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Systematic Review

Systematic Review and Meta-Analysis: Multimodal Abnormalities of Brain Structure and Function in Chronic Neck Pain

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Abstract

Background: Previous neuroimaging studies of patients with chronic neck pain (CNP) have revealed abnormal functional activity and structure of brain regions. However, these results often exhibit variability. Therefore, we have integrated existing research findings using a multimodal meta-analysis to obtain consistent and reliable results on brain functional activity and structural changes in CNP patients. **Methods:** Studies of the amplitude of low frequency fluctuations, regional homogeneity, or voxel-based morphometry that investigated the differences in brain function and structure between CNP patients and healthy controls were searched for in seven Chinese and English databases up to November 12, 2025. Meta-analysis of the relevant neuroimaging data from the eligible literature was performed using anisotropic effect size signed differential mapping. **Results:** This meta-analysis included a total of 36 datasets from 33 articles. The analytic results of resting-state functional magnetic resonance imaging indicate that the CNP patients exhibited abnormal functional activity in the right superior frontal gyrus (SFG), left median cingulate gyrus, right calcarine fissure cortex, right middle temporal gyrus (MTG), and left inferior parietal gyrus. Further, CNP patients exhibit abnormal gray matter volume (GMV) of the left paracentral lobule, right superior temporal gyrus (STG), right middle frontal gyrus (MFG), bilateral SFG, right cerebellum, right cuneus cortex, and left MTG. Additionally, the meta-regression analysis revealed that age is associated with increased functional activity in the right MTG, while disease duration is associated with decreased functional activity in the left median cingulate gyrus, as well as increased GMV in both the right MFG and STG. **Conclusions:** CNP patients exhibit widespread neuroimaging abnormalities, mainly involving pain perception, advanced cognition, and emotion regulation. These results may offer additional ideas for understanding the central mechanisms of CNP and the exploration of potential targets for CNP treatment. **The PROSPERO Registration:** CRD420251018254, https://www.crd.york.ac.uk/PROSPERO/view/CRD420251018254.

Keywords: chronic neck pain; meta-analysis; functional magnetic resonance imaging; neuroimaging; resting-state

1. Introduction

Chronic neck pain (CNP) is defined as pain perceived between the superior nuchal line and the spinous process of the first thoracic vertebra, which may be accompanied by headaches, stiffness, or numbness in the upper limbs [1,2]. It can be caused by degeneration of the cervical vertebrae joints, intervertebral discs, muscles, or ligaments [3]. In 2020, 203 million people worldwide were affected by CNP, which had the age-standardized years lived with disability rate of 244 per 100,000, with highest prevalence observed among individuals aged 45 to 74, and global cases projected to reach 269 million by 2050 [4]. CNP is one of the leading causes of disability worldwide [5]. CNP has severely reduced the quality of life of patients, imposing a heavy economic burden [6].

Substantial evidence suggests that the pathophysiological mechanisms of CNP are significantly related to brain function and structure [7,8]. Patients with CNP exhibited increased functional activity in the right precuneus, left superior frontal gyrus (SFG), left insula, and right cingulate gyrus [9,10], while functional activity decreased in the left insula, right postcentral gyrus (PoCG), and right cingulate gyrus [9,11]. CNP patients were found to exhibit decreased gray matter volume (GMV) in the left precuneus, right postcentral gyrus, and right middle cingulate gyrus [8,12,13], with increased GMV of the right middle cingu-

late gyrus [13]. Furthermore, some research has found no significant differences in GMV between CNP patients and healthy controls (HCs) [11].

Currently, two studies have conducted meta-analyses of the brain alterations of patients with cervical spondylosis [14,15]. One of those studies only performed a meta-analysis on the functional activities of patients with CNP caused by cervical spondylosis [15]. Subsequently, four new studies on CNP have been published after the latest retrieval cut-off date of April 30, 2024 for those studies. Therefore, conducting an updated meta-analysis of CNP patients has significant clinical and research implications.

Anisotropic effect-size signed differential mapping (AES-SDM) is a commonly used software for neuroimaging analysis that can analyze the differences in brain structure and function between different samples [16]. Hence, a multimodal meta-analysis of functional activity and gray matter structure among patients with CNP was conducted using AES-SDM. The aim was to reveal the neuroimaging characteristics of CNP patients. Additionally, potential correlations were explored between these abnormal changes in brain regions and clinical variables such as age and disease duration.

2. Methods

This meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD420251018254).

2.1 Search Strategies and Selection Criteria

A systematic and comprehensive search strategy was formulated for electronic English databases and Chinese databases of the literature up to November 12, 2025. It was conducted in seven databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com), Embase (https://www.embase.com/), Cochrane Central Register of Controlled Trials (CENTRAL, https://www.cochranelibrary.com/central/), China National Knowledge Infrastructure (https://www.cnki.net/), WanFang (https://www.wanfangdata.com.cn/), and Chongqing VIP (https://www.cqvip.com/). The publications in this search were not subject to any restrictions related to country or region. The following keywords were used to identify and retrieve literature: ("Chronic Neck Pain" OR "Neckache" OR "Neck Ache" OR "Cervical Pain" OR "Cervicalgia" OR "Cervicodynia" OR "Anterior Cervical Pain" OR "Anterior Neck Pain" OR "Posterior Cervical Pain" OR "Posterior Neck Pain" OR "Cervical spine pain" OR "Cervical spondylosis") AND ("magnetic resonance imaging" OR "MRI" OR "functional magnetic resonance imaging" OR "fMRI" OR "resting-state functional magnetic resonance imaging" OR "rs-fMRI") AND ("voxel-based morphometry" OR "voxel wise" OR "voxel" OR "VBM" OR "regional homogeneity" OR "ReHo" OR "amplitude of low frequency fluctuations" OR "ALFF" OR "fractional amplitude of low frequency fluctuations" OR "fALFF"). To ensure exhaustive coverage, the references of relevant studies and reviews were also scrutinized.

This meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist (**Supplementary PRISMA_2020_checklist**). Inclusion criteria for studies included: (1) Original research published in English or Chinese; (2) A positive CNP diagnosis, that included: Chronic neck and shoulder pain, chronic cervical spondylotic pain and neck and upper back pain, as well as various types of cervical spondylosis and degenerative cervical myelopathy (DCM); (3) Differences in brain functional activity or GMV had been compared between patients with CNP and HCs; (4) Data analyses included regional homogeneity (ReHo), or amplitude of low frequency fluctuations (ALFF), or fractional amplitude of low frequency fluctuations (fALFF), or voxel-based morphometry (VBM); (5) Results were reported in standardized coordinates such as the Talairach space or the Montreal Neurological Institute (MNI) coordinate system.

Exclusion criteria for studies included: (1) Conference proceedings, pathology reports, or animal studies; (2) Those that only reported results for the region of interest (ROI); (3) Those that failed to report convertible *t*-values or lacked necessary statistical values; (4) Where both the patient group and the control group had fewer than 10 participants [17]. If multiple studies utilized the same or similar datasets, only the study with the largest sample size or the most comprehensive information was included. For longitudinal or interventional studies, only baseline data were included. Article screening was conducted independently by two authors (CJ and XC) and supervised by another reviewer (SC).

2.2 Data Extraction

The data included in the study were extracted by two authors (CJ and XC), with the following information extracted: first author, publication year, analysis methods, sample size, mean age of patients, mean duration of illness, magnetic resonance imaging (MRI) scanner, full width at half maximum (FWHM), Visual Analog Scale (VAS) and Japanese Orthopaedic Association (JOA) scores. According to the usage method of AES-SDM, coordinates with statistical significance from the studies were also extracted (CJ and XC). In cases where data were not available, or information was unclear, the corresponding authors of the studies were contacted by e-mail for further clarification. In case of disagreement among the author groups, consensus was reached by discussion (JL).

2.3 Quality Assessment

Quality assessment of the included literature was achieved by use of a checklist consisting of 10 key points (**Supplementary Tables 1,2**) [18]. This checklist re-

flected essential variables critical for evaluating neuroimaging studies, including demographic data, imaging scan parameters, and research outcome quality [19]. The quality assessment process was independently determined by two authors (CJ and XC). In case of any discrepancies, consensus was reached through consultation with the third author (JL).

2.4 Meta-Analyses of Functional and Structural Differences

Two independent meta-analyses of functional (ALFF, ReHo) studies and structural (VBM) studies were conducted using the AES-SDM software (version 5.15, https://www.sdmproject.com/software). The p-values obtained in the study were converted to *t*-values using the online converter provided by the SDM official website. Initially, statistically significant data were extracted and synthesized from the included literature, combining peak coordinates with a Gaussian kernel to reconstruct effect size and variance maps and limiting FWHM to 20 mm to avoid false positive results. Subsequently, voxel-level study maps were plotted based on the average random effects model, taking into account sample size, variability within studies, and the heterogeneity between studies. The threshold parameters were set to: voxel threshold $p < 0.005$, peak height threshold $Z > 1.000$, and cluster size threshold >10 voxels [20].

2.5 Multimodal Analysis

To investigate the overlapping or conjunction of structural and functional changes in the brains of CNP patients, we utilized the multimodal meta-analysis function in the software to integrate the results of the aforementioned two individual meta-analyses and calculate the union of their *p*-values [20,21].

2.6 Analyses of Jackknife Sensitivity, Heterogeneity, and Publication Bias

A leave-one-out jackknife sensitivity analysis was conducted to assess the stability and generalizability of results. If a brain region remained significant in all or most studies, that result was considered to have high reproducibility. A random-effects model with Q-statistics was employed to examine the heterogeneity between studies [22]. Regarding potential publication bias, to assist visual inspection, funnel plot analyses were performed of the peak values of the main results. Egger's tests were performed, and a *p*-value less than 0.05 was assumed to be indicative of significant publication bias.

2.7 Subgroup Analyses

Subgroup analyses were conducted to examine the potential sources of heterogeneity in this meta-analysis. Specifically, subgroup analyses were performed on ALFF and ReHo to assess the impact of different data analytic methods on the results. Additionally, subgroup analyses were also conducted for the CNP of different disease types.

2.8 Meta-Regression Analyses

A meta-regression analysis was performed to assess the correlation between clinical characteristics such as age, duration of illness, and changes in brain structure and function. The probability threshold was set at 0.005 to reduce the number of false positive results.

3. Results

3.1 Clinical Characteristics of Included Studies

In this meta-analysis, a total of 2269 relevant articles were retrieved. After screening, 33 articles were included, involving a total of 2452 participants (1318 patients with CNP and 1134 HCs). Among these articles, thirteen reported changes in brain function using ALFF analysis [9,10,23,24,25,26,27,28,29,30,31,32,33], eight performed ReHo analysis [7,34,35,36,37,38,39,40], nine reported structural alterations using VBM [8,12,13,41,42,43,44,45,46], two studies performed ALFF and ReHo analysis [47,48], and one performed VBM and ReHo analysis [11]. There were no statistically significant differences in age and gender between CNP patients and HCs. The flowchart of the systematic literature search and the evaluation process of qualified studies is given in Fig. 1. Table 1 (Ref. [7,8,9,10,11,12,13,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48]) briefly summarizes the demographic data, clinical and imaging characteristics of these studies.

3.2 Meta-Analysis of Functional Abnormalities

The functional differences between CNP patients and HCs are illustrated in Fig. 2 and Table 2. CNP patients showed enhanced spontaneous functional activity in the right SFG ($z = 2.619$, $p < 0.0001$), left median cingulate gyrus ($z = 1.816$, $p = 0.0015$), and reduced spontaneous functional activity in the right calcarine fissure cortex ($z = –1.884$, $p = 0.0004$), right middle temporal gyrus (MTG, $z = –1.661$, $p = 0.0011$), and left inferior parietal gyrus (IPL, $z = –1.468$, $p = 0.0024$).

3.3 Meta-Analysis of Structural Changes

The structural changes between CNP patients and HCs are illustrated in Fig. 3 and Table 2. Patients with CNP displayed increased GMV in the left paracentral lobule ($z = 2.788$, $p < 0.0001$), right superior temporal gyrus (STG, $z = 1.541$, $p = 0.0017$), right middle frontal gyrus (MFG, $z = 1.447$, $p = 0.0035$), and reduced GMV in the left SFG ($z = –1.949$, $p = 0.0002$), right SFG ($z = –1.468$, $p = 0.0021$), right cerebellum ($z = –1.468$, $p = 0.0021$), right cuneus cortex ($z = –1.466$, $p = 0.0022$) and left MTG ($z = –1.409$, $p = 0.0031$).

3.4 Multimodal Analysis

Multimodal analysis shows that CNP patients have decreased GMV in the left SFG and increased GMV in the right MFG relative to HCs.

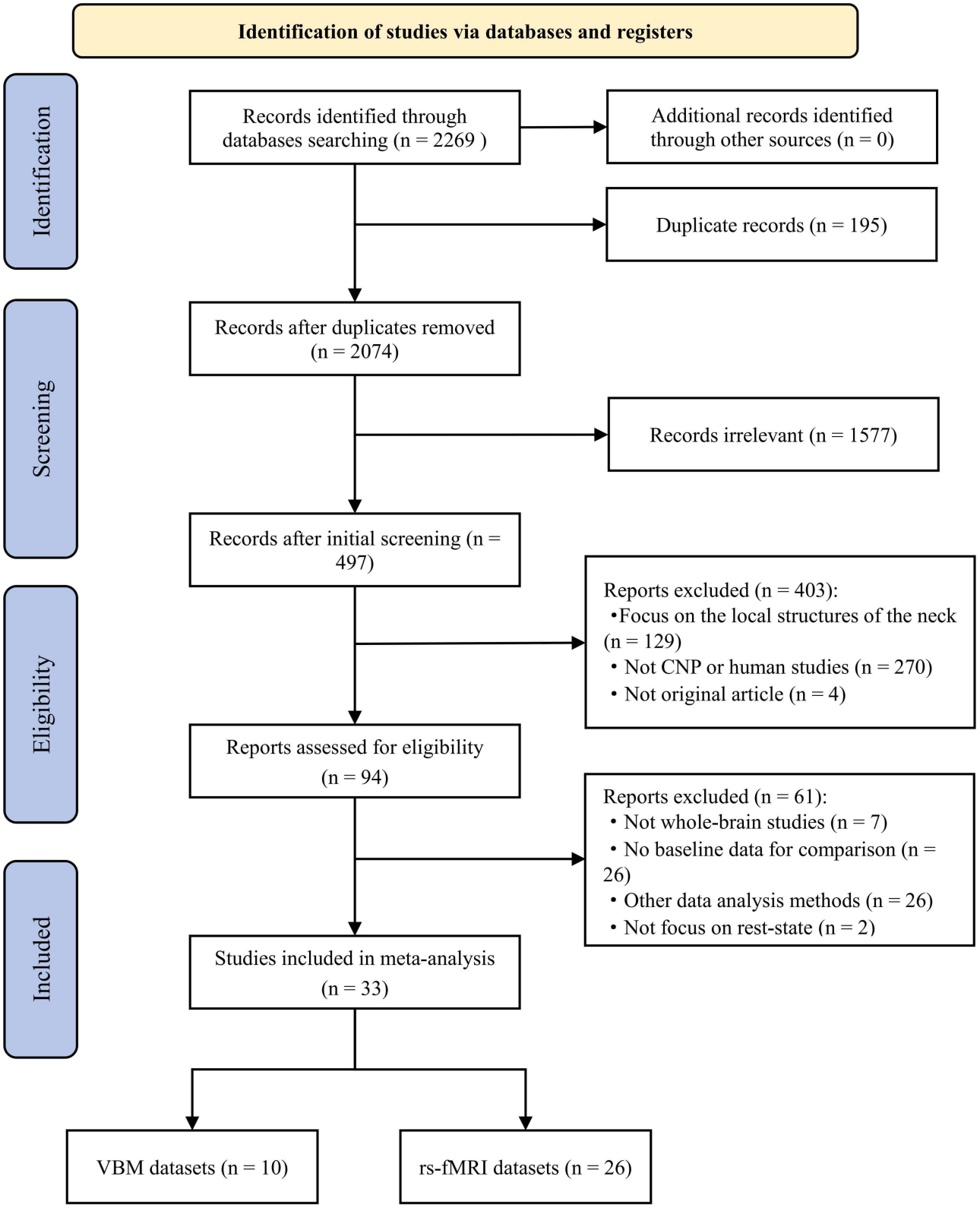

Fig. 1. The flow diagram of literature search and study selection. Abbreviations: n, number; rs-fMRI, resting-state functional magnetic resonance imaging; VBM, voxel-based morphometry; CNP, chronic neck pain.

Table 1. Demographic, clinical characteristics and technique details of the included studies.

	Analysis	Diagnosis	Sample size (male)		Mean age (y)		Mean duration (m)	Scanner	FWHM	Threshold	Quality score
			CNP	HCs	CNP	HCs	CNP				
VBM studies	10										
Mao et al. (2013) [41]	VBM	UBP	15 (5)	15 (5)	49.2	49.2	93.6	3 T	3 mm	FWE corrected	10.0
Yu et al. (2017) [11]	VBM	CNSP	25 (13)	20 (10)	47.68	42.5	NA	3 T	4 mm	AlphaSim corrected	8.5
Yang et al. (2020) [8]	VBM	cCSP	31 (20)	30 (20)	41.19	40.27	40.74	3 T	8 mm	uncorrected	9.5
Bernabéu-Sanz et al. (2020) [42]	VBM	CS	27 (14)	24 (12)	55.92	55.79	NA	3 T	8 mm	FDR corrected	9.0
Xu et al. (2021) [43]	VBM	CNP	73 (19)	27 (NA)	43.84	NA	51.1	3 T	NA	FDR corrected	8.5
Chen et al. (2022) [44]	VBM	CSM	10 (6)	10 (6)	52.1	52.7	NA	3 T	8 mm	FWE corrected	8.5
Tian et al. (2023) [12]	VBM	CSM	62 (31)	42 (21)	57.2	57.1	21.3	3 T	8 mm	FDR corrected	10.0
Kuang and Zha (2024) [13]	VBM	CSM	40 (25)	28 (17)	40.2	39.54	18.45	3 T	6 mm	FWE corrected	10.0
Wang et al. (2024) [45]	VBM	CSM	57 (23)	57 (26)	52.7	50.9	NA	3 T	6 mm	FDR corrected	10.0
Yu (2024) [46]	VBM	CSM	66 (30)	76 (36)	47.45	45.67	8.39	3 T	8 mm	FDR corrected	10.0
rs-fMRI studies	26										
Tan et al. (2015) [39]	ReHo	CSM	21 (13)	21 (13)	47.95	NA	24.5	3 T	6 mm	AlphaSim corrected	9.5
Li (2016) [38]	ReHo	CNSP	25 (14)	20 (9)	47.70	42.50	7.9	3 T	4 mm	AlphaSim corrected	9.5
Chen et al. (2015) [37]	ReHo	CSM	49 (21)	19 (8)	25.00	26	NA	1.5 T	NA	AlphaSim corrected	9.5
Yu et al. (2017) [11]	ReHo	CNSP	25 (13)	20 (10)	47.68	42.5	NA	3 T	4 mm	AlphaSim corrected	9.0
Xu et al. (2018) [40]	ReHo	CNSP	25 (NA)	20 (NA)	NA	NA	NA	3 T	4 mm	AlphaSim corrected	9.0
Chen Z et al. (2018) [47]	ReHo	CSM	27 (15)	11 (6)	57.9	54.8	NA	3 T	NA	FWE corrected	10.0
Chen J et al. (2018) [7]	ReHo	CS	104 (45)	96 (50)	24.9	24.8	36.49	3 T	4 mm	FWE corrected	10.0
Kuang and Zha (2019) [48]	ReHo	CSM	33 (16)	33 (15)	54.78	53.52	37	3 T	6 mm	FDR corrected	9.5
Gao (2022) [34]	ReHo	CS	46 (13)	44 (13)	23	22	NA	3 T	4 mm	FDR corrected	9.5
Zhang et al. (2024) [36]	ReHo	CNSP	60 (30)	60 (30)	46.7	47.2	14.9	3 T	8 mm	FDR corrected	10.0
Song et al. (2024) [35]	ReHo	CS	27 (7)	27 (6)	37.29	39.00	NA	3 T	NA	GRF corrected	9.0
Zhou et al. (2014) [23]	ALFF	CSM	19 (11)	19 (11)	49.63	49.46	8.68	3 T	6 mm	AlphaSim corrected	10.0
Zong (2015) [24]	ALFF	CSM	10 (5)	10 (5)	49.50	50.10	10.80	3 T	NA	AlphaSim corrected	8.5
Chen et al. (2018) [47]	ALFF	CSM	27 (15)	11 (6)	57.90	54.80	NA	3 T	NA	FWE corrected	10.0
Wang (2018) [30]	ALFF	CSM	30 (19)	25 (11)	51.32	51.2	NA	3 T	8 mm	GRF corrected	10.0
Kuang and Zha (2019) [48]	ALFF	CSM	33 (16)	33 (15)	54.78	53.52	37	3 T	6 mm	FDR corrected	9.5
Yue and Du (2020) [9]	ALFF	CNSP	28 (17)	25 (13)	47.04	43.56	32.56	3 T	4 mm	AlphaSim corrected	9.5
Takenaka et al. (2020) [26]	ALFF	CSM	28 (14)	28 (14)	67.00	67.00	36.00	3 T	6 mm	FDR corrected	10.0
Ge et al. (2021) [27]	ALFF	CSM	12 (5)	14 (6)	55.42	50.05	NA	3 T	NA	AlphaSim corrected	9.0
Fan et al. (2022) [31]	ALFF	CSM	44 (22)	38 (20)	51.30	51.70	30.5	3 T	6 mm	FWE corrected	9.5
Bai et al. (2022) [28]	ALFF	CS	31 (16)	31 (16)	51.79	51.52	NA	3 T	8 mm	FWE corrected	9.5
Zhao et al. (2022) [29]	ALFF	CSM	54	50	53.3	54.8	30	3 T	NA	FWE corrected	8.5
Su et al. (2023) [32]	ALFF	CSM	62 (31)	60 (30)	53.3	53.4	NA	3 T	NA	FWE corrected	9.0
Wu et al. (2024) [33]	ALFF	CSM	20 (9)	20 (7)	53.5	49.2	NA	3 T	6 mm	GRF corrected	9.5
Zhang et al. (2019) [25]	ALFF	CSM	43 (27)	41 (NA)	49.07	NA	24.45	3 T	NA	GRF corrected	9.5
Zhang and Chen (2024) [10]	ALFF	CNP	29 (10)	29 (14)	25.62	25.48	34.97	3 T	6 mm	Uncorrected	9.0

Abbreviations: ALFF, amplitude of low frequency fluctuations; ReHo, regional homogeneity; UBP, upper back pain; CNSP, chronic neck and shoulder pain; cCSP, chronic cervical spondylotic pain; CS, cervical spondylosis; CSM, cervical spondylotic myelopathy; FWE, family-wise error; FDR, false discovery rate; GRF, Gaussian random field; HCs, healthy controls; FWHM, full width at half maximum; NA, not applicable; y, year; m, month.

Table 2. Meta-analysis results of rs-fMRI and VBM abnormalities between CNP patients and HCs.

	Peak MNI coordinate			SDM z–score [a]	*p* value [b]	Number of voxels [c]	Cluster breakdown (No. of voxels)	Heterogeneity	Jackknife analysis	Egger's test (*p* value)
	X	Y	Z							
rs-fMRI abnormalities										
CNP > HCs										
R superior frontal gyrus, medial	4	54	20	2.619	<0.0001	1943	L superior frontal gyrus, medial, BA10, BA32 (602) R superior frontal gyrus, medial, BA10, BA32, BA9 (411) R anterior cingulate/paracingulate gyri, BA32, BA24, BA10 (305) L anterior cingulate/paracingulate gyri, BA32, BA24, BA10 (288) L superior frontal gyrus, dorsolateral, BA10 (13)	NO	21/26	0.940
L median cingulate gyrus	–2	–8	32	1.816	0.0015	40	R median cingulate/paracingulate gyri, BA32 (10) L median cingulate/paracingulate gyri, BA23 (12)	YES	23/26	0.310
CNP < HCs										
R calcarine fissure cortex	4	–70	14	–1.884	0.0004	549	R calcarine fissure/surrounding cortex, BA17, BA18, BA23 (123) R lingual gyrus, BA17 (37) R precuneus, BA23 (45)	NO	19/26	0.345
R middle temporal gyrus	60	–42	6	–1.661	0.0011	255	L calcarine fissure/surrounding cortex, BA17, BA18, BA23 (85) R middle temporal gyrus, BA22, BA21, BA42 (195) R superior temporal gyrus, BA22, BA42 (50)	NO	25/26	0.010
L inferior parietal gyrus	–52	–26	44	–1.468	0.0024	57	L inferior parietal gyri, BA3, BA2 (39)	NO	23/26	0.055
VBM abnormalities										
CNP > HCs										
L paracentral lobule	–6	–32	50	2.788	<0.0001	2872	L median cingulate/paracingulate gyri, BA23 (423) L paracentral lobule, BA4 (517) R median cingulate/paracingulate gyri, BA23, BA4 (305) L precuneus, BA5, BA4, BA3 (507) R paracentral lobule, BA4, BA5 (265) R precuneus, BA5 (242) R supplementary motor area, BA4, BA6 (103) R median network, cingulum (24) L postcentral gyrus, BA4 (19)	NO	2/10	0.799
R superior temporal gyrus	48	–26	10	1.541	0.0017	347	R superior temporal gyrus, BA48, BA42 (117) R heschl gyrus, BA48 (65) R rolandic operculum, BA48 (64)	NO	8/10	0.316
R middle frontal gyrus	42	20	38	1.447	0.0035	23	R middle frontal gyrus, BA44 (19)	NO	9/10	0.170

Table 2. Continued.

	Peak MNI coordinate			SDM z–score [a]	*p* value [b]	Number of voxels [c]	Cluster breakdown (No. of voxels)	Heterogeneity	Jackknife analysis	Egger's test (*p* value)
	X	Y	Z							
CNP < HCs										
L superior frontal gyrus, medial	–2	20	40	–1.949	0.0002	918	L median cingulate/paracingulate gyri, BA24, BA32 (159) L anterior cingulate/paracingulate gyri, BA24 (188) R median cingulate/paracingulate gyri, BA24, BA32 (106) L superior frontal gyrus, medial, BA8, BA32 (169) R anterior cingulate/paracingulate gyri, BA24 (78) L median network, cingulum (59) L supplementary motor area, BA8, BA32 (89) R median network, cingulum (22)	NO	6/10	0.473
R cerebellum	48	–62	–38	–1.468	0.0021	95	R cerebellum, crus I (82) R cerebellum, crus II (13)	NO	9/10	0.171
R cuneus cortex	8	–88	20	–1.466	0.0022	72	R cuneus cortex, BA18 (56)	NO	8/10	0.171
R superior frontal gyrus	26	12	66	–1.468	0.0021	31	R superior frontal gyrus, dorsolateral, BA8 (24)	NO	9/10	0.171
L middle temporal gyrus	–48	18	–30	–1.409	0.0031	19	L temporal pole, middle temporal gyrus, BA38 (19)	NO	9/10	0.168

[a] Peak height threshold: $z > 1$.

[b] Voxel threshold: $p < 0.005$.

[c] Cluster extent threshold: regions with ≤10 voxels not reported in the cluster breakdown.

Abbreviations: MNI, Montreal Neurological Institute; SDM, signed differential mapping; BA, Brodmann area; L, left; R, right.

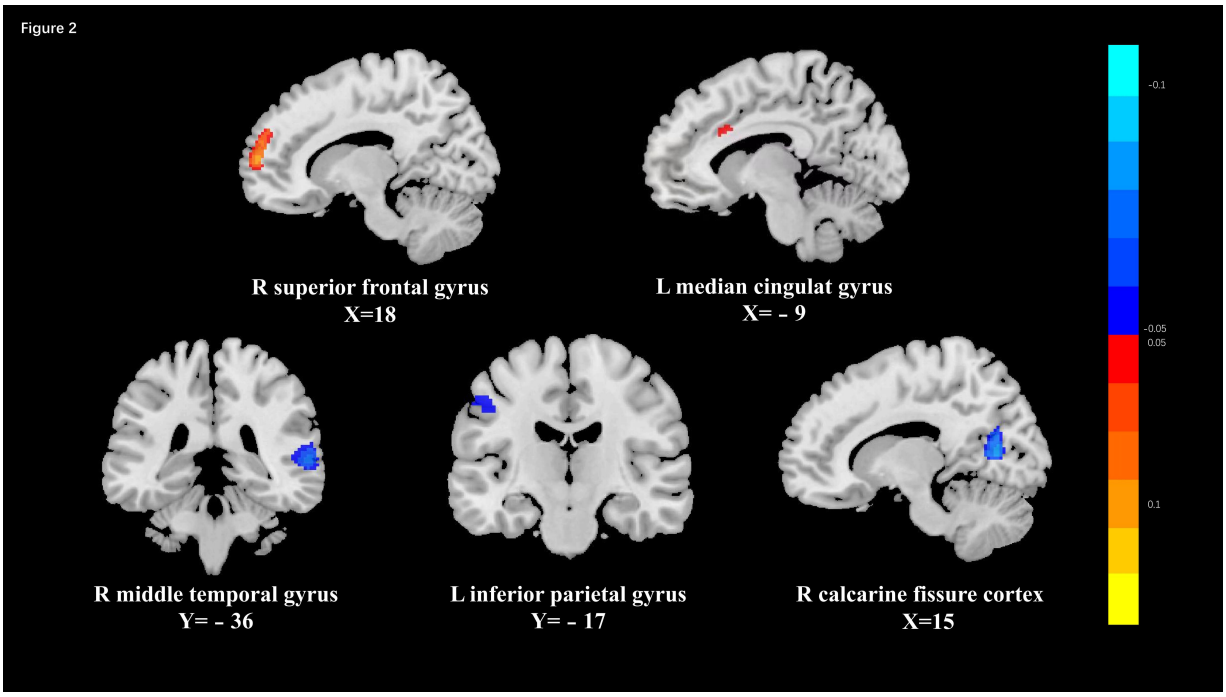

Fig. 2. Resting-state functional differences between CNP and HCs. Areas with increased resting-state functional activity are displayed in yellow, and areas with decreased resting-state functional activity are displayed in blue. Abbreviations: L, left; R, right.

3.5 Sensitivity Analysis, Heterogeneity Analysis, and Publication Bias

The jackknife sensitivity analysis indicated that most of the brain regions in this meta-analysis exhibited high reliability (Table 2). In the meta-analysis of resting-state functional magnetic resonance imaging and VBM, no significant heterogeneity was observed in any brain areas, except for the left median cingulate gyrus (p = 0.0015). The Egger's test revealed no significant publication bias ($p > 0.05$) in the meta-analysis, except for the right MTG.

3.6 Subgroup Analyses

Due to the significant differences between the ALFF and ReHo analysis [49], the subgroup analysis was conducted on the studies of functional changes. The results of the subgroup analysis are illustrated in **Supplementary Table 3**. The ALFF subgroup analysis revealed increased spontaneous neural activity in the right SFG (z = 3.066, $p <$ 0.0001), while decreased activity was observed in the right lingual gyrus (z = –2.119, $p < 0.0001$) and left postcentral gyrus (z = –1.535, p = 0.001). The ReHo subgroup analysis demonstrated increased functional activity in the right MFG (z = 2.022, $p < 0.0001$), left MFG (z = 1.912, p = 0.0002), left MTG (z = 1.611, p = 0.0015), and left postcentral gyrus (z = 1.696, p = 0.001) in CNP patients, while decreased activity was observed in the right MTG (z = –2.015, p = 0.0002), right precuneus (z = –2.081, p = 0.0002), and left postcentral gyrus (z = –1.711, p = 0.0014). The results of the subgroup analyses of CNP for different disease types are illustrated in **Supplementary Table 4A–J.**

3.7 Meta-Regression Analyses

The results of the meta-regression analysis are illustrated in **Supplementary Table 5A,B**. Age was associated with increased functional activity in right MTG (z = 2.163, p = 0.0017). The illness duration of CNP was associated with decreased functional activity of the left median cingulate gyrus (z = –2.339, p = 0.0003), and was associated with the increased GMV of right MFG (z = 1.23, p = 0.0018) and right STG (z = 1.074, p = 0.0032).

4. Discussion

This multimodal meta-analysis integrated whole-brain ALFF, ReHo, and VBM neuroimaging data utilizing AES-SDM software, investigating the consistent changes in brain structure and function among CNP patients. The findings indicated that CNP patients exhibited significantly increased functional activity in the right SFG and left median cingulate gyrus and decreased functional activity in the right calcarine fissure cortex, right MTG, and left IPL. Additionally, there was increased GMV observed in the right STG and right MFG in patients with CNP, as well as a decreased GMV in the bilateral SFG, right cerebellum, right cuneus cortex, and left MTG.

Both SFG and MFG are main components of the prefrontal cortex (PFC), responsible for sensation, emotion, and cognition [50]. The PFC involves a biopsychosocial approach to pain management by integrating emotional and cognitive information through modulation of nociceptive pathways [51,52,53]. The MFG plays an active regulatory role in pain perception by modulating corticosubcor-

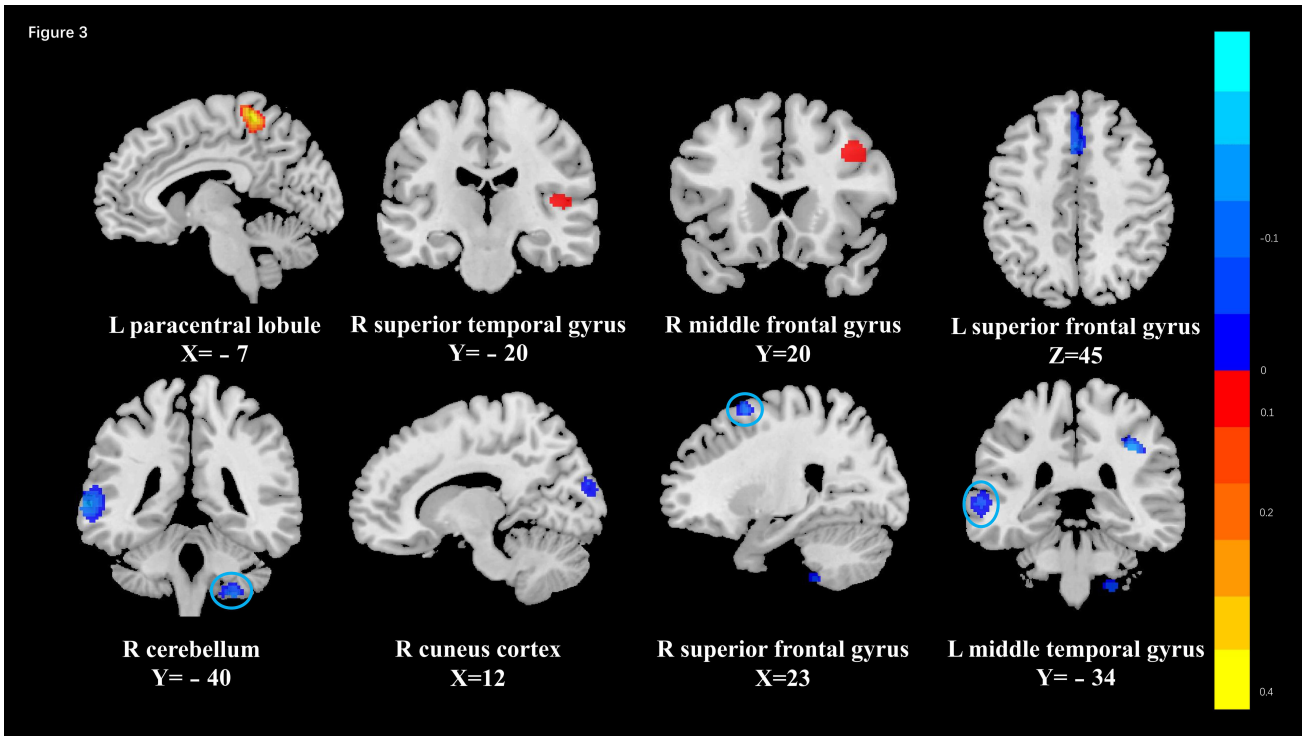

Fig. 3. Structural differences between CNP and HCs. Areas with increased gray matter volume are displayed in yellow, and areas with decreased gray matter volume are displayed in blue. The brain regions circled by the blue circle correspond to those indicated at the bottom of the figure. Abbreviations: L, left; R, right.

tical and corticocortical pathways [54]. The medial SFG is one of the core regions involved in homeostatic maintenance function [55]. There is evidence indicating that enhanced activity in the medial PFC, along with its functional disconnect from the attention-related networks, amplifies the suffering induced by pain [56]. Research by the current authors has found that CNP patients exhibit increased functional activity in the right SFG, decreased GMV in bilateral SFG, and increased GMV in the right MFG. Additionally, multimodal analysis showed that the left SFG and right MFG of CNP patients exhibited significant differences when compared to HCs. The abnormal changes in PFC functional activity and GMV suggest that there may be abnormalities in the regulation of pain conduction pathways in CNP patients that amplify their pain experience [57]. In treatments targeting chronic pain, the PFC often serves as a therapeutic target in strategies such as repetitive transcranial magnetic stimulation as well as pharmacological and non-pharmacological therapies [58,59], further confirming the important role of the PFC in pain management.

The research reported here found that patients with CNP showed increased functional activity in the median cingulate gyrus. The median cingulate gyrus is located in the anterior cingulate cortex (ACC), which is part of the limbic system and is responsible for emotion regulation and pain perception [60]. The ACC is a key region connecting multiple areas of the brain, receiving inputs from the orbitofrontal cortex and amygdala, while extensively projecting to other brain regions, including the autonomic areas of the brainstem and insula, the midcingulate cortex, the prefrontal cortex and striatum [61] and participating in a variety of functions such as emotion, cognition and pain [61,62]. Pain is a multidimensional experience that encompasses sensory and emotional experiences and also involves various other functions such as sensory recognition, emotional motivation, and cognitive evaluation [63,64]. Research has found that chronic pain patients exhibit significant synaptic plasticity changes in the ACC, changes in neural circuits, and functional activities that are closely related to the comorbidity of pain perception and anxiety [65]. The ACC/medial PFC and insula circuitry has been widely considered to be involved in the learning, persistence, and control of human threat behavior [66]. Abnormal functional connectivity and structural damage in this circuitry may lead to impaired control or downregulation of threat behavior [67]. CNP patients may be more prone to experiencing negative pain-related emotions, which in turn can lead to an increased development of negative emotions and more pessimistic interpretations of their pain. Previous studies have found that patients with depression and anxiety showed increased functional activity and connectivity in the dorsal medial prefrontal/anterior cingulate cortex (dmPFC/dACC) and the amygdala [68,69]. The functions of these regions are considered to be involved in fear conditioning and conscious evaluation of threat-related behaviors, which is highly consistent with the circuit functions

we propose, indicating that CNP and emotional disorders may share common neural circuit abnormalities. Notably, the results showed heterogeneity in the median cingulate gyrus, and the regression analysis showed that the changes in functional activity of the median cingulate gyrus were correlated with the duration of CNP. There are significant differences in the distribution of duration among CNP patients included in studies, which may be one of the sources of heterogeneity. However, the influence of various other factors on heterogeneity, including the severity of pain and various demographic characteristics of CNP patients, cannot be ruled out.

The current study also found a decrease in GMV of the cerebellum. Traditional views suggest that the cerebellum is primarily associated with motor coordination. However, more recent studies have revealed its significant role in emotion and cognition [70]. Research has found that the cognitive processing area of the cerebellum may be related to pain encoding and could serve as a cognitive modulator [71]. The cerebellum, which is closely related to the limbic system and participates in the regulation of emotions and fear-avoidance behaviors, has its cerebellar vermis and cerebellar nuclei contribute to the formation, consolidation, and extinction of fear memories and it transmits prediction or prediction error signals through its extensive connections with cortical and subcortical circuits, thereby influencing emotional and behavioral patterns [72,73,74].

The IPL is one of the key regions that constitute the default mode network [55]. It is involved in advanced cognitive functions, integrating initial sensory information such as visual-spatial information and basic motor instructions with stored conceptual knowledge, enabling individuals to understand and execute goal-oriented behaviors [75,76]. Numerous studies have reported abnormalities in the IPL of patients with chronic pain [17,77]. The current authors' research findings indicate that the functional activity of the left IPL in CNP patients is decreased. Abnormalities in the IPL may be one of the indicators of cognitive impairment [78,79].

The meta-analysis reported here has several limitations. Firstly, the study conducted a meta-analysis based on whole brain voxel-based analysis methods, while the brain is a complex functional network. Future research could perform meta-analyses based on functional networks. Secondly, although subgroup analyses based on different analytical methods (ALFF, ReHo, VBM) were conducted, because of the limitations of the included data, it is unclear whether factors such as gender and pain intensity had effects on the results. Thirdly, the different statistical heterogeneity correction methods used in the studies explored here may also have had some impact on the results. Although a sensitivity analysis indicated that most brain regions showed high credibility, the influence of different statistical heterogeneity correction methods on the results cannot be completely ruled out.

5. Conclusions

CNP patients have a wide range of functional and structural abnormalities in brain regions, mainly involving pain perception, advanced cognition, and emotion regulation. This study provides greater insight into the central mechanisms of CNP and may provide a new direction for exploring potential therapeutic targets in patients with CNP.

Availability of Data and Materials

This study analyzed publicly available datasets. For further inquiries, relevant data can be obtained by contacting the corresponding author.

Author Contributions

CJ: Data curation, Methodology, Software, Writing—original draft. XC: Data curation, Formal analysis, Writing—original draft. JL: Conceptualization, Writing—review & editing. NP: Methodology, Writing—review & editing. YZ: Methodology, Writing—review & editing. PL: Data curation, Writing—review & editing. JH: Methodology, Writing—review & editing. DZ: Conceptualization, Writing—review & editing. MX: Conceptualization, Validation, Visualization, Writing—review & editing. SC: Funding acquisition, Supervision, Validation, Visualization, Writing—review & editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN50345.

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