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ORIGINAL RESEARCH

Investigating Brain Structure and Functional Alterations in the Transition from Acute to Chronic Neck Pain: A Resting-State fMRI Study

Zhen Gao[1,*], Meng-Jie Cui[2,*], Hai-Jun Wang[2], Jing Zhang[3], Cheng Xu[4], Lai-Xi Ji[2]

[1]Experimental Management Center, Shanxi University of Traditional Chinese Medicine, Taiyuan, Shanxi, 030024, People's Republic of China; [2]Second Clinical Medical College, Shanxi University of Traditional Chinese Medicine, Taiyuan, Shanxi, 030024, People's Republic of China; [3]Acupuncture and Moxibustion Department II, Affiliated Hospital of Shanxi University of Traditional Chinese Medicine, Taiyuan, Shanxi, 030024, People's Republic of China; [4]Radiology Department, Shanxi Provincial People's Hospital, Taiyuan, Shanxi, 030012, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lai-Xi Ji, Second Clinical Medical College, Shanxi University of Traditional Chinese Medicine, Jinci Road Section 1, No. 89, Taiyuan, Shanxi, 030024, People's Republic of China, Email jlx@sxtcm.edu.cn

Purpose: The objective of this research is to delve into the central pathological mechanisms involved in the transformation from acute to chronic pain.

Patients and Methods: This study enrolled 86 individuals with acute neck pain and 89 with chronic neck pain. Utilizing a 3.0T MR scanner, we obtained three-dimensional T1-weighted imaging (3D-T1WI) images and analyzed structural differences between the two groups with Freesurfer software to evaluate alterations in cortical thickness. Additionally, Blood Oxygen Level-Dependent functional Magnetic Resonance Imaging (BOLD-fMRI) images were acquired to assess intergroup differences in low-frequency amplitude using DPARSF software.

Results: Chronic neck pain patients exhibited increased cortical thickness in the left rostral middle frontal, left isthmus cingulate, left superior frontal, and right precuneus regions compared to those with acute neck pain. Low-frequency amplitude measures revealed decreased activity in the left dorsolateral superior frontal gyrus and left postcentral gyrus, among other areas, and increased activity in the right middle frontal gyrus and the opercular part of the right inferior frontal gyrus.

Conclusion: Our findings indicate that dysfunction and structural changes in the limbic system and prefrontal cortex may play a pivotal role in the progression from acute to chronic neck pain. These insights provide a significant new direction for understanding the central mechanisms underlying pain chronicity.

Keywords: functional magnetic resonance imaging, amplitude of low frequency fluctuation, cortical thickness, neck pain, acute pain, chronic pain

Introduction

Addressing the challenge of pain management involves preventing the progression from acute to chronic pain. While acute pain typically resolves as the body heals from injury or trauma, it can persist and become chronic for many individuals. Neck pain stands out as a prevalent musculoskeletal issue, posing significant medical and societal concerns due to its high prevalence,[1] economic implications,[2] and the profound effect on daily living.[3] As modern habits evolve, with more time spent at desks, poor sitting postures, and increased use of electronic devices, the incidence of neck pain is escalating. Despite the initial relief of acute symptoms, almost half of individuals continue to suffer from lingering pain or recurrent episodes.[4] Investigating the chronicity of neck pain in patients is crucial for informing public health strategies and enhancing medical resource distribution.

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The mechanisms behind the progression of chronic pain remain largely unknown. The brain is instrumental in the chronicification process, with disrupted neural activity and altered plasticity contributing to enhanced pain perception, mood disorders, and cognitive abnormalities, leading to prolonged and intensified pain. The development of functional magnetic resonance imaging (MRI) has offered a contemporary, non-invasive method for visualizing the brain, widely employed in pain studies. The simplicity and dependability of the Amplitude of Low-Frequency Fluctuations (ALFF) analysis make it a valuable tool for characterizing disease features.[5] For example, research by Pan et al identified unusual brain activity in acute eye pain patients' anterior and posterior cingulate gyrus and limbic system using ALFF analysis,[6] while Hang et al linked acute low back pain to reduced ALFF in specific brain regions.[7] High-resolution structural MRI, with its non-invasive and radiation-free benefits, is used to detect minute brain morphological changes, aiming to uncover disease pathology from a neuroanatomical view. Cortical thickness (CT), a standard measure in structural MRI,[8] is effective in detecting early cortical alterations and is utilized to investigate disease-related cortical morphological patterns. Research indicates that neck pain patients exhibit abnormal cortical thickness in various brain areas,[9,10] potentially leading to functional disturbances and offering insights into the anatomical underpinnings of pain pathology.

Despite advancements in human brain imaging that have revealed connections between chronic pain and modifications in brain architecture and activity, the initial transformations that foreshadow the conversion from acute to chronic pain remain largely undetermined. Consequently, this investigation has enrolled both acute and chronic neck pain patients to undergo functional and structural magnetic resonance imaging scans. The objective is to discern variations in brain activity and anatomical features, with a particular emphasis on delineating the patterns of Amplitude of Low-Frequency Fluctuations (ALFF) and cortical thickness that may forecast the progression to chronic pain. This innovative strategy provides a fresh lens and an advanced tool for deciphering the pathological processes that underpin the progression from acute to chronic pain.

Materials and Methods

Participants

The study was approved by the Institutional Review Board of Shanxi Acupuncture Hospital (approved number: 2023–007). The data used in this study is from unpublished research which provided the foundational knowledge and rationale that guided the design and execution of the clinical trial (ITMCTR2023000001). No data used in the study is included in the clinical trial. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki before study enrolment.

Patients with neck pain were recruited at the campus of Shanxi University of Chinese Medicine and the Shanxi Provincial Hospital of Acupuncture and Moxibustion from March 2023 to May 2024. We included patients with NP, whose criteria were based on the guidelines developed by the Orthopedic Section of the American Physical Therapy Association.[11] Participants who meet all of the following criteria were included: 1) patients with NP as the main complaint and a visual analog scale (VAS) score of pain severity exceeding 3 points (range 0–10 points), 2) aged 18–60 years and right-handed, 3) agreeing to sign informed consent. Among them, patients with acute neck pain had a disease duration of less than 1 month, while those with chronic neck pain had a disease duration of more than 3 months.

Participants who meet any of the following criteria were excluded: 1) pregnant or lactating women, 2) had severe primary illness and psychiatric or neurological disorders, 3) had contraindications to MRI, such as pacemakers or claustrophobia, and 4) were participating in other clinical trials.

MRI Data Acquisition

Patients underwent resting state fMRI (RS-fMRI) using a 3.0T MR scanner (Siemens 3T Tim trio, Erlangen, Germany) at Shanxi Provincial People's Hospital. The scans were performed following these procedures: localizer, and three-dimensional T1-weighted imaging (3D-T1WI) and blood oxygenation level-dependent fMRI. The 3D-T1WI scanning parameters were as follows: repetition time (TR) = 1900 ms, echo time (TE) =

2.26 ms, data matrix = 128 × 128, field of view (FOV) = 256×256 mm^2. For the BOLD-fMRI, the scanning parameters were: 31 contiguous slices with a slice thickness of 5 mm, TR = 2000 ms, TE = 30 ms, FOV = 240×240 mm^2, Matrix = 128 × 128, flip angle = 90°, and total volumes = 240.

Data Preprocessing

Cortical Thickness

The raw DICOM files were converted to NIFTI files using the MRIcron software. Preprocessing was performed on each subject using Freesurfer 6.0 (http://surfer.nmr.mgh.harvard.edu) software: initially, the raw MRI data were imported into FreeSurfer, followed by motion correction to eliminate the impact of head movement during scanning, then the removal of non-brain tissues such as the skull, and bias field correction to improve image quality; subsequently, individual brain images were registered to a standard space, and gray and white matter segmentation, as well as cortical reconstruction and subcortical structure segmentation, were carried out; finally, preliminary and refined reconstructions were completed using the recon-all command. Based on the Desikan Killiany atlas template, the cerebral cortex was segmented into 34 regions each for the left and right hemispheres, and the cortical thickness metrics for each region were calculated for each subject.

Amplitude of Low-Frequency Fluctuation

Preprocessing of the ALFF data was conducted using the DPARSF software (http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB 2022b, including format conversion, slice timing correction, and head motion correction. To stabilize the signal, the first ten time points were removed from the analysis. The images were then corrected for slice timing and realigned to address temporal inconsistencies and motion-related artifacts. The images were normalized to the Montreal Neurological Institute (MNI) template space for a standardized anatomical reference. Spatial smoothing was applied using a Gaussian kernel with a full width at half maximum (FWHM) of 4 mm. Data with excessive head motion, defined as translation greater than 2 millimeters or rotation more than 2 degrees in any direction, were excluded to reduce motion-related confounding factors, thereby improving the quality and reliability of the results.

Statistical Analysis

Clinical Characteristic Measurement

Statistical analyses were performed using SPSS 26.0 (IBM, Chicago, IL, USA). Data that followed a normal distribution were reported as mean ± standard deviation ($\bar{X} \pm s$), while non-normally distributed data were presented as median (interquartile range), M (IQR). Categorical data were depicted as rates or percentages (%), with a significance level set at $P < 0.05$. Depending on the data type and normality test outcomes, appropriate parametric or non-parametric tests were applied to assess the balance of demographic and baseline characteristics among different groups.

MRI Measurement

Utilizing FreeSurfer, a GLM-based two-sample *t*-test was performed for DOSS analysis. A design matrix and contrast matrix were established. The data underwent smoothing with a 20 mm FWHM kernel. For multiple comparison correction, a cluster-level Monte Carlo method was employed, setting vertex $P < 0.05$ and cluster $P < 0.05$ as the thresholds for significance. This process revealed the significant disparities in cortical thickness between individuals suffering from acute versus chronic neck pain.

Processed ALFF data underwent Fourier transformation with DPABI software to convert into the frequency spectrum. Signals within the 0.01 to 0.08 hz band were isolated to capture low-frequency oscillations. The average power within this band was computed to determine the ALFF value, indicative of the brain's spontaneous activity at rest. Utilizing DPABI's statistical tools, a two-sample *t*-test was performed to assess ALFF differences between two groups. Gaussian random field correction was applied for multiple comparisons, with significance set at voxel $P < 0.05$ and cluster $P < 0.01$.

Results

Demographic and Clinical Characteristics

A total of 180 participants were included in this study. Among them, neuroimaging analysis was discontinued for 4 patients with acute neck pain and 1 patient with chronic neck pain due to maximum head movement exceeding 2 mm translation or 2° rotation. Ultimately, 86 patients with acute neck pain and 89 patients with chronic neck pain were included in the analysis.

The baseline demographic characteristics of all patients are summarized in Table 1. The gender, age, height, and weight were comparable between patients with acute neck pain and those with chronic neck pain ($P > 0.05$).

CT Differences Between Groups

Patients suffering from chronic neck pain showed a thicker cortex in the left rostral middle frontal, left isthmus cingulate, left superior frontal, and right precuneus regions when contrasted with individuals experiencing acute neck pain (Table 2 and Figure 1).

ALFF Differences Between Groups

Patients suffering from chronic neck pain, in contrast to those with acute neck pain, showed decreased activity in the left angular gyrus, left dorsolateral superior frontal gyrus, left postcentral gyrus, and right cerebellum_crus2, along with elevated activity in the right middle frontal gyrus and the opercular region of the right inferior frontal gyrus (Table 3 and Figure 2).

Table 1 Participant Demographic and Baseline Characteristics

Items	Acute Neck Pain (n=86)	Chronic Neck Pain (n=89)	*P*-value
Age (year)	23 (6)	25 (4)	0.126
Sex			
Male	34	28	0.264
Female	52	61	
Pain duration (day)	19 (11)	870 (765)	0.001*
Pain degree (VAS)	6 (1.25)	5.5 (1)	0.040*
Height (cm)	165 (14.25)	164 (11.5)	0.788
Weight (kg)	55 (18.88)	55 (14.50)	0.877

Note: *indicates *P* value less than 0.05.

Table 2 Differences in Cortical Thickness Between Patients With Acute and Chronic Neck Pain

Cluster	Annot	Hemi	Max	VtxMax	Size (mm2)	MNI (X,Y,Z)	CWP	CWPLow	CWPHi	NVtxs
Cluster 1	Rostral middle frontal	lh	27505	149,928	3471.97	−29.6 34.2 23.6	0.0006	0.0003	0.0009	6371
Cluster 2	Isthmus cingulate	lh	3.5347	62,065	2356.69	−11.5 −42.5 31.7	0.0194	0.0176	0.0212	5472
Cluster 3	Superior frontal	lh	2.4200	152,570	2305.03	−23.5 20 53.5	0.0222	0.0203	0.0241	3793
Cluster 4	Precuneus	rh	3.1046	125,576	2095.87	13.4 −43.3 36.2	0.0398	0.0373	0.0423	4230

Abbreviations: Annot, annotation of cluster peak; Hemi, hemisphere; lh, left hemisphere; rh, right hemisphere; Max, indicates maximum – log10 (P-value) in the cluster; VtxMax, vertex number at maximum; Size, surface area (in mm2) of cluster; CWP, clusterwise p-value; CWPLow and CWPHi, 90% confidence interval for CWP; NVtxs, number of vertices in cluster.

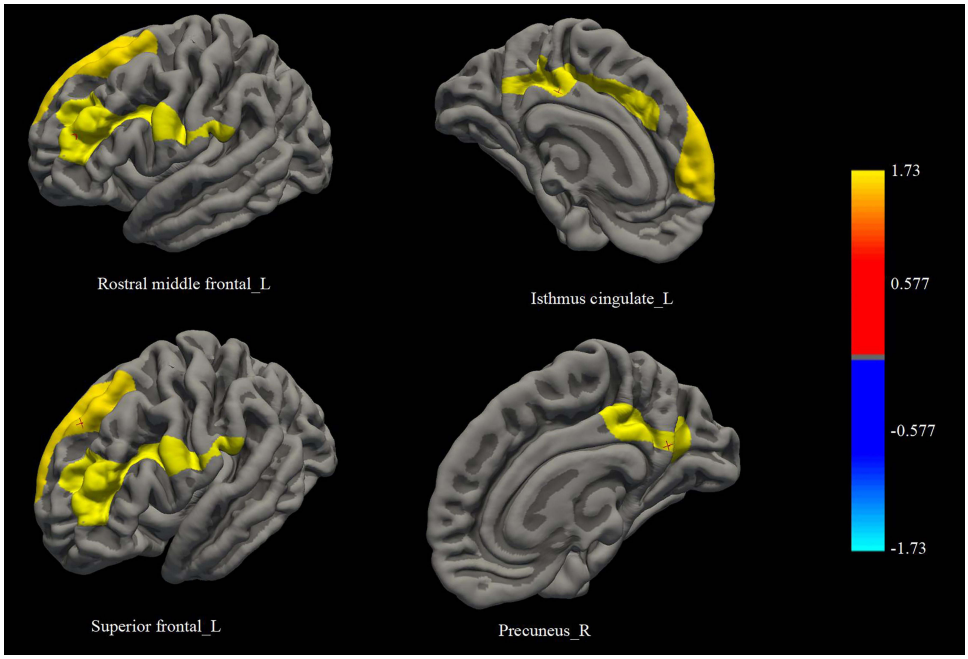

Figure 1 Differences in Cortical Thickness Between Patients with Acute and Chronic Neck Pain.

Discussion

To the best of our knowledge, no previous imaging research had concurrently gathered functional and structural MRI data to evaluate the pathological progression of brain function and gray matter structure during the transition from acute to chronic neck pain. Our study's results represented the first evidence to suggest that, in comparison to individuals with acute neck pain, patients suffering from chronic neck pain exhibited distinct alterations in the structure and function of brain regions implicated in sensory discrimination, emotional motivation, and cognitive appraisal, including the pre-frontal cortex.

Based on Brain Anatomy: Investigating the Anatomical Differences in the Brain Under Acute and Chronic Neck Pain

Research indicates that the risk of shifting from acute to chronic pain may be linked to the limbic system,[12] with subacute back pain patients at risk for chronic pain showing alterations in limbic system structure.[13] This study also verified

Table 3 Differences in ALFF Between Patients With Acute and Chronic Neck Pain

Brain Regions	MNI Coordinates			T value	Cluster Size
	X	Y	Z		
Angular_L	−33	−66	42	−4.1973	186
Frontal_Sup_L	−24	30	45	−4.0048	178
Postcentral_L	−42	−33	54	−3.8927	94
Cerebelum_Crus2_R	30	−81	−42	−3.7465	121
Frontal_Mid_R	27	30	30	3.5997	87
Frontal_Inf_Oper_R	48	9	24	4.2938	100

Abbreviations: L, left hemisphere; R, right hemisphere; Frontal_Sup, dorsolateral superior frontal gyrus; Frontal_Mid, middle frontal gyrus; Frontal_Inf_Oper, opercular part of the inferior frontal gyrus.

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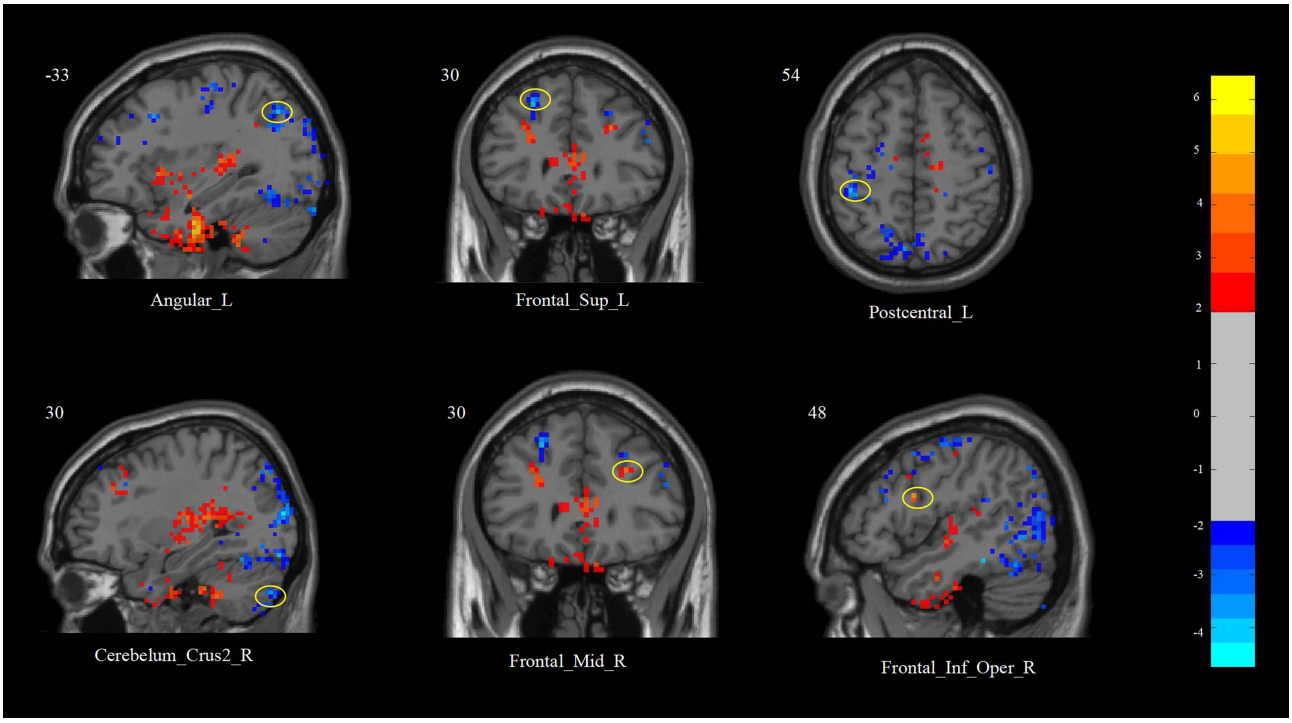

Figure 2 Differences in ALFF Between Patients with Acute and Chronic Neck Pain.
Notes: The yellow circles serve to accentuate the particular brain areas indicated within the figure.
Abbreviations: L, left; R, right; Frontal_Sup, dorsolateral superior frontal gyrus; Frontal_Mid, middle frontal gyrus; Frontal_Inf_Oper, opercular part of the inferior frontal gyrus.

increased cortical thickness in the isthmus cingulate and precuneus areas in those with chronic neck pain. Given that chronic pain is a multifaceted condition tied to distorted emotional and memory processes,[14] the isthmus cingulate, a component of the limbic system, is crucial for modulating emotional reactions, pain sensation, decision-making, and cognitive abilities.[15] Moreover, Woodworth et al have proposed that individuals with cervical spine-related neck pain demonstrate atypical cortical characteristics in areas involved in pain processing, such as the precuneus, and that these abnormalities correlate with the exacerbation of neurological and pain symptoms,[9] corroborating our own results.

The prefrontal cortex is key in governing emotions, cognitive abilities, and the perception of pain. Damage to this area can contribute to the progression of pain from acute to a persistent, hard-to-manage chronic state. The rostral middle frontal, part of the dorsolateral prefrontal region, is involved in pain perception adjustment and emotional response processing, as well as being tied to executive functions and stress reactions.[16,17] Thinning of the rostral middle frontal cortex in those with chronic pain might intensify pain sensation and emotional issues, fostering the chronicity of pain. The superior frontal is implicated in pain's cognitive regulation and emotional modulation, with altered cortex thickness noted in conditions like cervical spondylosis[9] and chronic lower back pain.[18] A study using machine learning on trigeminal neuralgia identified the isthmus cingulate and superior frontal cortex thickness as significant predictors of pain mitigation,[19] underscoring their role in the transition to chronic neck pain.

It's intriguing that despite most studies showing a reduction in prefrontal cortex gray matter volume or thickness in individuals with pain,[20] our study showed an increase in cortical thickness in the prefrontal area of patients suffering from chronic neck pain as opposed to those with acute neck pain. The variance between our findings and earlier research might stem from the differing reference groups used; previous research often compared against healthy individuals, overlooking the distinction between acute and chronic pain conditions. In a separate longitudinal neuroimaging study, enhanced prefrontal cortex connectivity was indicative of ongoing pain in individuals with subacute back pain over a 12-month period.[20] Furthermore, research has indicated that migraine patients who responded well to medication exhibited

decreased prefrontal cortex thickness,[21] indicating that prefrontal interventions could be a promising approach to hinder the progression from acute to chronic pain.

Based on Brain Functional Activity: Unveiling the Functional Dynamics of Brain Activity Across Various States

Pain, characterized as "an uncomfortable sensory and emotional response linked to, or similar to, actual or potential tissue harm"[22] integrates aspects of sensation, emotion, and cognition. The sensation of pain alerts the body to react to harm, aiming to ease the discomfort. Yet, chronic neck pain, with its alterations in posture and tactile sensation, results in a reduction of functional activity within the postcentral gyrus, the area tasked with interpreting sensory data from the body.

It is significant to observe that both the superior frontal gyrus and the middle frontal gyrus, situated within the dorsolateral prefrontal cortex (DLPFC), exhibit structural and functional anomalies in individuals with chronic neck pain. This highlights the DLPFC's pivotal involvement in the development and maintenance of chronic pain. Firstly, chronic pain is commonly linked to elevated stress levels,[23] and the DLPFC is essential in managing these stress responses.[24] Secondly, chronic pain sufferers often face emotional and cognitive challenges,[25,26] such as anxiety and depression, with the DLPFC being a key player in the governance of these processes.[27,28] The detected irregularities in the DLPFC among chronic neck pain patients may point to a compromised capacity for emotional and cognitive regulation, which could contribute to a self-perpetuating cycle that exacerbates the experience of pain. Furthermore, the DLPFC contributes to the descending pain modulation system,[29] which is crucial for dampening pain signals. In the context of chronic neck pain, any disruption in the DLPFC's structure or function may impede the effective activation of this pain-modulating pathway, resulting in the intensification and persistence of pain.

The ventrolateral prefrontal cortex (VLPFC), closely linked to the dorsolateral prefrontal cortex, is also involved in pain regulation.[30,31] Imaging research indicates a key role of the right VLPFC in managing negative emotions.[32,33] The VLPFC seems to act as an intermediary in adjusting emotional responses and pain sensations. Aligning with these findings, our study revealed altered functional activity in the right opercular part of the inferior frontal gyrus in chronic neck pain patients compared to those with acute pain. This could explain the emotional regulation challenges faced by chronic pain sufferers, potentially intensifying their pain perception and chronic condition. This concept is supported by studies on chronic low back pain.[34]

Limitations

The absence of longitudinal tracking in this study precluded continuous observation of participants, thereby preventing an accurate depiction of the temporal fluctuations in pain duration and intensity. Subsequent research will develop extended follow-up plans to elucidate the neural processes involved in the progression from acute to chronic pain. Additionally, the heterogeneity of participants' pain etiologies is one of the limitations of this study, which may restrict the uniformity and generalizability of the results.

Conclusion

Our study represents the pioneering effort to concurrently assess cortical thickness and low-frequency amplitude in individuals suffering from chronic neck pain, utilizing fMRI technology. For the first time, it reveals that dysfunctions and structural alterations within the limbic system and prefrontal cortex are potentially pivotal in the progression from acute to chronic pain. This breakthrough sheds light on novel therapeutic targets and conceptual directions for intercepting the chronicity of pain.

Data Sharing Statement

The data produced in this study is not accessible to the public due to the confidentiality agreement with the participants, however, it can be obtained from the contact author upon justified inquiry.

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Disclosure

The authors declare that there are no competing interests.

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