygdala and cortical sites[46]. Taking all these results together, we speculate that the precentral gyrus and parietal cortical areas first export pain inhibitory signals to the SF nucleus of the amygdala, from where they are relayed to the PAG to evoke the pain inhibitory system. The decreased FC of the SF amygdala with the precentral and parietal cortices would weaken inhibitory function and can thus explain the spontaneous pain of PHN patients. This idea needs to be confirmed by more in-depth studies. Similar to the LB amygdala, we found increased FC of the SF amygdala with the temporal lobe and frontal lobe, indicating that these two areas may also play an important role in chronic pain modulation.

Jiang *et al*.[15] found increased FC between the amygdala and the central executive network (CEN) in chronic low back pain patients, a resting state brain network that mainly includes the lateral prefrontal and posterior parietal cortices. In our study, we found increased FC between the LB nucleus of the amygdala and the prefrontal cortex but decreased FC between the SF nucleus and the parietal cortex. We plan to further examine such associations between the amygdala and regions in different brain networks in future experiments.

The correlation analyses we performed showed that FC strength of the LB amygdala has positive correlations with VAS score and disease duration in the temporal and frontal lobe. These findings suggest that some functions of these brain regions could become enhanced when pain exacerbates and disease duration is prolonged, making PHN pain difficult to relieve and refractory to treatment.

To our knowledge, our study is the first to investigate the FC of amygdala subregions in PHN patients. The altered FC of the LB and SF nuclei of the amygdala can be useful in understanding the mechanism of chronic neuropathic pain.

References

[1] Johnson R W, Rice A S. Clinical practice. postherpetic neuralgia. N Engl J Med, 2014, **371**(16): 1526−1533

[2] Kim H J, Ahn H S, Lee J Y, *et al*. Effects of applying nerve blocks to prevent postherpetic neuralgia in patients with acute herpes zoster: a systematic review and meta-analysis. The Korean Journal of Pain, 2017, **30**(1): 3−17

[3] Kawai K, Gebremeskel B G, Acosta C J. Systematic review of incidence and complications of herpes zoster: towards a global perspective. Bmj Open, 2014, **4**(6): e4833

[4] Drolet M, Brisson M, Schmader K E, *et al*. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. Can Med Assoc J, 2010, **182**(16): 1731−1736

[5] Forbes H J, Thomas S L, Smeeth L, *et al*. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. Pain, 2016, **157**(1): 30−54

[6] Cao S, Song G, Zhang Y, *et al*. Abnormal local brain activity beyond the pain matrix in postherpetic neuralgia patients: a resting-state functional mri study. Pain Physician, 2017, **20** (2): E303−E314

[7] Zhang Y, Yu T, Qin B, *et al*. Microstructural abnormalities in gray matter of patients with postherpetic neuralgia: a diffusional kurtosis imaging study. Pain Physician, 2016, **19**(4): E601−E611

[8] Jiang J, Gu L, Bao D, *et al*. Altered homotopic connectivity in postherpetic neuralgia: a resting state fmri study. J Pain Res, 2016, **9**: 877−886

[9] Guan M, Ma L, Li L, *et al*. Self-regulation of brain activity in patients with postherpetic neuralgia: a double-blind randomized study using real-time fmri neurofeedback. Plos One, 2015, **10** (4): e123675

[10] Zhang Y, Liu J, Li L, *et al*. A study on small-world brain functional networks altered by postherpetic neuralgia. Magn Reson Imaging, 2014, **32**(4): 359−365

[11] Geha P Y, Baliki M N, Chialvo D R, *et al*. Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. Pain, 2007, **128**(1−2): 88−100

[12] Liu J, Hao Y, Du M, *et al*. Quantitative cerebral blood flow mapping and functional connectivity of postherpetic neuralgia pain: a perfusion fmri study. Pain, 2013, **154**(1): 110−118

[13] Costafreda S G, Brammer M J, David A S, *et al*. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 pet and fmri studies. Brain Research Reviews, 2008, **58**(1): 57−70

[14] Simons L E, Moulton E A, Linnman C, *et al*. The human amygdala and pain: evidence from neuroimaging. Hum Brain Mapp, 2014, **35**(2): 527−538

[15] Jiang Y, Oathes D, Hush J, *et al*. Perturbed connectivity of the amygdala and its subregions with the central executive and default mode networks in chronic pain. Pain, 2016, **157**(9): 1970−1978

[16] Chen Z, Chen X, Liu M, *et al*. Altered functional connectivity of amygdala underlying the neuromechanism of migraine pathogenesis. The Journal of Headache and Pain, 2017, **18**(1): 7

[17] Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms [M]. Second. Seattle: International Association for the Study of Pain, 1994: 61−62

[18] Song X, Dong Z, Long X, *et al*. Rest: a toolkit for resting-state functional magnetic resonance imaging data processing: Plos One, 2011, **6**(9): e25031

[19] Chao-Gan Y, Yu-Feng Z. Dparsf: a matlab toolbox for "pipeline" data analysis of resting-state fmri. Front Syst Neurosci, 2010, **4**: 13

[20] Amunts K, Kedo O, Kindler M, *et al*. Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. Anatomy and Embryology, 2005, **210**(5-6): 343-352

[21] Eickhoff S B, Stephan K E, Mohlberg H, *et al*. A new spm toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage, 2005, **25**(4): 1325-1335

[22] Sehlmeyer C, Schöning S, Zwitserlood P, *et al*. Human fear conditioning and extinction in neuroimaging: a systematic review. Plos One, 2009, **4**(6): e5865

[23] Sergerie K, Chochol C, Armony J L. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. Neuroscience & Biobehavioral Reviews, 2008, **32**(4): 811-830

[24] Sripada R, King A, Garfinkel S, *et al*. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatr Neurosci, 2012, **37**(4): 241-249

[25] Hahn A, Stein P, Windischberger C, *et al*. Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. Neuroimage, 2011, **56**(3): 881-889

[26] Kim M J, Loucks R A, Palmer A L, *et al*. The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behav Brain Res, 2011, **223**(2): 403-410

[27] Neugebauer V, Li W, Bird G C, *et al*. The amygdala and persistent pain. Neuroscientist, 2004, **10**(3): 221-234

[28] Lumley M A, Cohen J L, Borszcz G S, *et al*. Pain and emotion: a biopsychosocial review of recent research. Journal of Clinical Psychology, 2011, **67**(9): 942-968

[29] Bernard J F, Huang G F, Besson J M. Nucleus centralis of the amygdala and the globus pallidus ventralis: electrophysiological evidence for an involvement in pain processes. J Neurophysiol, 1992, **68**(2): 551-569

[30] Gracely R H, Petzke F, Wolf J M, *et al*. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheumatol, 2002, **46**(5): 1333-1343

[31] Zhao Y P, Ma X C, Jin Z, *et al*. Cerebral activation during unilateral clenching in patients with temporomandibular joint synovitis and biting pain: an functional magnetic resonance imaging study. Chinese Med J-Peking, 2011, **124**(14): 2136-2143

[32] van Heeringen K, Van den Abbeele D, Vervaet M, *et al*. The functional neuroanatomy of mental pain in depression. Psychiatry Research: Neuroimaging, 2010, **181**(2): 141-144

[33] Yu S, Chen X, Chen Z, *et al*. Ehmti-0307. Chronification of migraine: a clinical and voxel-based morphometry study. The Journal of Headache and Pain, 2014, **15**(1): E43

[34] Denys K. The processing of visual shape in the cerebral cortex of human and nonhuman primates: a functional magnetic resonance imaging study. J Neurosci, 2004, **24**(10): 2551-2565

[35] Price J L. Comparative aspects of amygdala connectivity. Ann N Y Acad Sci, 2003, **985**: 50-58

[36] Kringelbach M L. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci, 2005, **6**(9): 691-702

[37] Apkarian A V, Bushnell M C, Treede R, *et al*. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain, 2005, **9**(4): 463-484

[38] Sah P, Faber Esl, Lopez de Armentia M, *et al*. The amygdaloid complex: anatomy and physiology. Physiol Rev, 2003, **83** (3): 803-834

[39] Roy A K, Shehzad Z, Margulies D S, *et al*. Functional connectivity of the human amygdala using resting state fmri. Neuroimage, 2009, **45**(2): 614-626

[40] Zhang X, Hu Y, Tao W, *et al*. The effect of motor cortex stimulation on central poststroke pain in a series of 16 patients with a mean follow-up of 28 months. Neuromodulation: Technology at the Neural Interface, 2017, **20**(5): 492-496

[41] Deogaonkar M, Sharma M, Oluigbo C, *et al*. Spinal cord stimulation (scs) and functional magnetic resonance imaging (fmri): modulation of cortical connectivity with therapeutic scs. Neuromodulation, 2016, **19**(2): 142-153

[42] Lefaucheur J, Holsheimer J, Goujon C, *et al*. Descending volleys generated by efficacious epidural motor cortex stimulation in patients with chronic neuropathic pain. Exp Neurol, 2010, **223**(2): 609-614

[43] Porro C, Martinig M, Facchin P, *et al*. Parietal cortex involvement in the localization of tactile and noxious mechanical stimuli: a transcranial magnetic stimulation study. Behav Brain Res, 2007, **178**(2): 183-189

[44] Porro C A. Functional imaging and pain: behavior, perception, and modulation. Neuroscientist, 2003, **9**(5): 354-369

[45] Bingel U, Schoell E, Buchel C. Imaging pain modulation in health and disease. Curr Opin Neurol, 2007, **20**(4): 424-431

[46] Ossipov M H, Dussor G O, Porreca F. Central modulation of pain. J Clin Invest, 2010, **120**(11): 3779-3787

带状疱疹后神经痛患者杏仁核的功能连接改变研究 *

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摘要 带状疱疹后神经痛(postherpetic neuralgia, PHN)是一种常见的神经病理性疼痛，但其中枢机制尚不明了．杏仁核在疼痛反应中的作用近年来受到关注．本研究的目的在于通过功能磁共振成像，研究带状疱疹后神经痛患者杏仁核各个亚区功能连接(functional connectivity, FC)的改变，探索慢性神经病理性疼痛的中枢机制．8 位带状疱疹后神经痛患者和 8 位健康者进行了普通核磁共振和静息态功能磁共振扫描．将杏仁核各个亚区分别进行的功能连接分析，并将功能连接和被试者的病程、视觉模拟评分(visual analog scale, VAS)进行了相关分析．与健康志愿者相比，PHN 患者杏仁核的基底外侧部(laterobasal groups, LB)和皮质部(superficial groups, SF)与多个脑区的 FC 表现出增强，主要位于颞叶和额叶．同时 SF 与多个区域的 FC 出现减低，主要位于额叶和顶叶．颞叶和额叶部分区域与 LB 的 FC 强度、与病程长短和 VAS 评分表现出关联性．研究结果提示，PHN 患者杏仁核功能连接的改变提示了在慢性神经病理性疼痛的产生和发展中，杏仁核以及多个涉及情绪、认知、注意的脑区发挥了重要作用．

关键词 带状疱疹后神经痛，神经病理性疼痛，功能核磁共振成像，功能连接

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