

# Hypoconnectivity of the Amygdala in Patients with Low-Back-Related Leg Pain Linked to Individual Mechanical Pain Sensitivity: A Resting-State Functional MRI Study

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**Purpose:** To explore resting-state functional connectivity (rsFC) of the amygdala in patients with low-back-related leg pain (LBLP).

**Patients and Methods:** For this prospective study, a total of 35 LBLP patients and 30 healthy controls (HCs) were included and underwent functional MRI and clinical assessments. Then, patients with LBLP were divided into acute LBLP (aLBLP) and chronic LBLP (cLBLP) subgroups. We further evaluated the between-group rsFC differences using left and right amygdala seeds in a whole-brain voxel analysis strategy. Finally, we performed correlation analysis between the rsFC values of altered regions and clinical indices.

**Results:** Compared to HCs, hypoconnectivity of the amygdala was observed in LBLP patients ( $P < 0.01$ , with correction). The amygdala's rsFC pattern was different between aLBLP and cLBLP patients: decreased the amygdala's FC to the right putamen, to the right paracentral lobule (PCL), or to the right posterior temporal lobe in aLBLP patients, while right amygdala to the bilateral anterior cingulate cortex (ACC) and the left postcentral gyrus (PoCG) in cLBLP patients. Correlation analysis showed that lower rsFC of the left amygdala to the right PCL was correlated with the von Frey filament (vF) test values of the left lumbar ( $p = 0.025$ ) and right lumbar ( $p = 0.019$ ) regions, and rsFC of the right amygdala to the left PoCG was correlated with lower vF test values of the left lumbar ( $p = 0.017$ ), right lumbar spine ( $p = 0.003$ ); to right PoCG was correlated with calf ( $p = 0.015$ ); the rsFC of the right amygdala to bilateral ACC was negatively correlated with the pain rating index ( $p = 0.003$ ).

**Conclusion:** LBLP patients showed amygdala hypoconnectivity, and the altered pattern of amygdala rsFC was different in the acute and chronic phases. Moreover, the amygdala hypoconnectivity was related to individual mechanical sensitivity (vF test) in LBLP patients.

**Keywords:** amygdala, resting-state functional MRI, low-back-related leg pain, acute pain, chronic pain

## Introduction

Low-back-related leg pain (LBLP) is one of the most common subgroups of low-back pain caused by intervertebral disc degeneration, disc herniation and nerve root compression.<sup>1</sup> Patients with LBLP can exhibit a variety of clinical symptoms, including dull or achy, stinging, burning pain or numbness from the low back to the backs of the thighs

and even some pain comorbidities/symptoms, such as anxiety, depression, and cognitive impairment.<sup>2,3</sup> Additionally, LBLP patients are usually associated with more serious disability, poorer outcomes and negative emotion than those with low-back pain alone.<sup>4</sup> Negative emotion will not only increase physiological pain sensitivity but also increase the incidence of complications, such as sleep disorders and abnormal decision-making, through the transition from acute low back pain to chronic low back pain.<sup>5</sup> These factors seriously affect patients' quality of social life, pain prognosis, and even outcomes.<sup>6,7</sup>

Multiple studies have demonstrated that the amygdala plays an important role in pain processing and regulation. For example, hyperactivity of basolateral amygdala (BLA) neurons and central amygdala (CeA) neurons leads to the impairment of amygdala-cortical control mechanisms, which allows the development of amygdala pain plasticity.<sup>8</sup> A neuroimaging meta-analysis showed that the location of peak activation within and outside the amygdala subregion in acute and chronic pain had great agreement with neuroanatomical landmarks derived from laboratory and neuroimaging modalities under the experimental induction, such as mechanical compression, thermal stimulation and capsaicin stimulation.<sup>9</sup> In patients with chronic pain exposed to threat and scare stimuli, it was observed that negative emotional states correlated with increased resting-state functional connectivity (rsFC) between the amygdala and the supramarginal gyrus.<sup>10</sup> Hyperconnectivity of the amygdala has also been observed in patients with irritable bowel syndrome-related abdominal pain.<sup>11</sup>

Furthermore, compared to acute low back pain, more emotion-related structural and functional alterations in the brain were observed in patients with chronic pain. This may be due to large-scale changes in the brain during the transition from acute pain to chronic pain, manifested by a shift from acute pain-related brain regions to chronic emotion-related circuits involving the amygdala.<sup>12</sup> However, functional connectivity in the amygdala has rarely been studied in patients with different pain durations of LBLP. In other words, the role of the amygdala in acute and chronic LBLP still remains unclear.

Therefore, we hypothesized that LBLP patients exhibit abnormal amygdala rsFCs, and the altered rsFC pattern is different in the acute phase and the chronic phase. We aimed to elucidate the amygdala functional connectivity differences between brain regions related to emotion arousal and pain processing matrix regions. For all participants, we selected the left and right amygdala as seeds, calculated whole-brain rsFC, compared the rsFC differences between LBLP patients or their subgroups (acute LBLP and chronic LBLP) and controls at the voxel-based level, and evaluated the relationship between rsFC and pain intensity, pain rating, mechanical sensitivity and mood (anxiety, depression).

## Materials and Methods

### Participants

Thirty-five clinically defined LBLP patients were recruited from the First Affiliated Hospital of Nanchang University from October 2021 to March 2023. The inclusion criteria included the following: 1) aged 22–65 years and voluntarily joined the study; 2) a diagnosis and full evidence of discogenic compression on back-computed tomography (CT) and/or magnetic resonance imaging (MRI) ( $\geq 1$  ruptured annulus fibrosus with compressed soft tissue); 3) visual analog scale (VAS) scores  $> 3/10$ ; and 4) ineffective prior conservative treatment with medications, eg, anti-inflammatory drugs (Motrin, Advil and Naproxen) and acetaminophen (eg, Tylenol) without opioids, exercise and physical therapy. The exclusion criteria for the LBLP group were a history of spinal stenosis due to calcification on the spinal protrusion, lateral recess stenosis, spinal stenosis, piriformis syndrome, or sciatica; a history of head and spinal cord injury or a major systemic disease; and a history of significant cardiac events. Pain for more than 3 months was defined as chronic pain. In this study, 21 patients were defined as having chronic LBLP (cLBLP), while 17 patients were defined as having acute LBLP (aLBLP). Healthy controls (HCs) were recruited by advertisements. All of the HCs were screened using the Clinical Diagnostic Interview Nonpatient Version and did not have significant cognitive disorders, head trauma, or magnetic resonance imaging (MRI) contraindications. All subjects provided informed written consent to the procedures approved by the Medical Research Ethics Committee of the First Affiliated Hospital of Nanchang University in accordance with the Declaration of Helsinki.

## Clinical Assessment

Before MRI scanning, each LBLP patient completed a series of clinical evaluations, including (1) the Japanese Orthopaedic Association (JOA) Back Pain Evaluation questionnaire (score range, –6 to 29) to examine the impact of neuropathic or nociceptive pain on quality of life; (2) the visual analogue scale (VAS) for pain intensity, ranging from 0 (no pain) to 10 (worst pain); (3) the Short-Form McGill Pain Questionnaire (SF-MPQ) to evaluate the pain intensity of subjects, including four major groups, sensory, affective, evaluative, and miscellaneous, with the sum of the rank values for each descriptor termed the pain rating index (PRI); (4) a manual von Frey filaments (vF) test (Item No. 514000-20C, Danmic Global, LLC, Inc., San Jose, CA, USA) for assessing the mechanical pain sensitivity of 8 regions (bilateral hand, back, calf, and foot), where a higher value indicates lower mechanical pain sensitivity;<sup>13–15</sup> and (5) the Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Scale (HAMA) for evaluating the symptoms of anxiety and depression.

## Imaging Data Acquisition

All MRI data were acquired on a 3.0T MRI (Signa Pioneer, GE Healthcare, Milwaukee, CA, USA) at the First Affiliated Hospital of Nanchang University. A high-resolution 3D T1-weighted imaging scanner was used with the following parameters: repetition time (TR)/echo time (TE) = 8.0 ms/3.0 ms, field of view (FOV) = 256 mm × 256 mm, matrix = 256 × 256, thickness/gap = 1.0/0 mm and 176 sagittal slices. To acquire resting-state fMRI data, we used an echo planar image (EPI) sequence with the following parameters: TR/TE = 2000 ms / 25 ms, FOV = 190 × 190 mm, matrix = 64 × 64, flip angle = 90°, slice thickness = 3.5 mm, 40 axial slices, and 240 volumes over 8 min. While participants were lying in the scanner, they were asked to follow the instruction: “Keep your eyes closed, avoid thinking about anything and maintain a clear head”.

## Data Preprocessing

All fMRI data were processed and analyzed using the toolbox for Data Processing & Analysis of Brain Imaging (DPABI v6.0; <http://rfmri.org/dpabi>). The processing steps were as follows: the first 10 image (volumes) were discarded to keep the signal steady, slice timing and head motion correction were performed; and images were segmented into white matter, gray matter, and cerebrospinal fluid (CSF) with the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm and normalized to Montreal Neurological Institute (MNI) space; Furthermore, we excluded images in which head motion exceeded 3 mm translation or 3° rotation according to the criteria of Van Dijk et al.<sup>16</sup> After normalization, we continued resampling the image to 3 mm isotropic voxels and spatial smoothing (6 mm using a full width at half-maximum Gaussian kernel). Additionally, detrended linear drift and nuisance linear regression, including the white matter, CSF and head motion parameters, were enforced according to the Friston-24 model.<sup>17</sup> Finally, to diminish the influence of low-frequency drift and high-frequency physiological noise, we applied temporal bandpass filtering (0.01–0.1 Hz).

## Seed Definition and Functional Connectivity Analysis

We selected the left and right amygdala as seeds based on the Harvard–Oxford atlas, which was implemented in DPABI v6.0 (<http://rfmri.org/dpabi>) and presented by the BrainNet Viewer. Subject-level rsFC was performed by calculating the Pearson correlation coefficient of average time courses of blood oxygenation level-dependent signals between the seed and all other brain voxels. For further statistical analysis, all correlation values were transformed by Fisher *r*-to-*z* transformation to fit the Gaussian distribution. A two-sample *t*-test was assessed for the LBLP and HC groups with age, sex and mean frame displacement (FD) as covariates (two-tailed, voxel-level *P* < 0.01, Gaussian random field (GRF) theory correction at cluster-level *P* < 0.05). In addition, two sub-groups comparisons for the aLBLP vs HC and cLBLP vs HC groups were conducted.

## Clinical Statistical Analysis

SPSS 23.0 package (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. We used Shapiro–Wilk tests and histograms to test the normality of the data, and we used means and standard deviations to characterize normally distributed data. Age, sex, mean FD and observed clinical scores among the groups were assessed through different

statistical methods. Normally distributed data were analyzed by two-samples *t* tests, whereas the Man-Whitney *U*-test was used for the non-normally distributed data. The chi-square test was used for categorical data, and all significance levels were set at  $P < 0.05$ . The log transformation was to reduce skewness of vF test data to approximately conform to normality. Partial or Spearman correlations were performed between the altered rsFC values and clinical assessments, with sex and age as covariates.

## Results

### Clinical and Demographic Analysis

Two healthy controls were excluded from the final analysis due to excessive 3 mm translation or 3° rotation during the scanning procedure. Table 1 summarizes the demographic and clinical data of the LBLP patients and HCs included in this study. There was no significant difference in age or sex between the LBLP and HC groups, between the aLBLP and HC groups (Table S1), or between the cLBLP and HC groups (Table S1). The average vF test values were 39.2–588 millinewton (mN), indicating significantly decreased mechanical sensitivity in LBLP patients, which the normal range is 0.08–0.70 mN (Table 1). There was no significant difference in the vF test values between aLBLP and cLBLP patients (Table S1,  $P: 0.376–0.973$ ). There was no significant difference in the clinical questionnaires between the aLBLP and cLBLP groups ( $P > 0.05$ ) (Table S1).

### Hypoconnectivity of the Amygdala in LBLP

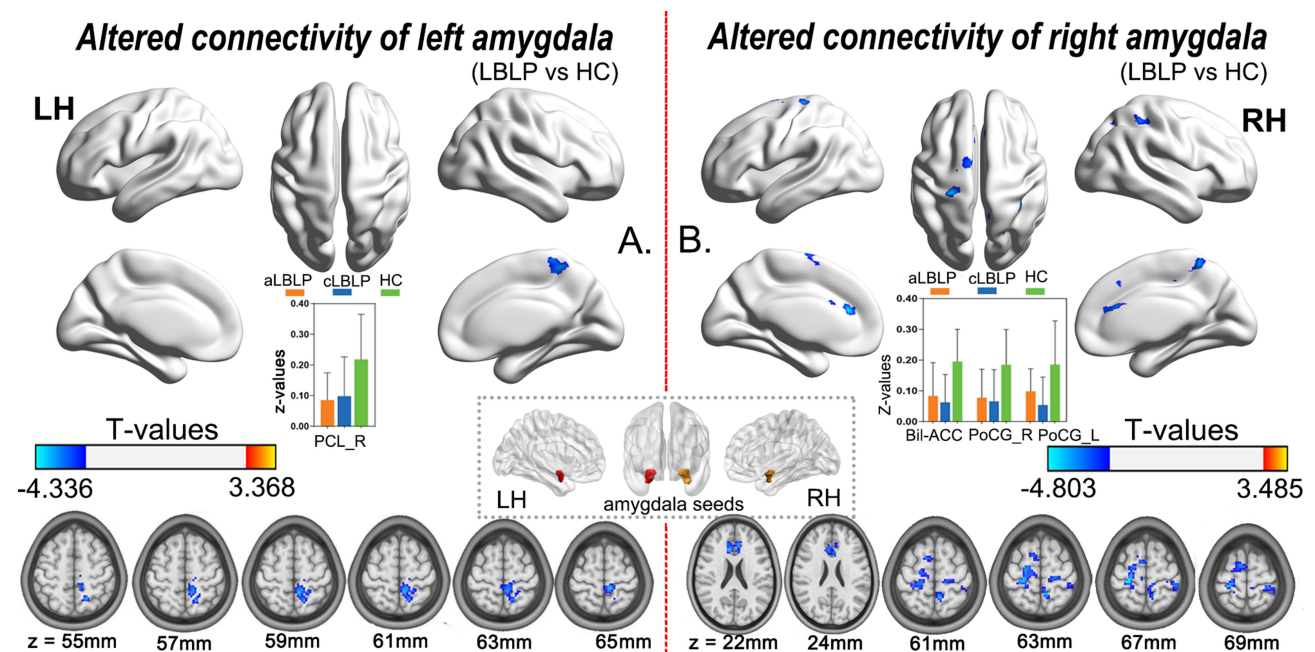
Compared to HCs, LBLP patients showed decreased rsFC between the left amygdala and right paracentral lobule (PCL), between the right amygdala and bilateral anterior cingulate cortex (ACC), and between the right amygdala and bilateral postcentral gyrus (PoCG) (voxel-level  $P < 0.01$ , Gaussian random field [GRF] correction at cluster-level  $P < 0.05$ ) (Figure 1 and Table 2).

**Table 1** Demographic Data and Clinical Characteristics of the LBLP and HC Groups

Characteristics	LBLP (n=35)	HC (n = 30)	P values
Demographic data			
Age (y) Median (p25, p75) <sup>a</sup>	53.0 (38.0, 60.0)	40.0 (38.0, 50.8)	0.076
Sex (M/F) <sup>b</sup>	25/10	16/14	0.132
Duration of disease (months) Median (p25, p75)	3.00 (1.00, 12.00)	n/a	n/a
Clinical data			
JOA	13.49±4.08	n/a	n/a
VAS	5.37±0.91	n/a	n/a
PRI	5.09±2.01	n/a	n/a
HAMD	4.29±2.30	n/a	n/a
HAMA	2.26±1.38	n/a	n/a
von Frey filament (vF) test values (mN) (p25, p75)			
vF test of left hand (mN)	588.0 (255.0, 588.0)	n/a	n/a
vF test of right hand (mN)	588.0 (255.0, 588.0)	n/a	n/a
vF test of left lumbar (mN)	58.8 (39.2, 147.0)	n/a	n/a
vF test of right lumbar (mN)	58.8 (39.2, 98.0)	n/a	n/a
vF test of left calf (mN)	58.8 (78.4, 147.0)	n/a	n/a
vF test of right calf (mN)	58.8 (78.4, 98.0)	n/a	n/a
vF test of left foot (mN)	39.2 (58.8, 78.4)	n/a	n/a
vF test of right foot (mN)	39.2 (58.8, 78.4)	n/a	n/a
Neuroimaging data (mN)			
Frame displacement Median (p25, p75)	0.012 (0.008, 0.026)	0.029 (0.016, 0.029)	0.506 <sup>a</sup>

**Notes:** <sup>a</sup>Mann–Whitney Test; <sup>b</sup>Chi-square tests.

**Abbreviations:** LBLP, low-back-related leg pain; HC, healthy control; y, years; M, male; F, female; JOA, Japanese Orthopaedic Association; VAS, visual analogue scale; PRI, pain rating index; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; n/a, not available; mN, millinewton.



**Figure 1** Altered connectivity of the left (A) and right (B) amygdala in LBLP patients (voxel-level  $P < 0.01$ , GRF correction at cluster-level  $P < 0.05$ ).

**Abbreviations:** LBLP, low-back-related leg pain; HC, healthy control; rsFC, resting-state functional connectivity; LH, left hemisphere; RH, right hemisphere. PCL\_R, right paracentral lobule; Bil-ACC, bilateral anterior cingulum; PoCG\_R, right postcentral gyrus; PoCG\_L, left postcentral gyrus.

### Different Connectivity Patterns of the Amygdala in aLBLP and cLBLP

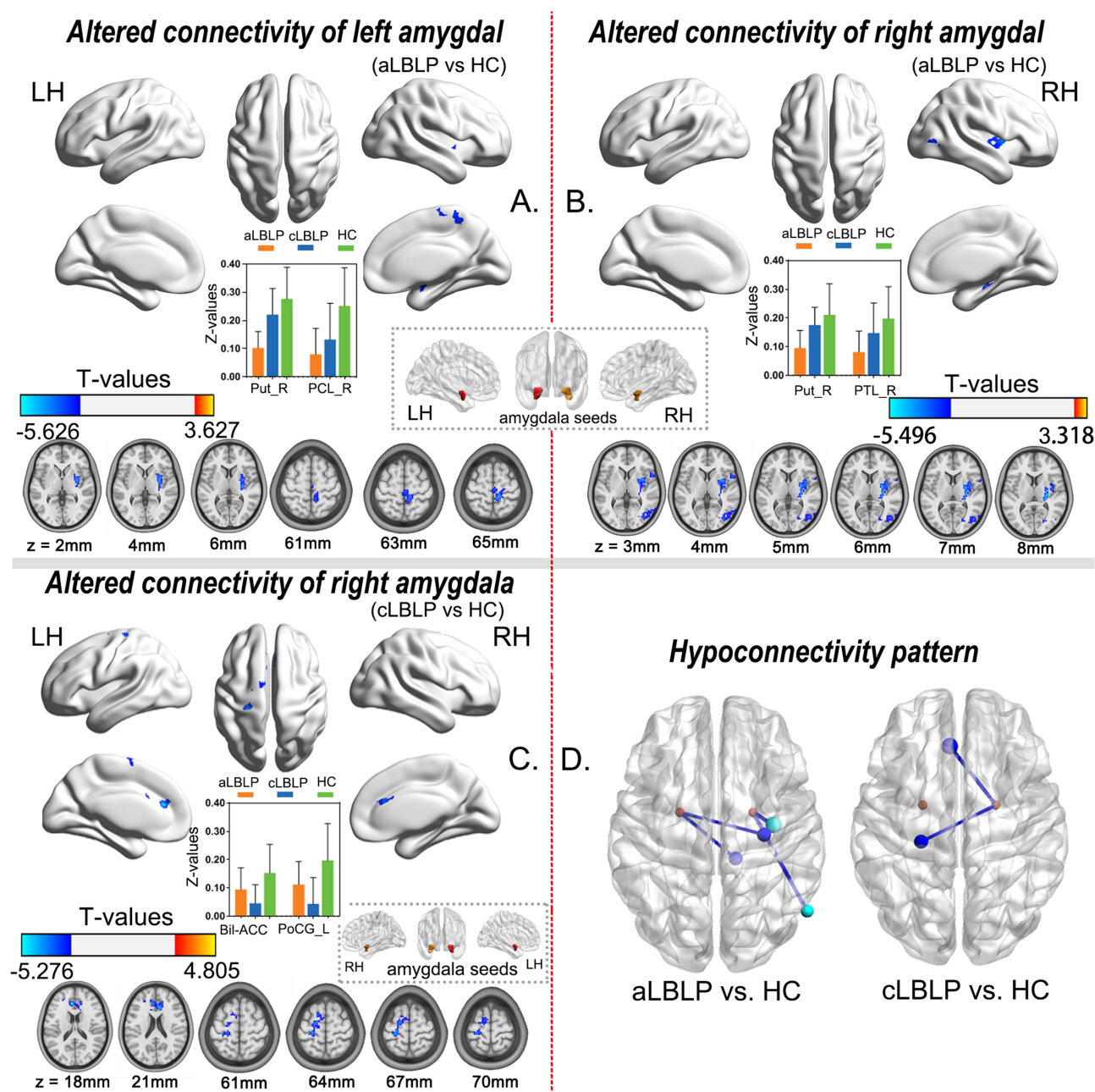
Figure 2A–C presents the altered connectivity of the amygdala in aLBLP and cLBLP patients (Table 2). Although the alterations in functional connectivity were all decrease, the amygdala rsFC patterns were different in acute and chronic LBLP patients (Figure 2D). Specifically, aLBLP patients showed lower rsFC between the amygdala and the bilateral

**Table 2** Brain Regions with Altered Amygdala Functional Connectivity of LBLP and LBLP Subgroups (Voxel-Level  $P < 0.01$ , GRF Correction at Cluster-Level  $P < 0.05$ )

Brain Regions	BA	Peak	Voxels	MNI Coordinates		
				X	Y	Z
Altered connectivity of left amygdala (LBLP vs HC)						
Right paracentral lobule (PCL)	5, 7	−3.963	169	9	−36	66
Altered connectivity of right amygdala (LBLP vs HC)						
Bilateral anterior cingulum (ACC)	32	−4.657	211	−6	33	18
Right postcentral gyrus (PoCG)	1, 2, 3	−4.285	307	9	−48	60
Left postcentral gyrus (PoCG)	1, 2, 3	−4.803	251	−24	−27	66
Altered connectivity pattern in acute or chronic LBLP						
Altered connectivity of left amygdala (aLBLP vs HC)						
Right putamen		−4.583	252	30	−18	9
Right paracentral lobule (PCL)	6	−4.484	156	12	−33	6
Altered connectivity of right amygdala (aLBLP vs HC)						
Right putamen		−5.209	370	36	−12	−3
Right posterior temporal lobe	37	−4.169	139	57	−66	−6
Altered connectivity of right amygdala (cLBLP vs HC)						
Bilateral ACC	32	−5.276	195	−6	33	18
Left PoCG	1, 2, 3	−4.341	162	−24	−27	66

**Abbreviations:** LBLP, low-back-related leg pain; HC, healthy control; aLBLP, acute LBLP; cLBLP, chronic LBLP; BA, Brodmann's area; MNI, Montreal Neurological Institute coordinate system.





**Figure 2** Altered pattern of amygdala rsFC in aLBLP and cLBLP patients (voxel-level  $P < 0.01$ , GRF correction at cluster-level  $P < 0.05$ ).

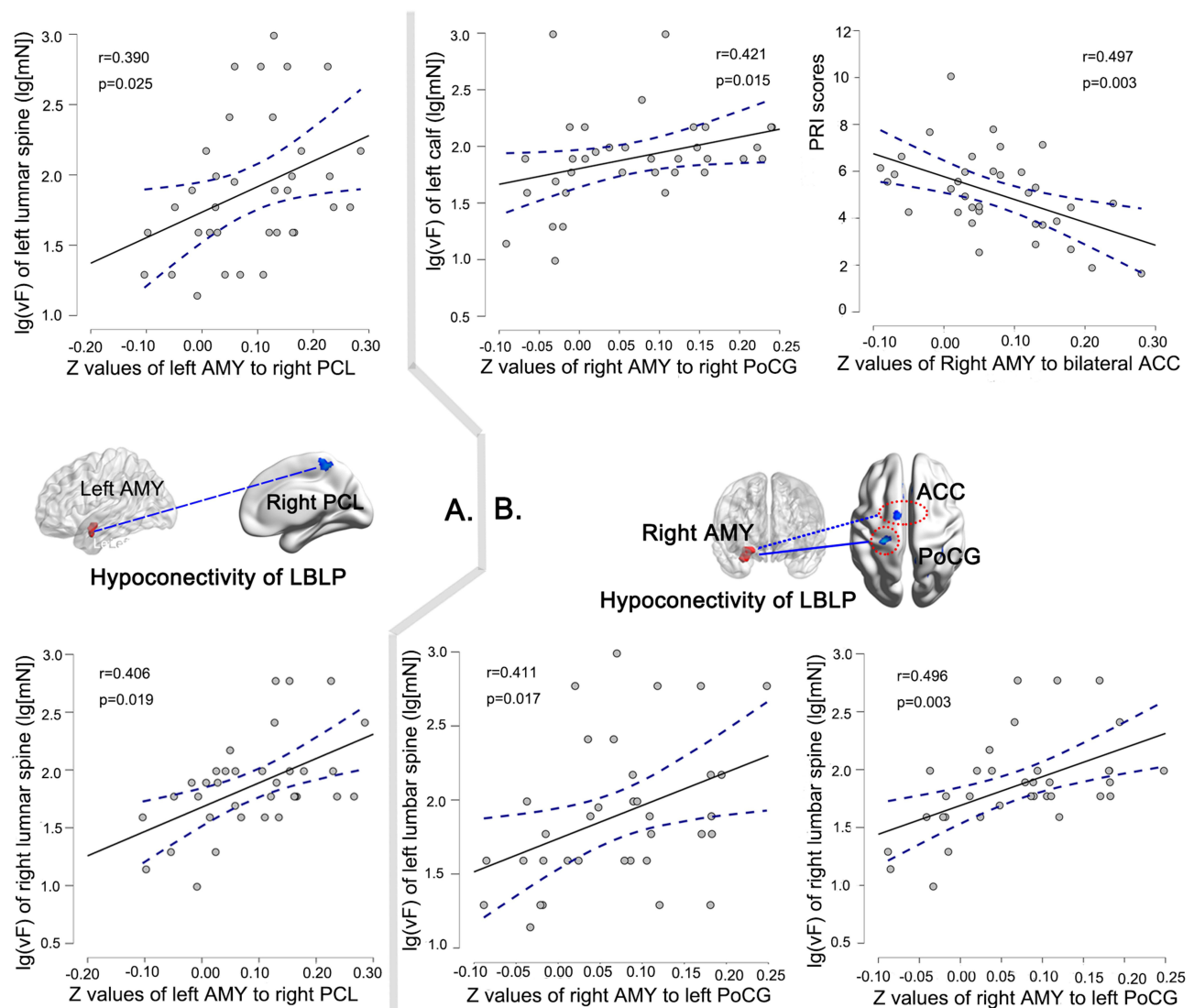
**Notes:** The top row is the results of group analysis for left (A) and right (B) amygdala rsFC for aLBLP patients and HCs (voxel-level  $P < 0.01$ , GRF correction at cluster-level  $P < 0.05$ ). The bottom row is the results of between-group analysis for the right amygdala rsFC for cLBLP patients and HCs (C) (voxel-level  $P < 0.01$ , GRF correction at cluster-level  $P < 0.05$ ), and a sketch map of the altered connectivity pattern in aLBLP and cLBLP (D).

**Abbreviations:** LBLP, low-back-related leg pain; HC, healthy control; aLBLP, acute LBLP; cLBLP, chronic LBLP; Bil-ACC, bilateral anterior cingulum; PoCG, postcentral gyrus; PTL, posterior temporal lobe; Put, putamen; AMY, amygdala; vF, von Frey filament; rsFC, resting-state functional connectivity; LH, left hemisphere; RH, right hemisphere.

putamen, right PCL, and right posterior temporal lobe, while cLBLP patients mainly exhibited lower rsFC between the right amygdala and the bilateral ACC, between the right amygdala and left PoCG.

## Correlation Analysis

When exploring the regions with altered amygdala connectivity in the LBLP group, we observed that lower rsFC of the left amygdala to the right PCL was related to the lg(vF) of the left lumbar ( $r = 0.390$ ,  $p = 0.025$ ) and right lumbar spine ( $r$



**Figure 3** Spearman correlational analysis between decreased rsFC of left amygdala (**A**) and right amygdala (**B**) and lg-transformed vF test values (lg(vF)), or partial correlational analysis between decreased rsFC of right amygdala (**B**) and the PRI scores in LBLP patients.

**Abbreviations:** LBLP, low-back-related leg pain; AMY, amygdala; PCL, paracentral lobule; ACC, anterior cingulum; PoCG, postcentral gyrus; vF, von Frey filament; PRI, pain rating index.

$r = 0.406$ ,  $p = 0.019$ ) (Figure 3A). Decreased rsFC of the right amygdala to the bilateral ACC was related to higher PRI scores ( $r = 0.497$ ,  $p = 0.003$ ), while lower rsFC of the right amygdala to the left PoCG was related to lower lg(vF) of left lumbar ( $r = 0.411$ ,  $p = 0.017$ ) and right lumbar spine ( $r = 0.496$ ,  $p = 0.003$ ), the right amygdala to right PoCG showed lower lg(vF) of left calf regions ( $r = 0.421$ ,  $p = 0.015$ ) (Figure 3B).

In acute or chronic LBLP subgroups, similar positive associations were found between the rsFC and the lg(vF) value (see Figure S1).

## Discussion

In this study, we examined rsFC of the amygdala in patients with LBLP, as well as associations between rsFC and clinical assessments within the patient group. The main findings were as follows: 1) LBLP patients showed a hypoconnectivity of the amygdala, mainly in the right PCL, bilateral ACC and bilateral PoCG, compared with HCs. More specifically, decreased amygdala rsFC in aLBLP patients was mainly located in the pain matrix, while decreased amygdala rsFC in cLBLP patients was mainly located in the affective/emotional processing area (ACC). 2) Hypoconnectivity of the

amygdala was associated with the lower mechanical pain sensitivity (vF test values) and higher pain intensity (PRI scores).

## Hypoconnectivity of the Amygdala in LBLP Patients

In this study, we found decreased amygdala rsFC in LBLP patients, specifically to the right PCL, bilateral ACC and PoCG. The PCL controls motor and sensory innervation of the contralateral calf and plays a key role in somatosensory perception.<sup>18</sup> Reduced region homogeneity and degree centrality were found in the PCL of persistent somatoform pain disorder patients,<sup>19,20</sup> and such abnormal alterations may be related to diminished inhibition of pain perception and mood disorders, which has been similarly reported in neuroimaging studies of trigeminal neuralgia.<sup>21</sup> In the negative stimuli of pain and fear, the activated PCL was associated with enhanced self-perceived pain responses.<sup>22</sup> The ACC is a part of the limbic system that is activated by noxious stimuli, most importantly, it is involved in affective pain processing. The amygdala participates in the limbic-cortical circuit, which is involved in pain processing and receives pain information input from the ACC.<sup>23</sup> Studies have found that injecting trace excitatory amino acids into the ACC-induced avoidance learning behavior, and blocking excitatory amino acid receptors in the ACC prevented avoidance learning from peripheral noxious stimuli, suggesting that the ACC modulates affective and motivational pain responses through neural projections to the amygdala.<sup>24</sup> The PoCG is well known as part of the brain network of the pain matrix information processing, there is extensive activation in the PoCG in patients with pain, which indicates that it plays an important role in the transmission and processing of sensory information of pain. Our previous study found that the amplitude of low-frequency fluctuation (ALFF) in LBLP patients was reduced mainly in the default mode network and processing system of the pain matrix (thalamus, midbrain, PoCG). In addition, decreased ALFF of the PoCG was inversely correlated with two-point tactile discrimination in the legs, which represents a fine modality measure, indicating a heightened sensitivity to pain and sensory disturbances in patients with LBLP.<sup>25</sup> We speculated that this may be related to the occurrence of abnormal functional damage in brain regions of pain-related afferent pathways in LBLP patients, and weaker connectivity predicted decreased inhibitory control of pain perception and pain behavior.

By further comparing the between-group differences in the decreased amygdala functional connectivity between aLBLP and cLBLP patients, we found that the pattern of connectivity changes in the amygdala was different. For aLBLP patients, reduced rsFC occurred between the amygdala and the right PCL, putamen and posterior temporal lobe, mainly in the regions of the pain matrix processing pathway. The putamen is the main part of the basal ganglia, which processes pain information through the cortex-basal ganglia-thalamus-cortical loop, including receiving sensory and emotional input of pain.<sup>26</sup> The volume of the putamen has been found to be reduced in patients with left trigeminal neuralgia.<sup>27</sup> A recent study reported that the shape of the putamen is closely related to the volume and pain score in acute pain models.<sup>28</sup> These results suggested that the putamen plays an important role in the perception of pain. The relationship between the temporal lobe and pain has not been well explored; a machine learning study of chronic low back pain found increased gray matter in the temporal lobe that correlated with unpleasant mood,<sup>29</sup> and similar findings were shown in patients with fibromyalgia,<sup>30</sup> suggesting that it may further represent the affective dimension of pain. However, cLBLP showed reduced rsFC only between the right amygdala and the bilateral ACC and PoCG, mainly located in the affective/emotional processing area. A study on the asymmetry of amygdala pain processing showed that during persistent pain in mice, the right amygdala played a dominant role in pain and emotion processing.<sup>31</sup> Furthermore, the ACC mediates information on emotional behavior and cognitive function and is the center of coordinating multiple signals and emotional pain processing. A study on the activation of inhibitory neural circuits by optogenetic stimulation of the ACC showed that inhibition of ACC output significantly reduced pain behavior in transgenic mice.<sup>32</sup>

## Associations Between rsFC Across All Altered Regions and Clinical Assessments in LBLP Patients

In patients with spine-related leg pain, according to the type of mechanism a sensory deficit of variable degrees can be present with different sensitivity to von Frey filaments, and the mechanical deficit can be associated with the neurological lesion that causes pain and not to altered central nervous system functionality.<sup>33</sup> But in the present study, we found that



patients with LBLP generally had decreased mechanical sensitivity, which was positively correlated with rsFC of left amygdala-right PCL and/or right amygdala-PoCG. It is consistent with a previous study of decreased tactile acuity (associated with gray matter volume of primary somatosensory cortex) in the low back pain.<sup>34</sup> A previous study found that the amygdala, a core region of the threat-processing neural circuit, could reduce susceptibility to perceptual disturbance and thereby protect the body from potential threats.<sup>35</sup> Therefore, the decreased rsFC between the amygdala and the right PCL and PoCG may be a compensatory or protective factor against the loss of protective sensation to cope with pain injuries in LBLP patients. At the same time, our study provides new evidence for amygdala connectivity link to individual mechanical pain sensitivity in patients with LBLP.

Moreover, PRI was used to evaluate the pain perception and pain emotion of LBLP patients. The lower rsFC coefficient of the right amygdala to the bilateral ACC was negatively correlated with PRI in LBLP patients, suggesting that decreased rsFC of the amygdala may be involved in more pain perception and emotional disorders. This finding may be an important implication for understanding the underlying pathophysiological mechanisms of pain-related affective disorders in LBLP patients.

## Limitations

This study included a relatively small sample size of acute and chronic LBLP patients. Therefore, our results should be interpreted cautiously. We did not investigate the rsFC of subregions of the amygdala, although previous studies have suggested that different subregions may have different roles in pain, which should be further analyzed in future studies.

## Conclusion

Taken together, our findings demonstrate that LBLP patients exhibited amygdala hypoconnectivity, and interestingly, the decreased rsFC was related to individual mechanical pain sensitivity. In acute LBLP patients, the decreased amygdala functional connections were mainly located in the pain perception cortex, while in the chronic LBLP patients, the decreased amygdala functional connections involved the emotional processing area.

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## Disclosure

The authors report no conflicts of interest in this work.

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