

Disrupted Resting-State Functional Connectivity and Effective Connectivity of the Nucleus Accumbens in Chronic Low Back Pain: A Cross-Sectional Study

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Purpose: Chronic low back pain (cLBP) is a recurring and intractable disease that is often accompanied by emotional and cognitive disorders such as depression and anxiety. The nucleus accumbens (NAc) plays an important role in mediating emotional and cognitive processes and analgesia. This study investigated the resting-state functional connectivity (rsFC) and effective connectivity (EC) of NAc and its subregions in cLBP.

Methods: Thirty-four cLBP patients and 34 age- and sex-matched healthy controls (HC) underwent resting-state functional magnetic resonance imaging (rs-fMRI). Seed-based rsFC and Dynamic Causal Modelling (DCM) were used to examine the alteration of the rsFC and EC of the NAc.

Results: Our results showed that the cLBP group had increased rsFC of the bilateral NAc-left superior frontal cortex (SFC), orbital frontal cortex (OFC), left angular gyrus, the left NAc-bilateral middle temporal gyrus, as well as decreased rsFC of left NAc-left supramarginal gyrus, right precentral gyrus, left cerebellum, brainstem (medulla oblongata), and right insula pathways compared with the HC; the results of the subregions were largely consistent with the whole NAc. In addition, the rsFC of the left NAc-left SFC was negatively correlated with Hamilton's Depression Scale (HAMD) scores ($r = -0.402$, $p = 0.018$), and the rsFC of left NAc-OFC was positively correlated with present pain intensity scores ($r = 0.406$, $p = 0.017$) in the cLBP group. DCM showed that the cLBP group showed significantly increased EC from the left cerebellum to the right NAc ($p = 0.012$) as compared with HC.

Conclusion: Overall, our findings demonstrate aberrant rsFC and EC between NAc and regions that are associated with emotional regulation and cognitive processing in individuals with cLBP, underscoring the pivotal roles of emotion and cognition in cLBP.

Keywords: low back pain, nucleus accumbens, resting-state functional connectivity, dynamic causal modelling

Introduction

Low back pain (LBP) is the leading cause of disability worldwide, and its prevalence has increased over the years.¹⁻⁵ Chronic LBP (cLBP) is characterized by continued pain or frequency of pain for a duration exceeding 3 months. Because of the lack of effective treatment, patients are often accompanied by emotional dysregulation such as depression, anxiety, and fear.^{3,6} Recent studies have showed that some conservative treatments are effective in reducing pain intensity, improving disability and pain sensitivity variables related to chronic pain, such as exercise therapy and orthopedic manual therapy.⁷⁻⁹ A previous study showed that biopsychosocial intervention therapeutic approach is effective for recovery from cLBP. Certain patients' expectations could be related to a better recovery outcomes,¹⁰ and positive verbal can activate the same brain areas as those related to pain relief and have favorable effects on osteoarthritis pain and LBP.^{11,12}

A previous study showed that cognitive and emotional factors strongly influence the connectivity of brain regions that modulate pain perception, emotional states, attention, and expectations.^{13,14} A growing body of research has suggested

that alterations in the brain play an important role in the maintenance and development of pain. Therefore, we studied the central regulatory mechanisms of cLBP, with the aim to identify new targets for effective treatment of cLBP.

The nucleus accumbens (NAc) is a key component of reward processing,¹⁵ and it mainly mediates the hedonic perception of rewards, which is related to reward evaluation and expectation.^{16–20} Previous studies have shown that reward-associated circuits around the NAc appear to promote the transition from acute to chronic pain.^{21,22} Furthermore, the altered volume and activity of the NAc may confer further risk of developing chronic pain.²⁰ Multiple studies have suggested that negative emotions and pain are closely related and cognitive-affective integration-related brain regions in patients with chronic pain are now recognized as key components of pain.^{23–25} Dopamine in the NAc is critical for pain relief and to regulate emotion perception.^{26,27} Recent research has shown that the NAc can be divided into two subregions, namely the core-like part and shell-like part, each with different function and connectivity patterns.^{16,28,29}

The FC of spatially distinct regions is one of the most widely used resting-state functional magnetic resonance imaging (rs-fMRI),³⁰ which has been widely used to explore the brain regulation mechanism of pain. Dynamic causal modelling (DCM) has been widely used to infer the effective connectivity (EC) of distinct regions, as it can indicate the specific intensity and reflect the direction of information communication between brain regions.^{31,32}

Studies on the subregions of the NAc in cLBP are relatively limited, and their findings lack consistency. Furthermore, most previous studies have relied on resting-state functional connectivity (rsFC), which fails to provide directional information regarding interregional communication within the brain. Thus, in this study, we combined the methods of seed-based rsFC and DCM with the aim to investigate the rsFC and EC of the NAc and its subregions in cLBP and clarify the regulatory mechanisms of the NAc in cLBP.

Materials and Methods

Participants

GPower software (version 3.1) was used to estimate the sample size. In response to the power analysis ($\alpha = 0.05$, $\beta = 0.1$, effect size = 0.8),³³ the calculated sample size was found to be 34 patients and 34 HC. A total of 34 cLBP patients (29 female and 5 male; mean age (\pm SD): 40.1 \pm 9.6 years) and 34 age- and sex-matched healthy controls (HC) (29 female and 5 male; mean age: 38.2 \pm 12.8 years) were recruited in this study. The participants were mainly recruited from the Department of Orthopedics of the Second Affiliated Hospital of Xi'an Jiaotong University and the community. This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (number: 2023512). All participants provided written informed consent prior to the MRI scan. All participants were equipped with disposable silent earplugs before the examination to reduce noise, and they were instructed to remain relaxed and awake during the examination. The inclusion criteria were as follows: (1) age between 18 and 60 years; (2) right handedness; (3) LBP duration of at least one year; (4) pain intensity of at least 4 on the 0–10 visual analog scale (VAS). The exclusion criteria were as follows: (1) specific causes of back pain (eg, cancer, fractures, infections); (2) history of nervous system, cardiac, or respiratory disease (eg, stroke, asthma, diabetes); (3) history of psychotic and/or mood disorders (eg, depression, schizophrenia); (4) presence of any contraindications to MRI scanning (eg, claustrophobia, cardiac pacemaker, or metal implants).

Questionnaire

All participants completed the following scales: Edinburgh Handedness Inventory, which was used to judge handedness; Montreal Cognitive Assessment (MoCA) to assess cognitive states; and the 17-item Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA), which were used to assess depressive and anxious states. Furthermore, all cLBP patients completed the Short-Form McGill Pain Questionnaire, including Visual Analog Scale (VAS) and present pain intensity scores, which were used to evaluate the pain intensity of the subjects.³⁴

Image Acquisition

All subjects underwent functional scanning on a 3.0-T MR scanner (GE Architect) using a 48-channel head coil. T1-weighted images were obtained for each participant by using a 3-dimensional MP-RAGE sequence with the following

parameters: repetition time (TR) = 900 ms, echo time (TE)=3.1 ms, field of view (FOV) = 256 mm, slice thickness = 1.0 mm (no gaps), flip angle = 8, and slices = 150. The rs-fMRI used the following parameters: TR = 2000 ms, TE = 35 ms, matrix = 80 × 80, FOV = 240 mm, flip angle = 90, slice thickness = 3 mm, number of slices = 49, and 198 volumes per participant.

fMRI Data Analysis

Image Preprocessing

The CONN toolbox version 22a (<http://www.nitrc.org/project/conn/>) in MATLAB (MathWorks, Inc., Natick, MA, USA) was used to perform the fMRI data preprocessing. The first four volumes of the fMRI data were discarded. The FC data of functional connectivity were all preprocessed using a default preprocessing pipeline for volume-based analyses (direct normalization to MNI-space) in the CONN toolbox. The specific steps including functional Slice-Timing correction (correction for inter-slice differences in acquisition time), functional Realignment & unwarp (subject motion estimation and correction), functional Outlier detection (ART-based identification of outlier scans for scrubbing), functional Direct Segmentation & Normalization (simultaneous Grey/White/Cerebrospinal Fluid (CSF) segmentation and MNI normalization), structural Segmentation & Normalization (simultaneous Grey/White/CSF segmentation and MNI normalization) and functional smoothing (spatial convolution with Gaussian kernel; full-width-at-half maximum [FWHM] = 6 mm). The DCM data were preprocessed using the above steps without smoothing.

rsFC Analysis of the NAc

A “seed-to-voxel” rsFC analysis was performed using the CONN toolbox. The left and right NAc as the seed regions were defined using the Harvard–Oxford subcortical atlas, and the subregions as the seed regions were obtained from the website (<http://atlas.brainnetome.org/download.html>) and combined literature.³⁵ The first-level FC analysis yielded Fisher’s *r*-to-*z* transformed bivariate correlations between the NAc and other voxels of the brain. Then, second-level analyses were performed to determine group-based differences in rsFC of the NAc and the whole brain. Age, sex, and HAMD score were included as covariates. The results were considered significant at a threshold of cluster-level $p < 0.05$. Family Wise Error (FWE) was corrected for between-group comparisons.

EC of the NAc

Spectral DCM analyses were conducted using DCM 12 implemented in SPM12 software (Wellcome Department of Imaging Neuroscience, London, UK; <https://www.fil.ion.ucl.ac.uk/spm/>). The region of interest (ROI) used in DCM analysis was obtained from the rsFC analyses and combined physiological functions of brain regions. Four ROIs were selected, namely the left SFC ($x = -12, y = 56, z = 34$, radius = 5 mm); left NAc ($x = -10, y = 14, z = -6$, radius = 3 mm); right NAc ($x = 8, y = 14, z = -6$, radius = 3 mm); and left cerebellum (Cer, $x = -12, y = -38, z = -32$, radius = 5 mm). Then, the time series of these four ROIs were extracted. Five models were established, including a fully connected model, a model that did not consider the interactions of the bilateral NAc, a model that did not consider the interactions of the left SFC and right NAc, a model that excluded the left cerebellum, and a model that excluded the SFC. Fixed effects (FFX) Bayesian model selection (BMS)³² was used to determine the best model for each subject. Bayesian model averaging (BMA)³⁶ was conducted to analyze the connectivity parameters at the group level to identify the best model.

Statistical Analyses

Statistical analysis was performed using SPSS statistics version 18.0 (IBM Corporation, Armonk, NY, USA). The age, MoCA scores, HAMD, and HAMA scores between the two groups were compared by two-sample *t*-tests. Sex differences were characterized by the chi-square test, and one-sample *t*-test and independent two-samples *t*-test were performed for effective connectivity parameters. Significance was set at $p < 0.05$.

Pearson’s correlation analysis was performed to assess the associations between network parameters and clinical features in the cLBP group. $P < 0.05$ (FDR corrected) was considered to indicate statistically significant differences.

Results

Demographic and Clinical Data

The demographic data of all participants are presented in Table 1. No significant differences were observed in age ($p = 0.49$), sex ($p = 1$), MoCA scores ($p = 0.31$) and HAMA scores ($p = 0.12$) between the two groups, the HAMD scores ($p = 0.049$) have significant differences between the two groups. The mean of HAMD and HAMA scores in the cLBP patients were higher than in the HC group (4.76 ± 6.55 and 3.65 ± 7.63 , respectively), indicating low depressive and anxiety symptoms in these patients. The VAS scores, present pain intensity scores and pain duration of the cLBP patients are also detailed in Table 1.

rsFC Results

Compared with HC, patients with cLBP showed increased rsFC of the left NAc-left SFC ($p < 0.001$, PWE corrected); left NAc-left middle temporal gyrus ($p = 0.002$, PWE corrected); left NAc-left angular gyrus ($p = 0.005$, PWE corrected); left NAc-right middle temporal gyrus ($p = 0.043$, PWE corrected); left NAc-OFC ($p = 0.011$, PWE corrected); right NAc-left SFC ($p < 0.001$, PWE corrected); right NAc-OFC ($p = 0.028$, PWE corrected); and right NAc-left angular gyrus ($p = 0.03$, PWE corrected). Patients with cLBP showed decreased rsFC of the left NAc-left supramarginal gyrus ($p < 0.001$, PWE corrected); left NAc-right precentral gyrus ($p = 0.001$, PWE corrected); left NAc-left cerebellum ($p = 0.007$, PWE corrected); left NAc-brainstem ($p = 0.01$, PWE corrected); and left NAc-right insula ($p = 0.008$, PWE corrected) (Table 2, Figures 1 and 2).

Table 1 Demographic and Clinical Data of Patients

Item	Control (n = 34)	cLBP (n = 34)	P
Age (years)	38.2 ± 12.8	40.1 ± 9.6	0.49
Sex (male/female)	5/29	5/29	1 ^a
VAS scores	NA	6.7 ± 1.2	NA
Present pain intensity scores	NA	1.9 ± 1.6	NA
Pain duration (years)	NA	8.3 ± 7.1	NA
MoCA scores	27.1 ± 1.5	26.7 ± 1.8	0.31
HAMD scores	2.26 ± 3.16	4.76 ± 6.55	0.049
HAMA scores	1.44 ± 2.72	3.65 ± 7.63	0.12

Note: ^aChi-squared test.

Abbreviations: cLBP, chronic low back pain; VAS, Visual Analog Scale; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton's Depression Scale; HAMA, Hamilton Anxiety Scale; NA, not applicable.

Table 2 Resting-State Functional Connectivity of the Nucleus Accumbens

Comparison	Seed	Region	MNI Coordinates			Cluster Size	Z Value
			X	Y	Z		
Control>cLBP	L_NAc	L_SMG	-64	-34	26	1505	4.54
		R_Pre	8	-12	46	918	3.82
		L_cerebellum	-12	-38	-32	136	3.88*
		Brainstem	6	-34	-48	60	3.56*
		R_Ins	32	16	6	86	3.64*
Control<cLBP	L_NAc	L_SFC	-12	26	56	1445	4.19
		L_MTG	-64	-14	-10	1091	4.08
		L_AnG	-44	-56	28	858	3.87
		R_MTG	64	-8	-26	798	3.67
		OFC	4	50	-20	682	4.24

(Continued)

Table 2 (Continued).

Comparison	Seed	Region	MNI Coordinates			Cluster Size	Z Value
			X	Y	Z		
	R_NAc	L_SFC	-12	56	34	1203	4.1
		OFC	0	44	-14	648	4.01
		L_AnG	-56	-68	24	542	3.84

Note: *Small volume corrected.

Abbreviations: cLBP, chronic low back pain; MNI, Montreal Neurologic Institute; NAc, nucleus accumbens; SMG, supramarginal gyrus; Pre, precentral gyrus; Ins, insula; SFC, superior frontal cortex; MTG, middle temporal gyrus; AnG, angular gyrus; OFC, orbital frontal cortex; L, left; R, right.

Compared with HC, patients with cLBP showed increased rsFC of left core-left middle temporal gyrus ($p = 0.001$, PWE corrected); left core-left temporal pole ($p = 0.037$, PWE corrected); left core-left angular gyrus ($p = 0.002$, PWE corrected); left core-right middle temporal gyrus ($p = 0.005$, PWE corrected); left core-left SFC ($p = 0.021$, PWE corrected); left core-right thalamus proper ($p = 0.017$, PWE corrected); left shell-OFC ($p = 0.008$, PWE corrected); left shell-left SFC ($p = 0.013$, PWE corrected); right shell-left angular gyrus ($p = 0.002$, PWE corrected); and right shell-left SFC ($p = 0.003$, PWE

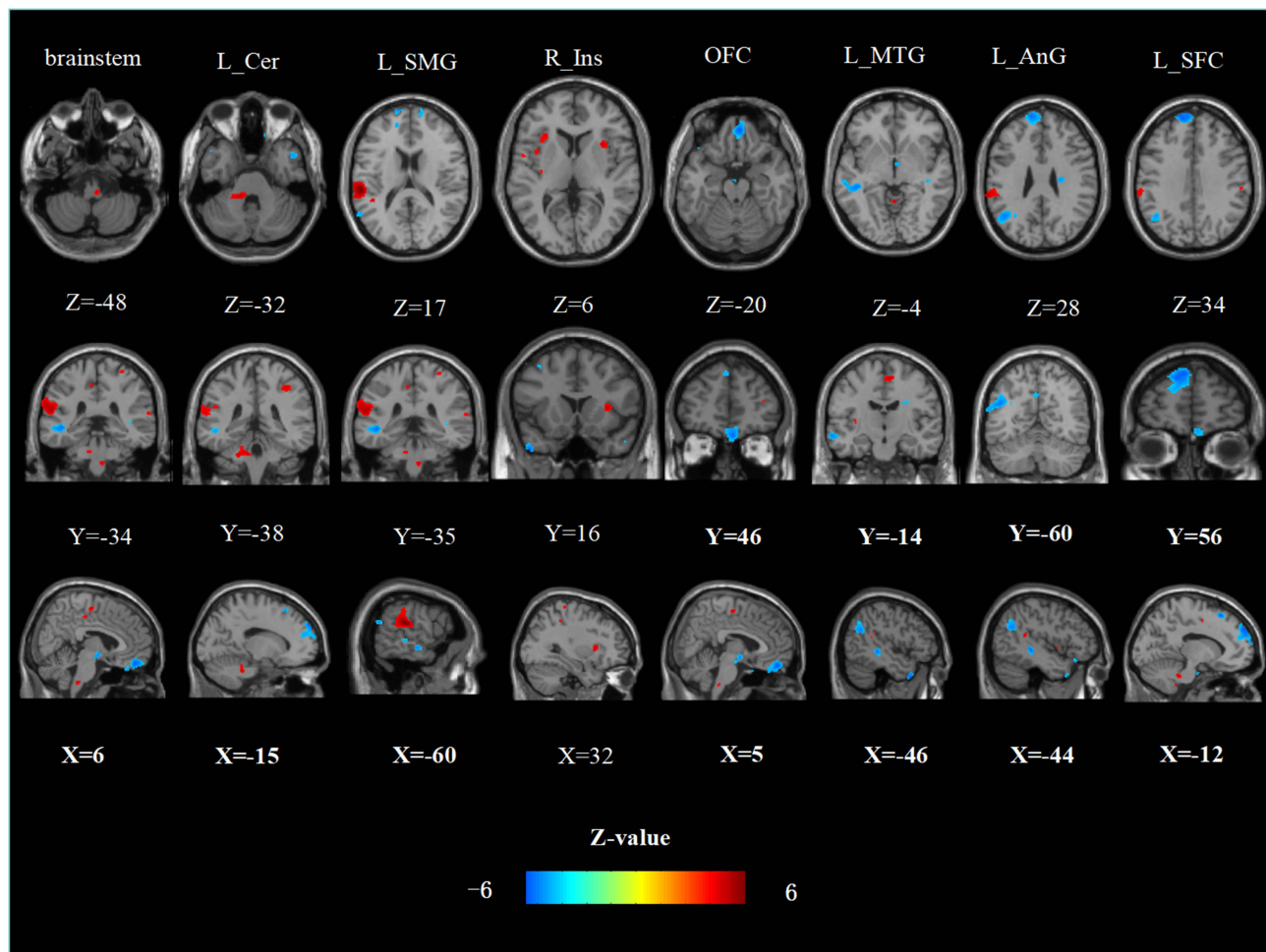


Figure 1 Group-differences of the resting-state functional connectivity of the left NAc. Higher (blue) and lower (red) resting-state functional connectivity was found in the patients with cLBP compared to the HC.

Abbreviations: cLBP, chronic low back pain; HC, healthy controls; NAc, nucleus accumbens; Cer, cerebellum; SMG, supramarginal gyrus; Ins, insula; OFC, orbital frontal cortex; MTG, middle temporal gyrus; AnG, angular gyrus; SFC, superior frontal cortex; L, left; R, right.

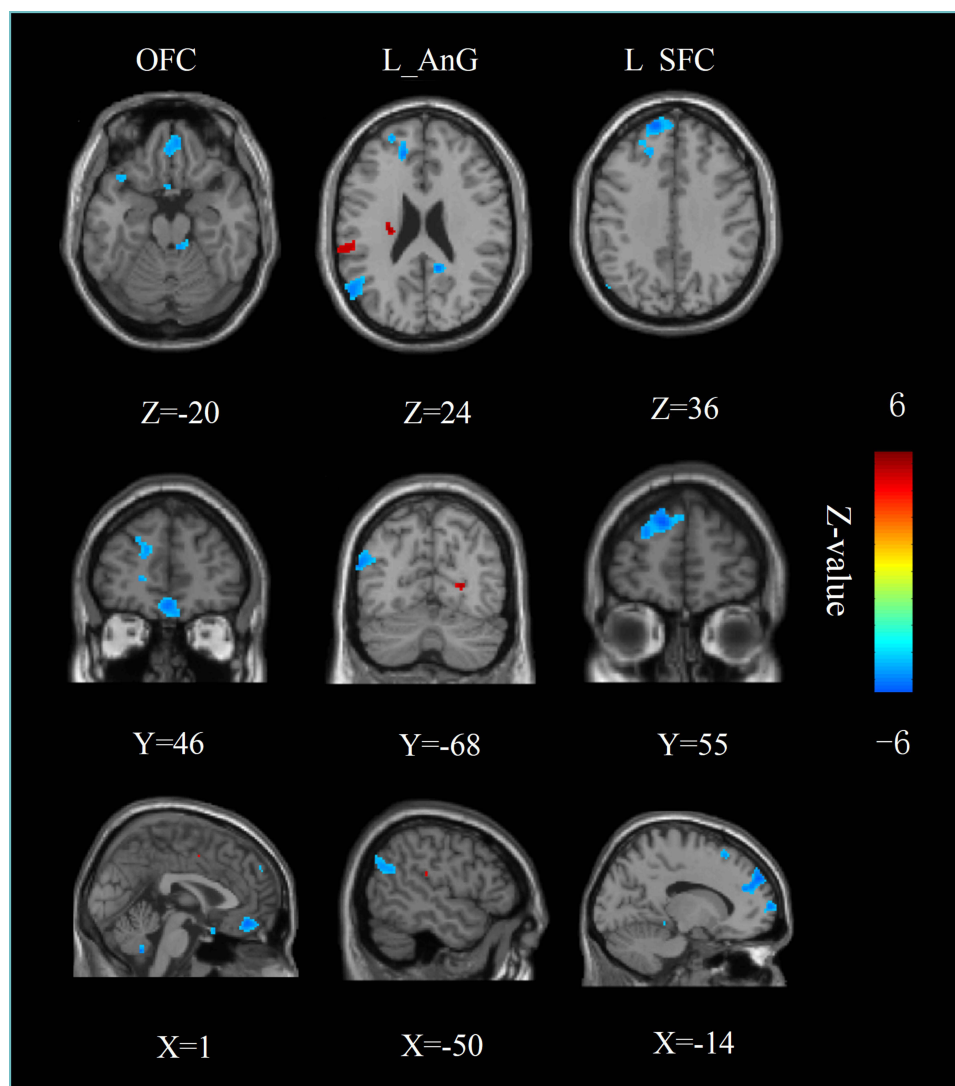


Figure 2 Group-differences of the resting-state functional connectivity of the right NAc. Higher (blue) and lower (red) resting-state functional connectivity was found in the patients with cLBP compared to the HC.

Abbreviations: cLBP, chronic low back pain; HC, healthy controls; NAc, nucleus accumbens; OFC, orbital frontal cortex; AnG, angular gyrus; SFC, superior frontal cortex; L, left.

corrected). Patients with cLBP showed decreased rsFC of left shell-left supramarginal gyrus ($p < 0.001$, PWE corrected); shell-left cerebellum ($p = 0.007$, PWE corrected); left shell-right supramarginal gyrus ($p = 0.04$, PWE corrected); left shell-left SFC ($p < 0.001$, PWE corrected); and left shell-right posterior insula ($p = 0.007$, PWE corrected) (Table 3, Figures S1 and S2).

Results from DCM Analysis

The five models used in DCM are shown in Figure 3. The results from BMS revealed that the fully connected model was the best model in both the cLBP and HC groups, and it was the best model for 28 of 34 subjects in the HC group and for 31 of 34 patients in the cLBP group. For HC, models 2–4 were the best models for four, one, and one subjects, respectively. For patients with cLBP, models 2 and 4 were the best models for two and one subjects, respectively. The EC values in the cLBP and HC groups are shown in Table 4. Patients showed significantly increased EC from the left cerebellum to the right NAc ($p = 0.012$) compared with HC (Figure 4).

Table 3 Resting-State Functional Connectivity of the Nucleus Accumbens Subregions

Comparison	Seed	Region	MNI Coordinates			Cluster Size	Z Value
			X	Y	Z		
Control>cLBP	L_shell	L_SMG	-58	-26	18	1709	5.07
		L_cerebellum	-16	-40	-22	130	3.8*
		R_SMG	58	-26	40	498	3.9
		R_SFC	18	-10	72	2257	4.27
		R_Pins	40	-10	10	94	3.99*
Control<cLBP	L_core	L_MTG	-66	-28	-20	1021	4.23
		L_TMP	-48	14	-38	514	5.52
		L_AnG	-46	-62	26	858	3.62
		R_MTG	58	-2	-30	763	4.45
		L_SFC	-8	54	36	579	3.54
		R_thalamus Proper	6	-4	-4	47	3.65*
	L_shell	OFC	6	50	-20	688	3.84
		L_SFC	-12	60	30	628	4.43
	R_shell	L_AnG	-52	-68	28	864	4.32
		L_SFC	-10	58	32	844	4.08

Note: *Small volume corrected.

Abbreviations: cLBP, chronic low back pain; MNI, Montreal Neurologic Institute; SMG, supramarginal gyrus; SFC, superior frontal cortex; Pins, posterior insula; MTG, middle temporal gyrus; TMP, temporal pole; AnG, angular gyrus; OFC, orbital frontal cortex; L, left; R, right.

Correlation Analysis

The rsFC of left NAc-left SFC was negatively correlated with HAMD scores ($r = -0.402$, $p = 0.018$) in patients with cLBP. The rsFC of left NAc-OFC was positively correlated with the present pain intensity scores ($r = 0.406$, $p = 0.017$) in patients with cLBP (Figure 5). There were no significant correlations between the EC of NAc and pain characteristics, depression, or anxiety scores.

Discussion

In this study, we combined rs-fMRI and DCM studies to investigate the functional alterations in the NAc and its subregions in cLBP. We found that the rsFC of bilateral NAc and its subregions with SFC, OFC, left angular gyrus, bilateral middle temporal gyrus, right thalamus showed an increase in cLBP, while that of the bilateral NAc and its subregions with bilateral supramarginal gyrus, right insula, right SFC, right precentral gyrus, brainstem, left cerebellum were decreased in cLBP; the left NAc-left SFC pathway was negatively correlated with HAMD scores, while the left NAc-OFC pathway was positively correlated with present pain intensity scores. In addition, patients showed significantly increased EC from the left cerebellum to the right NAc compared with HC.

The NAc is one of the most commonly activated brain regions in response to pain³⁷ and receives both direct input from excitatory glutamatergic projections and indirect input from dopaminergic projections.^{18,26,38–41} Dopamine holds a central position in reward circuitry.⁴² A study showed that the baseline dopamine metabolism is reduced in cLBP patients;⁴³ it can also integrate cognitive and affective information processed by frontal and temporal areas,⁴⁴ as well as can produce m-opioids via activating the descending pain inhibitory system to alleviate pain.⁴⁵ The changes in NAc-cortical connectivity are regarded as one of the known risk factors for the transition from acute to chronic pain.⁴⁶ Studies have suggested that the shell and core play prominent roles in reward and aversion processing, respectively.^{28,35} Pain relief is associated with increased dopamine levels in the NAc shell.¹⁷

We found that the rsFC was increased in the pathway of NAc-SFC/OFC, a finding that is consistent with previous studies, who found that the connection between the PFC and the NAc increases in patients who experience the cLBP.^{47,48} In addition, the rsFC of the left NAc-SFC pathway was negatively correlated with HAMD scores, while the rsFC of left NAc-OFC was

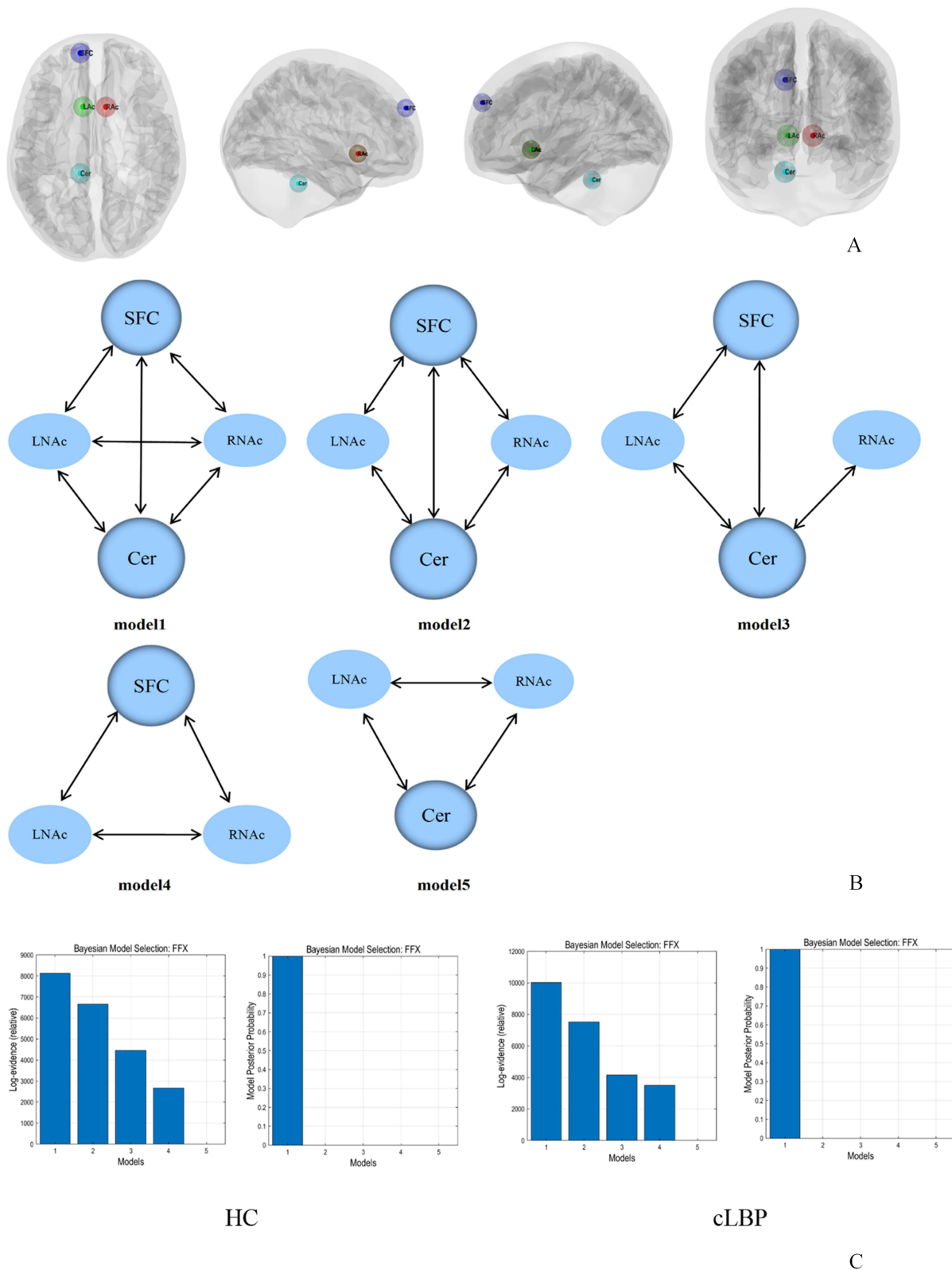


Figure 3 Effective connectivity of the NAc. **(A)** Locations of brain regions used in the dynamic causal modelling. **(B)** Five models used in the DCM analysis. **(C)** Results from Bayesian model selection; the single-group level t-test showed that the fully connected model was the best model for the two groups.

Abbreviations: HC, healthy controls; cLBP, chronic low back pain; SFC, superior frontal cortex; NAc, nucleus accumbens; Cer, cerebellum; FFX, fixed effects; L, left; R, right.

Table 4 The Effective Connectivity of the Nucleus Accumbens

Group	Item	From SFC	From LNAc	From RNAc	From LCer
HC	To SFC	0	-0.044	-0.053	-0.043
	To LNAc	-0.069	0	0.164*	-0.191*
	To RNAc	-0.178*	-0.121	0	-0.22**
	To LCer	0.07*	0.085	0.134*	0
cLBP	To SFC	0	-0.018	0.015	-0.177*
	To LNAc	-0.04	0	0.074	-0.305*
	To RNAc	-0.029	-0.004	0	-0.431** ^Δ
	To LCer	0.054	0.047	0.093*	0

Notes: There are source regions in rows and target regions in columns. *Significant differences within group ($p < 0.05$); **significant differences within group ($p < 0.001$); ^ΔSignificant differences between groups ($p < 0.05$).

Abbreviations: HC, healthy controls; cLBP, chronic low back pain; SFC, superior frontal cortex; NAc, nucleus accumbens; Cer, cerebellum; L, left; R, right.

positively correlated with present pain intensity scores in the cLBP group. The PFC and NAc are important compositions of the corticolimbic system,^{14,17,25,46,49} which plays a crucial role in the development, amplification, and prediction of chronic pain and its emotional-affective dimension.^{20,25,46} A study showed that the corticolimbic system plays a crucial role in the chronic transformation of pain in patients with primary dysmenorrhea.⁵⁰ The PFC affects several structures involved in pain perception, motivational drive, substance seeking, and anxiodepressive states.^{17,40} The PFC-NAc pathway is an important node in the reward circuitry and plays an important role in regulating affective and motivational components of pain.⁵¹ A longitudinal study found that the increased FC of PFC-NAc pathway can predict pain persistence.⁴⁷ Another study reported that the OFC is of vital importance for the adaptive regulation of emotional states and pain,^{38,52} as it mediates pain inhibition.⁵³

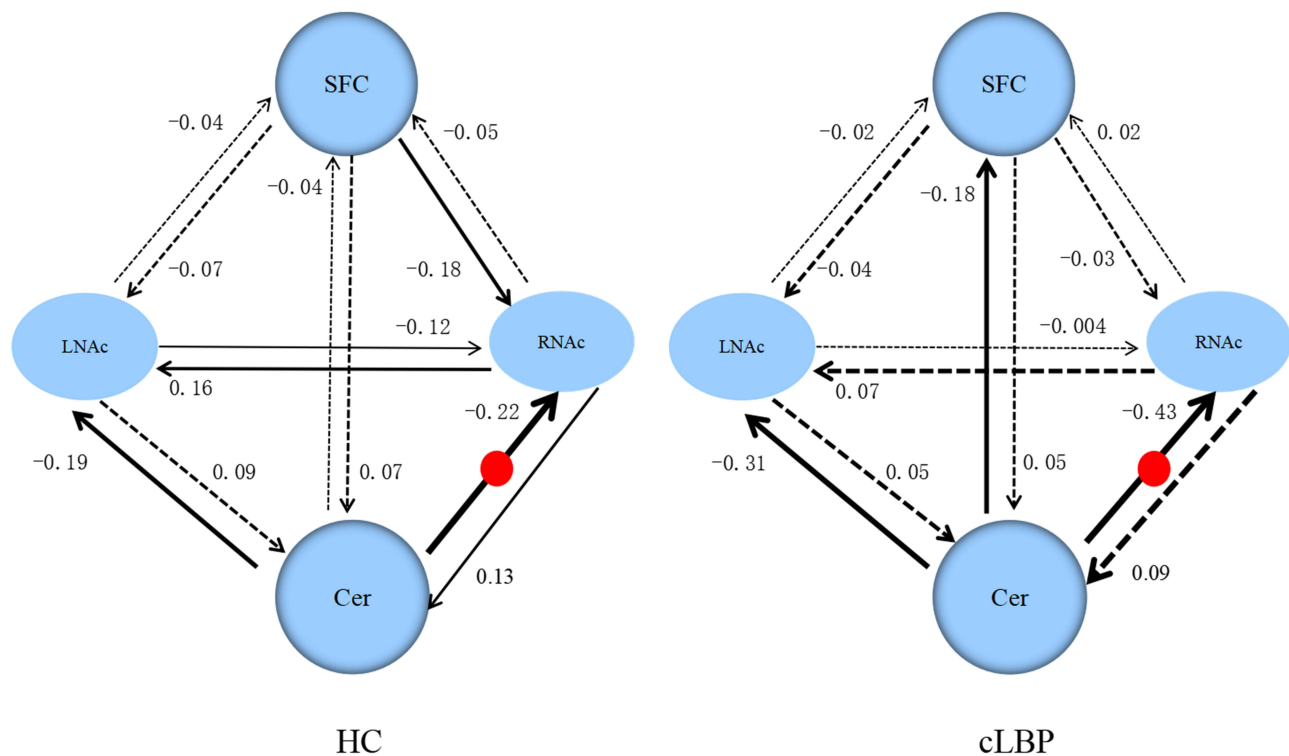


Figure 4 The winning model and the connectivity parameters for the two groups. The solid lines represent connectivity values greater than 0.1 Hz, the dotted lines represent the connectivity values below 0.1 Hz, and their thickness reflects the size of the value. The red round represents the significant group differences between cLBP and HC.

Abbreviations: HC, healthy controls; cLBP, chronic low back pain; SFC, superior frontal cortex; NAc, nucleus accumbens; Cer, cerebellum; L, left; R, right.

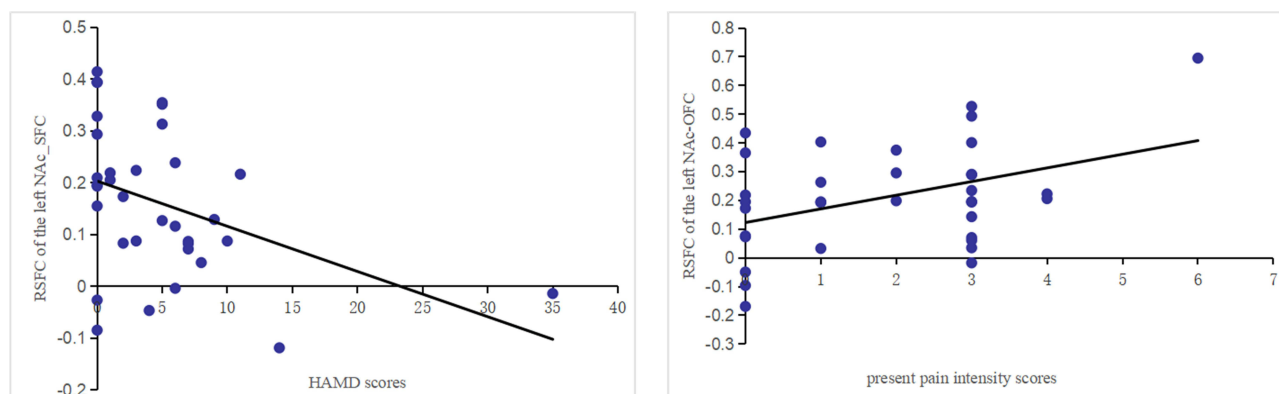


Figure 5 Results of the correlation analysis. There was a significant negative correlation between the rsFC values of the left NAc-SFC and HAMD scores ($r = -0.402$, $p = 0.018$), a significant positively correlation between the rsFC values of the left NAc-OFC and the present pain intensity scores ($r = 0.406$, $p = 0.017$) in patients group.

Abbreviations: NAc, nucleus accumbens; SFC, superior frontal cortex; OFC, orbital frontal cortex; HAMD, Hamilton's Depression Scale.

Therefore, we hypothesized that the abnormalities in the FC of PFC-NAC pathway may be one of the most critical reasons for the persistence of pain and negative emotions in cLBP.

We also found that rsFC of the left NAc-right brainstem (medulla oblongata), left cerebellum pathway decreased in the cLBP group, and the EC increased from the left cerebellum to the right NAc. The brainstem is the origin of the descending pain inhibitory system,⁵⁴ and it is a critical area for nociception and pain processing that also plays an important role in relaying and coordinating signaling between the cerebrum, cerebellum, and spinal cord.^{39,55} The cerebellum is crucially implicated involved in the modulation of sensorimotor responses and higher level cognitive and affective function.^{31,56,57} The neocortex-cerebellum and basal ganglia-cerebellum circuit are important in reward-related cognitive and emotion processing.^{58–60} A study found a positive relationship between the local pontine network activity and the intensity of cLBP,⁶¹ wherein compared with HC, patients with cLBP showed significantly decreased rsFC between the habenula and pons compared with HC.³² Another study reported significantly altered EC in the cerebellum-neocortex and cerebellum-basal ganglia circuits in patients with major depressive disorder,³¹ and decreased rsFC between bilateral cerebellar and cortical brain regions in patients with cLBP after motor control exercise.⁶² Both the brainstem and the cerebellum have important roles in the regulation of pain and emotion; therefore, the abnormalities of the rsFC and EC between them and NAC may be an important reason for the persistence of pain and negative emotions in cLBP.

The thalamus relays nociceptive information to the insula, PFC, and cerebellum to process sensory-discriminative properties and affective components of the pain sensation and the formation of pain memory.^{37,63} The role of the thalamus in pain has been extensively studied, and numerous studies have confirmed the abnormality in thalamic structure and function with cLBP.^{2,64,65} Previous studies have shown that compared to the control group, patients with diabetic peripheral neuropathy who had pain for >2 years showed decreased rsFC between the primary somatosensory cortex, ventral posterior lateral thalamic nucleus, and medial dorsal thalamic nucleus compared to the control group.⁶⁶ The insula integrates sensory with emotional and cognitive processes and is involved in aversive motivational salience,⁶⁷ that plays critical roles in pain perception and chronic pain.^{68–72} Another previous study showed that the PAG-bilateral posterior insular rsFC is reduced in patients with chronic neck and shoulder pain.⁷³

The angular gyrus is a major posterior component of the default-mode networks (DMNs), which may participate in regulation of memory and emotion.⁷⁴ The temporal lobe has an important influence on higher neural activities such as memory and emotion.⁷⁵ Therefore, we hypothesized that the abnormalities in the rsFC of NAC-angular gyrus and middle temporal gyrus pathway may likely mainly contribute to the dysfunction of emotions in cLBP.

Clinical Implications

Our study highlights the important role of NAC in cLBP, which has contributed to understanding the brain's regulatory role in cLBP and provided a theoretical basis for understanding the relationship between emotions and chronic pain. Our

study is important for understanding the underlying mechanisms that positive emotions improve symptoms in patients with cLBP and provide a theoretical basis for identifying effective treatments.

Limitations

Our study has some limitations. First, the sample size is relatively small; thus, we plan to include a larger sample of patients and controls in future studies, as this study is still ongoing. Second, this study used a cross-sectional design, and the causal relationship between brain changes and cLBP is still unclear. A longitudinal study is necessary to understand the causal relationships of NAc alterations and the pathogenesis underlying cLBP. Third, the scales describing the cognitive states are not sufficient. In future studies, more cognitive and emotional scales will be included.

Conclusion

Our results show that the altered rsFC and EC of the NAc were mainly located at regions that were related to both pain and emotion processing, which suggests that the reward system is involved in the regulation of cLBP. Our results suggest that NAc plays an important role in relieving pain and improving the prognosis of patients with cLBP. The NAc may be an important target for pain relief and to improve the emotional discomfort caused by pain.

Data Sharing Statement

The data of the 68 participants are in-house dataset and are available from the corresponding author upon reasonable request.

Ethics Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Disclosure

The authors declare no conflicts of interest in this work.

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