



---

*Review*

## Large-scale brain network interactions and motor control in chronic pain: A systematic review

Farhad Rezazadeh<sup>1,\*</sup>, Shirin Aali<sup>2</sup>, Parinaz Fahimi<sup>3</sup> and Georgian Badicu<sup>4</sup>

<sup>1</sup> Department of Sports Biomechanics, Faculty of Educational Sciences and Psychology, University of Mohaghegh Ardabili, Ardabil, Iran

<sup>2</sup> Department of Physical Education, Farhangian University, P.O. Box 889–14665, Tehran, Iran

<sup>3</sup> Department of Sports Biomechanics, Faculty of Educational Sciences and Psychology, University of Mohaghegh Ardabili, Ardabil, Iran

<sup>4</sup> Department of Physical Education and Special Motricity, Faculty of Physical Education and Mountain Sports, Transilvania University of Braşov, Braşov, Romania

\* **Correspondence:** Email: Rezazadeh.farhad@uma.ac.ir; Tel: +989120198026; Fax: +453331505627.

**Abstract:** *Background:* Chronic pain is increasingly understood as a disorder involving maladaptive central nervous system plasticity and alterations in distributed brain networks, particularly limbic-cingulate, cerebellar, and sensorimotor networks, rather than being solely explained by persistent peripheral nociception. *Objective:* This systematic review synthesized evidence on alterations in large-scale brain networks in chronic pain, including functional connectivity as well as other functional and structural neuroimaging markers involving the limbic-cingulate, cerebellar, and sensorimotor networks, and examined the available evidence regarding their potential associations with motor control and postural control related outcomes. *Methods:* This review was conducted according to a prospectively developed protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD420261369982). Searches of PubMed, Scopus, Web of Science, PEDro, and Google Scholar (2000–2025) identified quantitative human studies that investigated large-scale brain network alterations in chronic pain. Two reviewers independently performed the study selection, data extraction, methodological quality assessment using the McMaster Critical Review Form, and risk-of-bias assessment using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist. Owing to substantial clinical and methodological heterogeneity, a narrative synthesis was undertaken. *Results:* Eleven cross-sectional studies (805 participants) met the inclusion criteria. Chronic pain was

consistently associated with altered functional connectivity in insular and cingulate regions, often extending to sensorimotor, prefrontal, and parietal areas. These changes correlated with the pain intensity. Task-based findings showed increased engagement of emotion, salience, and motor inhibition regions during pain- or movement-related contexts. A small number of studies also reported motor-related outcomes, suggesting possible sensorimotor alterations; however, objective motor control and postural measures were inconsistently assessed across studies, limiting a direct evaluation of the relationship between brain network alterations and motor function. *Conclusion:* Current evidence supports a network-level perspective in which chronic pain is consistently associated with alterations in the limbic-cingulate, cerebellar, and sensorimotor networks. Nevertheless, direct evidence linking these neural alterations to objectively measured motor control and postural function remains limited and preliminary. Future longitudinal and mechanistic studies which integrate multimodal neuroimaging with standardized objective motor assessments are needed to clarify these relationships.

**Keywords:** chronic pain; motor control; sensorimotor network; functional connectivity; cerebellum

---

## 1. Introduction

Chronic pain is a highly prevalent and disabling condition that involves complex interactions between persistent peripheral nociceptive mechanisms and adaptive or maladaptive changes within the central nervous system (CNS). Increasing evidence indicates that maladaptive CNS plasticity contributes to pain persistence and disability, although the relative contribution of peripheral and central mechanisms varies across chronic pain conditions [1]. Given its high prevalence, long duration, and the complex relationship between tissue pathology and symptom severity, chronic pain provides an important model to study how peripheral and central mechanisms interact to influence pain persistence. Within traditional biomedical models, pain chronicity has often been primarily attributed to ongoing structural damage and biomechanical abnormalities, particularly in conditions where persistent peripheral pathology remains clinically relevant [2]. However, over the past two decades, evidence from human neuroimaging and translational neuroscience has demonstrated that chronic pain is associated with widespread and lasting changes within the CNS [3]. These findings suggest that understanding chronic pain requires consideration of both ongoing peripheral mechanisms and maladaptive changes within distributed brain networks [4]. In addition to the limbic and cingulate regions involved in affective and salience-related aspects of pain, somatosensory regions such as the secondary somatosensory cortex (SII) contribute to the sensory-discriminative processing and integration of nociceptive information [5,6]. Alterations within the limbic-cingulate network are increasingly understood as part of broader reorganization across large-scale brain networks rather than isolated regional changes [7]. In addition to cortico-limbic circuits, the cerebellum and cingulate cortex have been implicated as important nodes in distributed network dynamics in chronic musculoskeletal pain (CMP) [8,9]. Although historically associated with motor coordination and execution, cerebellar-cortical circuits are now recognized to contribute to predictive processing, error-based learning, and the integration of sensory, affective, and motor information [10,11]. These computational roles are particularly relevant in chronic pain conditions, where persistent nociceptive signaling and altered affective states may influence motor prediction and adaptive motor planning.

Alterations in brain network dynamics have important implications for motor behavior. Individuals with chronic musculoskeletal pain frequently demonstrate changes in motor performance, including altered postural control, increased movement variability, modified muscle activation patterns, and impaired anticipatory postural control [12–14]. In this context, motor control refers to the organization and regulation of movement at the level of coordination, timing, and variability of muscle and joint activity during functional tasks. Although these motor alterations have traditionally been attributed to peripheral injury, pain-related guarding, or biomechanical compensation strategies, their persistence beyond tissue healing and their weak association with structural pathology suggest additional central contributions. In particular, emerging evidence supports the involvement of altered functional interactions within sensorimotor and associated brain networks in shaping these motor changes [15–17], although causal mechanisms remain to be fully established.

Emerging evidence suggests that interactions among limbic, cerebellar, and sensorimotor networks may be associated with processes involved in motor planning and execution [18,19]. Within this framework, the heightened engagement of the limbic-cingulate network may influence movement selection through increased threat-related processing and avoidance-related biases, whereas disruptions in cerebellar-sensorimotor communication may affect predictive motor control and error-based adaptation. Together, these mechanisms may contribute to less flexible or more variable movement strategies [20]. However, it is important to emphasize that the current evidence is largely correlational. Most neuroimaging studies included in this review used cross-sectional designs and identified associations between alterations in large-scale brain networks and clinical characteristics rather than demonstrating directional or causal relationships. Consequently, these findings cannot determine whether network alterations precede changes in motor behavior, emerge as adaptations to persistent pain and altered movement strategies, or reflect shared influences such as symptom severity and psychological factors [17,21,22]. Therefore, longitudinal investigations which integrate repeated neuroimaging assessments with objective motor evaluations are required to clarify the temporal and mechanistic relationships between brain network alterations and motor control changes [23]. Accordingly, altered motor control should be considered a putative downstream correlate of distributed brain network reorganization rather than a fully established mechanistic endpoint [24].

Despite substantial progress in pain neuroscience, the relationship between chronic pain-related brain network alterations and motor behavior remains incompletely characterized. Existing studies have largely focused on pain perception, affective processing, or cognitive outcomes, whereas motor control research has often examined behavioral and biomechanical alterations without directly integrating the underlying neural mechanisms [18,25]. Consequently, relatively few studies have examined how alterations in large-scale brain networks relate to objectively measured motor or postural outcomes [18,19].

Although chronic musculoskeletal pain represents an important clinical population, neurobiological mechanisms linking persistent pain to altered movement behavior may also be relevant across other chronic pain conditions, including postsurgical pain, complex regional pain syndrome, neuropathic pain, and pelvic pain syndromes [17,26]. However, the heterogeneity of these conditions, including differences in pain etiology, chronicity, affected body systems, and symptom characteristics, introduces variability that must be carefully considered when interpreting cross-condition findings. Therefore, a systematic synthesis which integrates neuroimaging findings with motor control outcomes is needed to clarify convergent patterns of brain network alterations, identify condition-specific

variability, and define the current limitations of evidence linking neural reorganization to motor behavior [21,22].

Accordingly, this systematic review aims to synthesize evidence on alterations in large-scale brain networks in individuals with chronic pain, including functional connectivity, regional brain activity, and structural neuroimaging involving the limbic-cingulate, cerebellar, and sensorimotor networks, and to evaluate how these neural alterations are associated with motor performance and postural control.

## **2. Materials and methods**

This systematic review was conducted in 2025 to synthesize evidence on functional and structural neurophysiological alterations in large-scale brain networks, including limbic, cingulate, cerebellar, and sensorimotor systems, in individuals with chronic pain conditions, and to examine how these network-level alterations relate to motor control and postural control.

### *2.1. Protocol and registration*

This review was conducted according to a prospectively developed protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO; [CRD420261369982]). Reporting follows the PRISMA 2020 statement, including a PRISMA flow diagram to document the study identification and selection [27]. In anticipation of clinical and methodological heterogeneity across interventions, comparators, and outcomes, we prespecified a structured and transparent narrative synthesis, guided by the SWiM framework for systematic reviews without meta-analyses [28]. We assessed the certainty of the evidence for each prespecified critical outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [29]. As a quantitative meta-analysis was not possible due to significant clinical and methodological heterogeneity in pain conditions, neurophysiological methods, analytical pipelines and outcome reporting, certainty assessments were made based on the body of evidence affecting each outcome in a structured narrative synthesis. Because the included studies employed heterogeneous neuroimaging modalities (e.g., functional magnetic resonance imaging (MRI), structural MRI, positron emission tomography (PET), magnetoencephalography (MEG), and diffusion tensor imaging (DTI)), direct comparisons between imaging techniques were not performed. Instead, findings were synthesized according to the specific neurophysiological information provided by each modality. Disagreements were resolved by discussion and, where necessary, by a third reviewer (Supplementary File 1).

### *2.2. Search strategy & eligibility criteria*

In addition to databases hosted by EBSCO (accessed via institutional subscription), a systematic literature search was conducted across major international bibliographic databases relevant to pain neuroscience, neuroimaging, rehabilitation, and motor control. These included PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Physiotherapy Evidence Database (PEDro). To capture pertinent grey literature, the search was supplemented by screening Google Scholar results. Previous methodological studies and many systematic reviews commonly recommend screening the first 100 Google Scholar results sorted by relevance as a pragmatic approach to identify grey literature [30,31]. However, to further maximize the search comprehensiveness and minimize the possibility of missing

eligible studies, we extended the screening to the first 200 results sorted by relevance for each search query, regardless of the total number of records retrieved. Additionally, the reference lists of all included studies were manually screened to identify any further relevant publications that may not have been captured through the electronic search. The search was limited to studies published between 1 January 2000 and 31 December 2025. This time frame was selected because substantial advances in neuroimaging techniques and analytical methods have occurred since the early 2000s, allowing more reliable investigation of large-scale brain networks. Restricting the search to this period ensured the inclusion of contemporary studies that employed modern imaging technologies and current methodological approaches.

Search strategies combined controlled vocabulary terms (e.g., medical subject headings (MeSH) in PubMed) with free-text keywords aligned with the main conceptual domains of the review. These included four key domains: (1) chronic pain conditions (e.g., chronic musculoskeletal pain, low back pain, neck pain, fibromyalgia, temporomandibular myofascial pain, myofascial pain syndrome, chronic postsurgical pain, complex regional pain syndrome, pelvic pain syndrome/chronic prostatitis, and chronic ankle pain/instability); (2) brain regions and large-scale networks implicated in pain processing (e.g., anterior cingulate cortex [ACC], posterior cingulate cortex [PCC], insula, amygdala, hippocampus; salience network, default mode network, and sensorimotor network); (3) neuroimaging and neurophysiological modalities (e.g., resting-state and task-based fMRI, structural MRI, DTI, electroencephalogram (EEG)/MEG, PET/ single-photon emission computed tomography (SPECT)); and (4) movement-related outcomes (e.g., motor control, postural control, gait, motor variability, and motor planning).

Boolean operators were applied to structure the search strategy, with “AND” used to combine major conceptual domains and “OR” used to include synonyms and related terms. Where appropriate, database-specific indexing fields were used (e.g., MeSH term mapping in PubMed, TITLE-ABS-KEY in Scopus, and TS fields in Web of Science Core Collection). No additional restrictions were applied beyond the predefined publication date range. To further enhance the search completeness, reference lists of the included review articles were manually screened to identify additional potentially eligible studies not captured by the electronic database searches. Any records identified through this supplementary process were screened using the same predefined eligibility criteria. Full database-specific search strings, controlled vocabulary terms, and applied filters are provided in Supplementary File 2.

Inclusion and exclusion criteria were predefined using the PICOS framework in accordance with PRISMA 2020 and Cochrane guidelines. Table 1 summarizes the PICOS eligibility criteria. The selection criteria for this systematic review were designed to identify studies that examined neurophysiological and neuroimaging changes within cingulate–limbic and related large-scale brain networks in individuals with chronic musculoskeletal pain, and their association with motor control–related outcomes. The motor control outcomes were extracted when available. Studies without motor outcomes were not excluded a priori; however, they were included only in the synthesis of neural network alterations and not in analyses relating brain changes to motor behavior. Accordingly, studies were eligible if they employed quantitative research designs, including cross-sectional, case-control, cohort, quasi-experimental, or randomized controlled trial designs, and involved human participants of either sex. The study population included individuals with chronic musculoskeletal pain, such as chronic low back pain, chronic neck pain, or other chronic regional or widespread musculoskeletal pain conditions. Studies were included regardless of whether a pain-free control group was present, provided that the relevant neurophysiological outcomes were reported. Studies without pain-free

control groups were considered eligible because the primary objective of this review was to synthesize evidence regarding neurophysiological alterations and their associations with clinical or motor-related outcomes in chronic pain. In studies comparing different chronic pain subgroups (e.g., acute versus chronic pain or high versus low symptom severity), within-condition comparisons may provide valuable information regarding mechanisms underlying pain chronicity and network reorganization, even in the absence of healthy controls. Therefore, these studies were only included to contribute evidence regarding neural alterations and were cautiously interpreted because they do not permit the attribution of findings exclusively to chronic pain relative to pain-free individuals. Eligible studies were required to employ at least one objective neurophysiological or neuroimaging method capable of assessing brain structure, function, or connectivity within cingulate–limbic and related large-scale networks implicated in pain processing and motor integration. These included, but were not limited to, functional measures of brain activity and connectivity derived from resting-state or task-based fMRI, structural MRI metrics (e.g., cortical thickness or voxel-based morphometry), white matter microstructure assessed using DTI, electrophysiological recordings from EEG or MEG, and metabolic or receptor-based measures obtained from PET or SPECT imaging. Only full-text articles published in peer-reviewed journals between January 2000 and December 31, 2025, and written in English were included. Review articles (including systematic reviews, meta-analyses, and scoping reviews), study protocols, case reports, letters to the editor, theses, abstracts, and conference proceedings were excluded; additionally, studies were excluded if they did not report eligible neurophysiological or neuroimaging outcomes related to cingulate-limbic or associated brain networks, including objective measures of brain structure, function, or connectivity. Studies exclusively relying on self-reported outcomes (e.g., questionnaire-based assessments without neurophysiological measures) were also excluded. Importantly, studies solely conducted on healthy participants using experimentally induced pain paradigms (e.g., capsaicin, thermal, ischemic, or pressure pain models) were excluded, as the focus of this review was on chronic clinical pain conditions. Finally, studies were excluded if the full text was unavailable or if the report lacked sufficient methodological or outcome detail for data extraction, or if they fell outside the predefined language and time restrictions.

Title and abstract screening, followed by full-text eligibility assessment, was conducted independently by two reviewers. Any discrepancies were resolved through discussion and consensus. Where consensus could not be reached, a third reviewer was consulted to adjudicate disagreements.

**Table 1.** PICOS eligibility criteria.

| Component           | Inclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population<br>(P)   | Individuals with chronic pain in any setting (e.g., community, clinic, laboratory), including musculoskeletal pain (e.g., back pain, neck pain, temporomandibular joint disorder, myofascial pain), chronic post-surgical pain, complex regional pain syndrome (CRPS), neuropathic pain, and pelvic pain syndromes (e.g., CP/CPPS). No gender restriction. Studies conducted in healthy participants with experimental pain were excluded. |
| Intervention<br>(I) | The presence of chronic pain as the primary exposure provided that eligible neurophysiological outcomes were measured. Eligible studies were those that measured neurophysiological changes in the limbic-cingulate networks and/or adjacent networks (e.g., ACC/PCC, insula, amygdala, hippocampus; salience/DMN/sensorimotor networks).                                                                                                  |
| Comparison<br>(C)   | Healthy controls without pain; alternative clinical comparison groups; chronic pain subgroups (e.g., higher vs. lower disability/fear). Studies without comparisons were only eligible if they reported extractable neurophysiological associations. Studies without pain-free control groups were eligible if they provided relevant neurophysiological outcomes contributing to the understanding of chronic pain mechanisms.            |
| Outcomes<br>(O)     | At least one objective neurophysiological/neuroimaging outcome reflecting brain structure, function, or connectivity in limbic-cingulate and related brain networks, assessed using methods such as resting-state/task fMRI, structural MRI (cortical thickness/VBM), DTI, EEG/MEG, PET/SPECT.                                                                                                                                             |
| Study design<br>(S) | Quantitative experimental designs including cross-sectional, case-control, cohort, laboratory-based observational studies, quasi-experimental studies, and randomized controlled trials. Only full-text peer-reviewed articles published in English between 1 January 2000 and 31 December 2025 were included.                                                                                                                             |

### 2.3. Selection process and data extraction

All retrieved records were imported into EndNote 2025 (Clarivate Analytics), where duplicates were identified and removed using both automated and manual procedures prior to screening. The study selection was conducted in two sequential stages by two independent reviewers: (1) title and abstract screening based on predefined eligibility criteria (PICOS), followed by (2) full-text assessment for final inclusion. The reasons for exclusion at the full-text stage were systematically recorded and categorized, and the overall selection process was summarized using a PRISMA 2020 flow diagram. Data extraction was conducted using a standardized data extraction form that was pilot-tested on a subset of included studies to ensure consistency and completeness. The extracted data were recorded in a predefined evidence table and included the following items: (1) author(s), journal, and year of publication; (2) study design; (3) study objectives; (4) sample characteristics (including sample size, sex distribution, and age); (5) study groups and comparators (if applicable); (6) study duration and timing of assessments; (7) assessment instruments and measurement methods; (8) neurophysiological or neuroimaging measures, including brain regions or networks assessed; (9) key variables of interest; and (10) main findings relevant to the review objectives. Disagreements primarily concerned study eligibility during full-text screening (e.g., uncertainty regarding whether specific neuroimaging outcomes met the predefined inclusion criteria) and were resolved through discussion until a consensus was reached. When a consensus could not be achieved, a third reviewer was consulted to make the final decision.

## 2.4. Quality assessment & risk of bias

The methodological quality of the included studies was independently assessed by two reviewers using the McMaster Critical Review Form for Quantitative Studies [32]. This standardized appraisal tool includes 17 criteria designed to evaluate key methodological domains, such as clarity of study objectives, appropriateness of study design, sampling strategy, validity and reliability of outcome measures, intervention characteristics (where applicable), statistical analyses, and the appropriateness of conclusions. The assessment was conducted in accordance with the McMaster guidelines for quantitative research (Table 2). Each item was dichotomously scored, with a score of “1” indicating that the criterion was met and “0” indicating that it was not met or insufficiently reported. The total scores were calculated by summing the individual item scores. For interpretative purposes, the overall methodological quality was categorized as poor (0–8), fair (9–10), good (11–12), very good (13–14), or excellent (15–16). These categories were descriptively used to facilitate the comparison across studies rather than as strict thresholds for study inclusion or exclusion. Item 3 of the checklist, which relates to study design, was separately reported in the results Table 3 to provide a clear description of the study characteristics. Because all included studies employed the same cross-sectional design, this item showed no variability across studies and therefore had no discriminatory value for assessing methodological quality. Including it in the total quality score would have assigned the same score to every study without contributing to a meaningful differentiation. Therefore, Item 3 was excluded from the total quality score and was marked as “not applicable” (N/A) for the score calculation. Discrepancies in the quality ratings between the two reviewers were resolved through discussion and consensus, with consultations from a third reviewer when necessary.

**Table 2.** Items and descriptions of the McMaster Critical Review Form for quantitative studies.

| No. | Item: Description                                                                     |
|-----|---------------------------------------------------------------------------------------|
| 1   | Objective: Was the purpose clearly stated?                                            |
| 2   | Literature Review: Was the relevant background literature reviewed?                   |
| 3   | Study Design: What type of study design was used?                                     |
| 4   | Sample Size Justification: Was the method for determining sample size justified?      |
| 5   | Sample Description: Was the sample described in sufficient detail?                    |
| 6   | Outcome Measure Reliability: Were the outcome measures reliable?                      |
| 7   | Outcome Measure Validity: Were the outcome measures valid?                            |
| 8   | Intervention Description: Was the intervention described in sufficient detail?        |
| 9   | Contamination: Was contamination avoided?                                             |
| 10  | Co-intervention: Was co-intervention avoided?                                         |
| 11  | Statistical Significance: Were results reported in terms of statistical significance? |
| 12  | Statistical Analysis: Were the statistical analysis methods appropriate?              |
| 13  | Clinical Importance: Was clinical importance reported?                                |
| 14  | Withdrawal Criteria: Were withdrawal criteria reported?                               |
| 15  | Conclusions: Were conclusions appropriate given the methods and results?              |
| 16  | Clinical Implications: Were the clinical implications of the findings reported?       |
| 17  | Study Limitations: Were major limitations or potential sources of bias reported?      |

**Table 3.** Characteristics of studies.

| Author,<br>Journal, Year                                             | Study<br>Design     | Objective                                                                                                                                                                                                                                              | Sample Size,<br>Sex, and Age         | Groups<br>(Experimental<br>group & Control<br>group)                                                                              | Study<br>Duration                                                                                                                                                               | Assessment Tools<br>& Measurement<br>Instruments                                                                                                                                                                                                              | Neurophysiologic<br>al Brain Regions<br>Examined                                                                                                                                                                                                  | Measured Variables                                                                                                                  | Main Results                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ching et al.,<br>Frontiers in<br>Human<br>Neuroscience,<br>2018 [33] | Cross-<br>sectional | To examine<br>alterations in<br>resting-state<br>insular<br>functional<br>connectivity<br>before and after<br>acute heat pain<br>stimulation in<br>individuals<br>with chronic<br>post-<br>hysterectomy<br>pain compared<br>with pain-free<br>controls | N = 33, F,<br>Age = 40–55            | Experimental<br>group: Chronic<br>post-<br>hysterectomy<br>pain group versus<br>hysterectomy<br>control group:<br>Healthy control | From<br>preoperative<br>assessment to<br>four-month<br>postoperative<br>follow-up;<br>magnetic<br>resonance<br>imaging<br>conducted one<br>to two months<br>after follow-<br>up | Resting-state<br>functional<br>magnetic<br>resonance<br>imaging; tonic heat<br>pain stimulation<br>using a<br>thermosensory<br>analyzer; pain<br>catastrophizing<br>scale; temporal<br>summation testing;<br>continuous visual<br>analog pain rating<br>scale | Sensorimotor<br>subregion of the<br>insular cortex;<br>chemosensory<br>subregion of the<br>insular cortex;<br>angular gyrus;<br>middle occipital<br>gyrus; large-scale<br>salience-related<br>cortical networks<br>involved in pain<br>processing | Functional<br>connectivity<br>between insular<br>subregions and<br>whole-brain cortical<br>areas; clinical pain<br>intensity scores | Healthy controls<br>demonstrated increased<br>insular functional<br>connectivity following<br>pain stimulation,<br>whereas patients with<br>chronic post-<br>hysterectomy pain<br>showed absent<br>connectivity modulation;<br>higher baseline insular<br>connectivity and reduced<br>post-stimulation changes<br>were associated with<br>greater chronic pain<br>severity |
| Freund et al.,<br>The Clinical<br>Journal of<br>Pain, 2010<br>[34]   | Cross-<br>sectional | To investigate<br>differences in<br>cerebral pain<br>processing<br>between<br>patients with                                                                                                                                                            | N = 25,<br>(10F,15M),<br>Age = 25–64 | Experimental<br>group: Complex<br>regional pain<br>syndrome type<br>one group;<br>Control group:                                  | Single<br>experimental<br>session                                                                                                                                               | Functional<br>magnetic<br>resonance<br>imaging; graded<br>electrical pain<br>stimulation;                                                                                                                                                                     | Anterior insular<br>cortex; posterior<br>insular cortex;<br>opercular cortex<br>including<br>secondary                                                                                                                                            | Blood oxygen level<br>dependent brain<br>activation patterns<br>during graded<br>painful stimulation;<br>pain perception            | Patients with complex<br>regional pain syndrome<br>showed stronger<br>posterior cingulate cortex<br>activation and reduced<br>opercular activation                                                                                                                                                                                                                         |

|                                                    |                 |                                                                                                                           |                                  |                                                                                                        |                                                                                |                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                        |                                                                                                            |                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    |                 | complex regional pain syndrome type one and healthy individuals during electrically induced pain                          |                                  | healthy control group                                                                                  |                                                                                | numerical pain rating scale; psychophysical pain discrimination task                                                                                                                                                                                                            | somatosensory cortex; posterior cingulate cortex; caudate nucleus; primary somatosensory cortex; prefrontal cortex                                                                                                                                                     | ratings                                                                                                    | during painful stimulation compared with controls; findings indicate a shift from sensory-discriminative processing toward affective and motor-inhibitory pain processing                                                                                                                                 |
| Gao et al.,<br>Journal of Pain Research, 2025 [35] | Cross-sectional | To investigate structural and functional brain alterations associated with the transition from acute to chronic neck pain | N = 175, (113F,62M), Age = 18–30 | Experimental group: Acute neck pain group; Control group: chronic neck pain group (No healthy control) | Single assessment during clinical presentation between March 2023 and May 2024 | Resting-state functional magnetic resonance imaging; three-dimensional T1-weighted structural magnetic resonance imaging; cortical thickness analysis using Freesurfer software; low-frequency amplitude analysis using DPARSF software; visual analog scale for pain intensity | Rostral middle frontal cortex; isthmus cingulate cortex; superior frontal cortex; precuneus; dorsolateral superior frontal gyrus; postcentral gyrus; angular gyrus; middle frontal gyrus; opercular part of the inferior frontal gyrus; limbic and prefrontal networks | Cortical thickness values; amplitude of low-frequency spontaneous neural activity; clinical pain intensity | Patients with chronic neck pain showed increased cortical thickness in prefrontal, cingulate, and precuneus regions and altered resting-state neural activity in prefrontal, sensorimotor, and limbic areas, indicating that dysfunction of limbic–prefrontal networks is associated with pain chronicity |

|                                                        |                     |                                                                                                                                                                                                                                     |                                      |                                                                                                                                                                                                                                  |                                     |                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|--------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gracely et al.,<br>Brain, 2004<br>[36]                 | Cross-<br>sectional | To examine the<br>association<br>between pain<br>catastrophizing<br>and neural<br>responses to<br>experimentally<br>induced<br>pressure pain in<br>individuals<br>with<br>fibromyalgia,<br>independent of<br>depressive<br>symptoms | N = 29,<br>(19F,10M),<br>Age = 18–60 | Experimental<br>group: High pain<br>catastrophizing<br>group; Control<br>group: low pain<br>catastrophizing<br>group, based on<br>residual<br>catastrophizing<br>scores controlling<br>for depression<br>(No healthy<br>control) | Two-day<br>experimental<br>protocol | Functional<br>magnetic<br>resonance<br>imaging;<br>controlled pressure<br>pain stimulation<br>using hydraulic<br>pressure device;<br>Coping Strategies<br>Questionnaire<br>catastrophizing<br>subscale; Center<br>for<br>Epidemiological<br>Studies Depression<br>Scale; McGill Pain<br>Questionnaire<br>short form; visual<br>analog pain rating<br>scales | Anterior cingulate<br>cortex (rostral and<br>dorsal divisions);<br>insular cortex;<br>primary<br>somatosensory<br>cortex; secondary<br>somatosensory<br>cortex;<br>dorsolateral<br>prefrontal cortex;<br>medial frontal<br>cortex; inferior<br>parietal lobule;<br>posterior cingulate<br>cortex;<br>cerebellum;<br>claustrum;<br>lentiform nuclei;<br>thalamus | Blood oxygen level<br>dependent neural<br>activation during<br>pressure pain;<br>clinical pain<br>intensity and<br>affective pain<br>ratings;<br>catastrophizing<br>scores | Higher pain<br>catastrophizing was<br>associated with increased<br>activation in brain<br>regions related to<br>attention, emotional<br>processing, and motor<br>control, including the<br>anterior cingulate cortex,<br>dorsolateral prefrontal<br>cortex, cerebellum, and<br>claustrum; individuals<br>with high catastrophizing<br>showed greater<br>secondary<br>somatosensory cortex<br>activation and unique<br>anterior cingulate and<br>lentiform activation<br>compared with low<br>catastrophizing<br>individuals |
| Kutch et al.,<br>NeuroImage:<br>Clinical, 2015<br>[37] | Cross-<br>sectional | To determine<br>whether<br>resting-state<br>brain networks<br>controlling<br>pelvic floor                                                                                                                                           | N = 55, M,<br>Age = 40–46            | Experimental<br>group: Chronic<br>prostatitis and<br>chronic pelvic<br>pain syndrome<br>group; Control                                                                                                                           | Single-session                      | Resting-state<br>functional<br>magnetic<br>resonance<br>imaging; task-<br>based functional                                                                                                                                                                                                                                                                  | Pelvic floor motor<br>region of the<br>primary motor<br>cortex; hand<br>motor region of<br>the primary motor                                                                                                                                                                                                                                                    | Functional<br>connectivity<br>strength between<br>motor cortical<br>regions and whole-<br>brain areas; pain                                                                | Men with chronic<br>prostatitis and chronic<br>pelvic pain syndrome<br>showed significantly<br>reduced functional<br>connectivity between the                                                                                                                                                                                                                                                                                                                                                                               |

|                          |                 |                                                                                                                                                                           |                                |                                                                                          |                |                                                                                                                                                                                                  |                                                                                                                                                                                                                                                       |                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                            |
|--------------------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |                 | muscles show altered functional connectivity in men with chronic prostatitis and chronic pelvic pain syndrome                                                             |                                | group: Healthy control                                                                   |                | magnetic resonance imaging for motor region localization; Genitourinary Pain Index questionnaire; Brief Pain Inventory pain mapping                                                              | cortex; posterior insular cortex; superior temporal gyrus; inferior frontal gyrus; widespread insular subregions identified through atlas-based connectivity analysis                                                                                 | intensity and symptom severity scores                                                                                                                    | pelvic floor motor cortex and the right posterior insular cortex compared with healthy controls; reduced motor–insula connectivity was strongly associated with greater pain intensity, indicating disrupted integration of viscerosensory and motor control processes                                                     |
| Niddam et al., 2008 [38] | Cross-sectional | To investigate abnormal central pain processing and hyperalgesia in patients with myofascial pain syndrome during stimulation of hypersensitive myofascial trigger points | N = 30, (18F,12M), Age = 20–50 | Experimental group: Myofascial pain syndrome group; Control group: healthy control group | Single-session | Event-related functional magnetic resonance imaging; intramuscular electrostimulation using needle electrodes; numerical descriptor scale for pain intensity; pressure pain threshold assessment | Primary somatosensory cortex; secondary somatosensory cortex; inferior parietal lobule; anterior insular cortex; middle insular cortex; posterior insular cortex; anterior cingulate cortex; posterior cingulate cortex; hippocampus; parahippocampal | Blood oxygen level dependent neural activation during painful intramuscular stimulation; pain intensity ratings; pressure and electrical pain thresholds | Compared with healthy controls, patients with myofascial pain syndrome exhibited hyperalgesia accompanied by enhanced activation in somatosensory and limbic regions, including the primary and secondary somatosensory cortices and anterior insula, as well as suppressed activity in the dorsal hippocampus, indicating |

|                                                    |                     |                                                                                                                                                                   |                                       |                                                                                                                  |                                   |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                 |                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    |                     |                                                                                                                                                                   |                                       |                                                                                                                  |                                   |                                                                                                                                                                                                                                                             | gyrus; thalamus;<br>claustrum;<br>cerebellum;<br>primary motor<br>cortex                                                                                                                                                        |                                                                                                                                                                         | altered central processing<br>of pain and stress-related<br>modulation                                                                                                                                                                                                                                                                                                                                                                             |
| Qiu et al.,<br>Scientific<br>Reports, 2025<br>[39] | Cross-<br>sectional | To investigate<br>alterations in<br>resting-state<br>brain activity<br>and functional<br>connectivity<br>associated with<br>chronic non-<br>specific neck<br>pain | N = 140,<br>(74F,66M),<br>Age = 20–70 | Experimental<br>group: Chronic<br>non-specific neck<br>pain group;<br>Control group:<br>healthy control<br>group | Single-session                    | Resting-state<br>functional<br>magnetic<br>resonance<br>imaging;<br>amplitude of low-<br>frequency<br>fluctuation<br>analysis; regional<br>homogeneity<br>analysis;<br>functional<br>connectivity<br>analysis; visual<br>analog scale for<br>pain intensity | Precuneus;<br>posterior cingulate<br>cortex; anterior<br>cingulate cortex;<br>medial prefrontal<br>cortex; insular<br>cortex; postcentral<br>gyrus; superior<br>frontal gyrus;<br>default mode<br>network and<br>limbic network | Amplitude of<br>spontaneous neural<br>activity; regional<br>synchronization of<br>neural signals;<br>functional<br>connectivity<br>strength; clinical<br>pain intensity | Patients with chronic<br>non-specific neck pain<br>showed decreased<br>spontaneous neural<br>activity and regional<br>homogeneity in the<br>precuneus and posterior<br>cingulate cortex, along<br>with altered functional<br>connectivity between<br>limbic and default mode<br>network regions; these<br>neural alterations were<br>significantly associated<br>with higher pain<br>intensity, indicating<br>disrupted central pain<br>modulation |
| Taylor et al.,<br>PLOS ONE,<br>2015 [40]           | Cross-<br>sectional | To investigate<br>central neural<br>processing of<br>chronic<br>musculoskeletal                                                                                   | N = 37,<br>(24F,13M),<br>Age = 18–65  | Experimental<br>group: Chronic<br>musculoskeletal<br>pain group;<br>Control group:                               | Single<br>experimental<br>session | Functional<br>magnetic<br>resonance<br>imaging; Picture<br>and Imagination                                                                                                                                                                                  | Insular cortex;<br>anterior cingulate<br>cortex; posterior<br>cingulate cortex;<br>precuneus;                                                                                                                                   | Blood oxygen level<br>dependent neural<br>activation during<br>imagined and<br>observed                                                                                 | Patients with chronic<br>musculoskeletal pain<br>showed significantly<br>greater neural activation<br>in limbic, cingulate, and                                                                                                                                                                                                                                                                                                                    |

|                                                                         |                     |                                                                                                                                                                                                  |                                       |                                                                                                                              |                |                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                     |                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                         |                     | pain during<br>imagined and<br>observed<br>physical<br>activities<br>associated with<br>fear and pain                                                                                            |                                       | healthy control<br>group                                                                                                     |                | Task involving<br>observation and<br>imagination of<br>daily activities;<br>self-reported<br>anxiety ratings<br>during task; post-<br>scan pain intensity<br>ratings                                       | thalamus;<br>amygdala;<br>orbitofrontal<br>cortex;<br>paracingulate<br>cortex;<br>supplementary<br>motor cortex;<br>inferior and<br>superior parietal<br>cortices; putamen;<br>pallidum; caudate<br>nucleus;<br>substantia nigra<br>and ventral<br>tegmental region | movement; task-<br>related anxiety<br>ratings; post-task<br>pain intensity                                                                                                      | sensorimotor-related<br>regions compared with<br>healthy controls,<br>accompanied by higher<br>anxiety during task<br>performance and higher<br>perceived pain after<br>scanning, indicating<br>altered affective–<br>motivational and<br>cognitive processing of<br>movement-related pain                        |
| Wang et al.,<br>Frontiers in<br>Molecular<br>Neuroscience,<br>2023 [41] | Cross-<br>sectional | To investigate<br>differences in<br>resting-state<br>functional<br>connectivity<br>between pain-<br>related brain<br>regions and<br>ankle motor-<br>related brain<br>regions in<br>patients with | N = 167,<br>(82F,85M),<br>Age = 18–75 | Experimental<br>group: Chronic<br>ankle pain or<br>chronic ankle<br>instability groups;<br>Control group:<br>healthy control | Single-session | Resting-state<br>functional<br>magnetic<br>resonance<br>imaging; region-<br>of-interest based<br>functional<br>connectivity<br>analysis; clinical<br>questionnaires<br>including Tegner<br>Activity Rating | Cingulate motor<br>area; insular<br>cortex; primary<br>sensorimotor<br>cortex;<br>supplementary<br>motor area;<br>premotor cortex;<br>secondary<br>somatosensory<br>cortex; basal<br>ganglia including                                                              | Functional<br>connectivity<br>strength between<br>pain-related and<br>ankle motor-related<br>brain regions;<br>clinical motor<br>function scores;<br>physical activity<br>level | Patients with chronic<br>ankle pain and chronic<br>ankle instability showed<br>significantly reduced<br>functional connectivity<br>between the cingulate<br>motor area and the<br>insular cortex compared<br>with healthy controls in<br>both datasets; reduced<br>connectivity was<br>positively correlated with |

|                                 |                 |                                                                                                                                            |                        |                                                                                                           |                |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                        |                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------|-----------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 |                 | chronic ankle instability and to examine the relationship between pain-related neuroplasticity and motor function                          |                        |                                                                                                           |                | Scale and American Orthopedic Foot and Ankle Society score                                                                                                                                                                  | putamen; Rolandic operculum; cerebellum; pain-related cortical and subcortical regions derived from meta-analytic pain maps                                                                                                                                                                            |                                                                                                                 | lower physical activity levels, indicating maladaptive neuroplasticity linking pain processing and impaired motor control                                                                                                                                                                                                                                                                 |
| Younger et al., Pain, 2010 [42] | Cross-sectional | To investigate whether chronic myofascial temporomandibular pain is associated with structural abnormalities in the central nervous system | N = 29, F, Age = 23–61 | Experimental group: Chronic myofascial temporomandibular pain group; Control group: healthy control group | Single-session | High-resolution T1-weighted structural magnetic resonance imaging; voxel-based morphometry analysis; numerical rating scale for jaw pain severity; pressure algometry for pain tolerance; clinical pain duration assessment | Trigeminal sensory and motor nuclei in the pons; ventral posterior and ventral lateral thalamic nuclei; primary somatosensory cortex; anterior insular cortex; inferior frontal gyrus; posterior putamen; globus pallidus; rostral anterior cingulate cortex; posterior cingulate cortex; hippocampus; | Regional gray matter volume; self-reported jaw pain severity; pressure pain tolerance; duration of chronic pain | Patients with chronic myofascial temporomandibular pain showed increased gray matter volume in trigeminothalamocortical and limbic regions and decreased gray matter volume in the primary somatosensory cortex compared with controls; pain severity, pain tolerance, and pain duration were differentially associated with gray matter alterations in cingulate, limbic, brainstem, and |

|                                                      |                     |                                                                                                                                                                                                                                             |                                      |                                                                                                   |                               |                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      |                     |                                                                                                                                                                                                                                             |                                      |                                                                                                   |                               |                                                                                                                                                                                                                                                   | midbrain<br>including<br>substantia nigra;<br>cerebellum                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                     | cerebellar regions,<br>indicating central<br>neuroplastic changes<br>related to chronic pain                                                                                                                                                                                                                                                                                                                                                 |
| Smith et al.,<br>Journal Pre-<br>proof, 2025<br>[43] | Cross-<br>sectional | Comparing<br>brain function<br>in young adults<br>with and<br>without a<br>history of<br>chronic low<br>back pain and<br>determining the<br>relationships<br>between brain<br>function, pain,<br>and postural<br>control<br>characteristics | N = 85,<br>(49F,50M),<br>Age = 18–35 | Experimental<br>group: Group of<br>people with back<br>pain; Control<br>group: healthy<br>control | Two<br>laboratory<br>sessions | Functional<br>magnetic<br>resonance imaging<br>(fMRI), Surface<br>electromyography,<br>Force plate, Visual<br>Analogue Scale<br>(VAS), Oswestry<br>Disability Index,<br>Fear-Avoidance<br>Beliefs<br>Questionnaire,<br>Physical Activity<br>Scale | Precentral gyrus<br>and postcentral<br>gyrus,<br>supplementary/pre<br>motor areas,<br>cingulate cortex<br>(anterior, middle,<br>posterior),<br>superior/inferior<br>parietal lobule,<br>angular gyrus,<br>supramarginal<br>gyrus, precuneus,<br>paracentral lobule,<br>basal ganglia<br>(putamen, globus<br>pallidus, caudate),<br>cerebellum<br>(vermis and motor<br>observations) | Brain activity,<br>postural control,<br>muscle EMG,<br>vertical ground<br>reaction force, pain<br>characteristics: pain<br>intensity, pain<br>duration, pain<br>impact, pain-related<br>disability, fear of<br>pain | Abnormalities in brain<br>sensorimotor function<br>are present in young<br>adults with a history of<br>low back pain, even<br>when they are<br>asymptomatic. These<br>changes are specific to<br>tasks requiring<br>lumbopelvic postural<br>control and are<br>associated with clinical<br>features of pain. The<br>findings suggest that<br>such neural changes may<br>serve as early biomarkers<br>for risk of developing<br>chronic pain. |

Note: F = Female, M = Male, N = Number of participants.

The risk of bias of the included cross-sectional studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies (Table 4) [44]. This tool was selected due to its suitability for evaluating observational study designs commonly used in neuroimaging and pain research. Two reviewers independently evaluated each study across eight JBI domains: (1) clarity of inclusion criteria; (2) adequacy of description of participants and study setting; (3) validity and reliability of exposure measurement; (4) use of objective and standardized criteria for condition measurement; (5) identification of potential confounding factors; (6) strategies to address confounding; (7) validity and reliability of outcome measurement; and (8) appropriateness of statistical analysis. Each item was rated as “yes,” “no,” “unclear,” or “not applicable,” in accordance with JBI guidance. Discrepancies between the reviewers were resolved through discussions and consensus. Where agreement could not be reached, a third reviewer was consulted for adjudication. For interpretative purposes, studies were not assigned an overall numerical score; instead, risk of bias judgments were considered at the domain level to avoid oversimplification. The results of the risk of bias assessment are presented in tabular form (Table 5), and the results of the methodological quality assessment are visually summarized in Figure 1. This figure was prepared by the authors based on the overall JBI Critical Appraisal Checklist ratings of all included studies and provides an overall summary of the risk of bias judgments for each assessment domain (Q1–Q8).

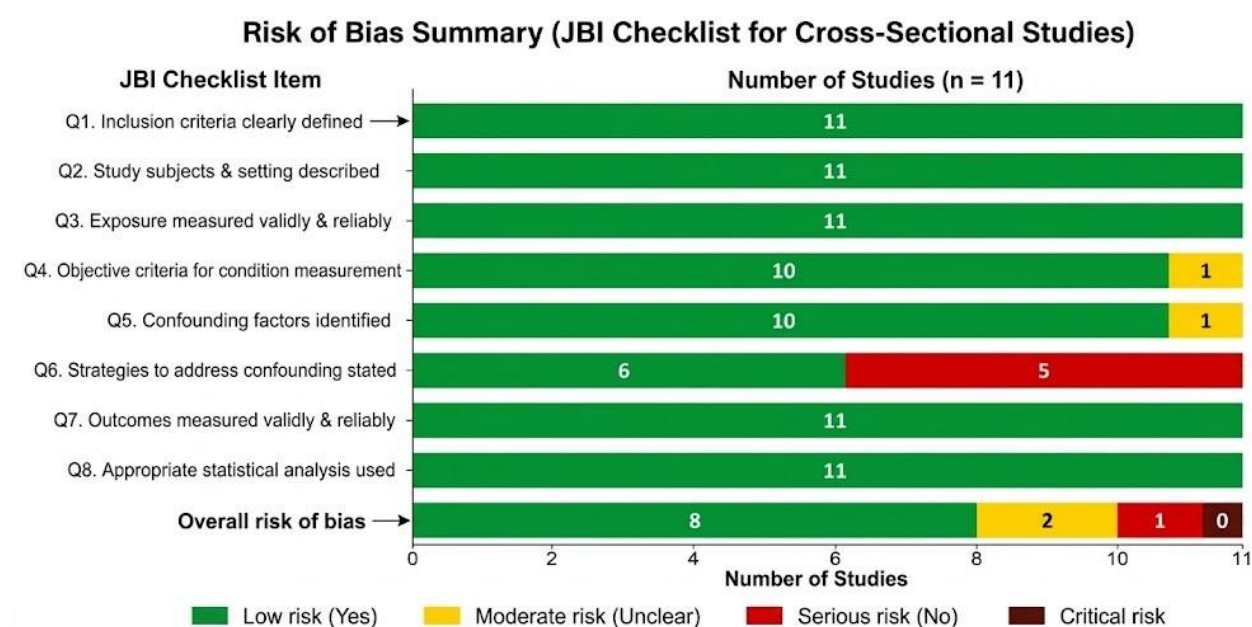


**Figure 1.** Summary of risk of bias judgments across included cross-sectional studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist (Q1–Q8).

**Table 4.** Joanna Briggs Institute (JBI) critical appraisal checklist for cross sectional studies.

| NO. | Questions                                                                | Yes                      | NO                       | Unclear                  | Not applicable           |
|-----|--------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Q1  | Were the criteria for inclusion in the sample clearly defined?           | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q2  | Were the study subjects and the setting described in detail?             | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q3  | Was the exposure measured in a valid and reliable way?                   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q4  | Were objective, standard criteria used for measurement of the condition? | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q5  | Were confounding factors identified?                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q6  | Were strategies to deal with confounding factors stated?                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q7  | Were the outcomes measured in a valid and reliable way?                  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Q8  | Was appropriate statistical analysis used?                               | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Table 5.** Joanna Briggs Institute (JBI) Critical Appraisal Checklist.

| NO. | Author/Year               | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|-----|---------------------------|----|----|----|----|----|----|----|----|
| 1   | Ching et al., 2018 [33]   | Y  | Y  | Y  | Y  | U  | N  | Y  | Y  |
| 2   | Freund et al., 2010 [34]  | Y  | Y  | Y  | Y  | Y  | N  | Y  | Y  |
| 3   | Gao et al., 2025 [35]     | Y  | Y  | Y  | Y  | Y  | N  | Y  | Y  |
| 4   | Gracely et al., 2004 [36] | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| 5   | Kutch et al., 2015 [37]   | Y  | Y  | Y  | Y  | Y  | N  | Y  | Y  |
| 6   | Niddam et al., 2008 [38]  | Y  | Y  | Y  | U  | Y  | Y  | Y  | Y  |
| 7   | Qiu et al., 2025 [39]     | Y  | Y  | Y  | Y  | Y  | N  | Y  | Y  |
| 8   | Taylor et al., 2015 [40]  | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| 9   | Wang et al., 2023 [41]    | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| 10  | Younger et al., 2010 [42] | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |
| 11  | Smith et al., 2025 [43]   | Y  | Y  | Y  | Y  | Y  | Y  | Y  | Y  |

Note: Q1 = Were the criteria for inclusion in the sample clearly defined, Q2 = Were the study subjects and the setting described in detail, Q3 = Was the exposure measured in a valid and reliable way, Q4 = Were objective, standard criteria used for measurement of the condition, Q5 = Were confounding factors identified, Q6 = Were strategies to deal with confounding factors stated, Q7 = Were the outcomes measured in a valid and reliable way? Q8 = Was appropriate statistical analysis used? Yes = Y, NO = N, Unclear = U.

### 3. Results

#### 3.1. Study selection

The systematic search identified a total of 480 records. After removal of duplicates, 417 unique records remained for screening. Following the title and abstract screening, 342 records were excluded based on the predefined eligibility criteria. The full texts of the remaining 75 articles were assessed for eligibility, of which 64 were excluded. The primary reasons for full-text exclusion included unavailability of full text ( $n = 12$ ), absence of eligible neuroimaging or neurophysiological outcomes ( $n = 10$ ), use of experimentally induced pain models in healthy participants ( $n = 26$ ), and inclusion of populations without chronic pain conditions ( $n = 16$ ). A total of 11 studies met the inclusion criteria and were included in the final review. The study selection process is summarized in the PRISMA 2020 flow diagram (Figure 2).

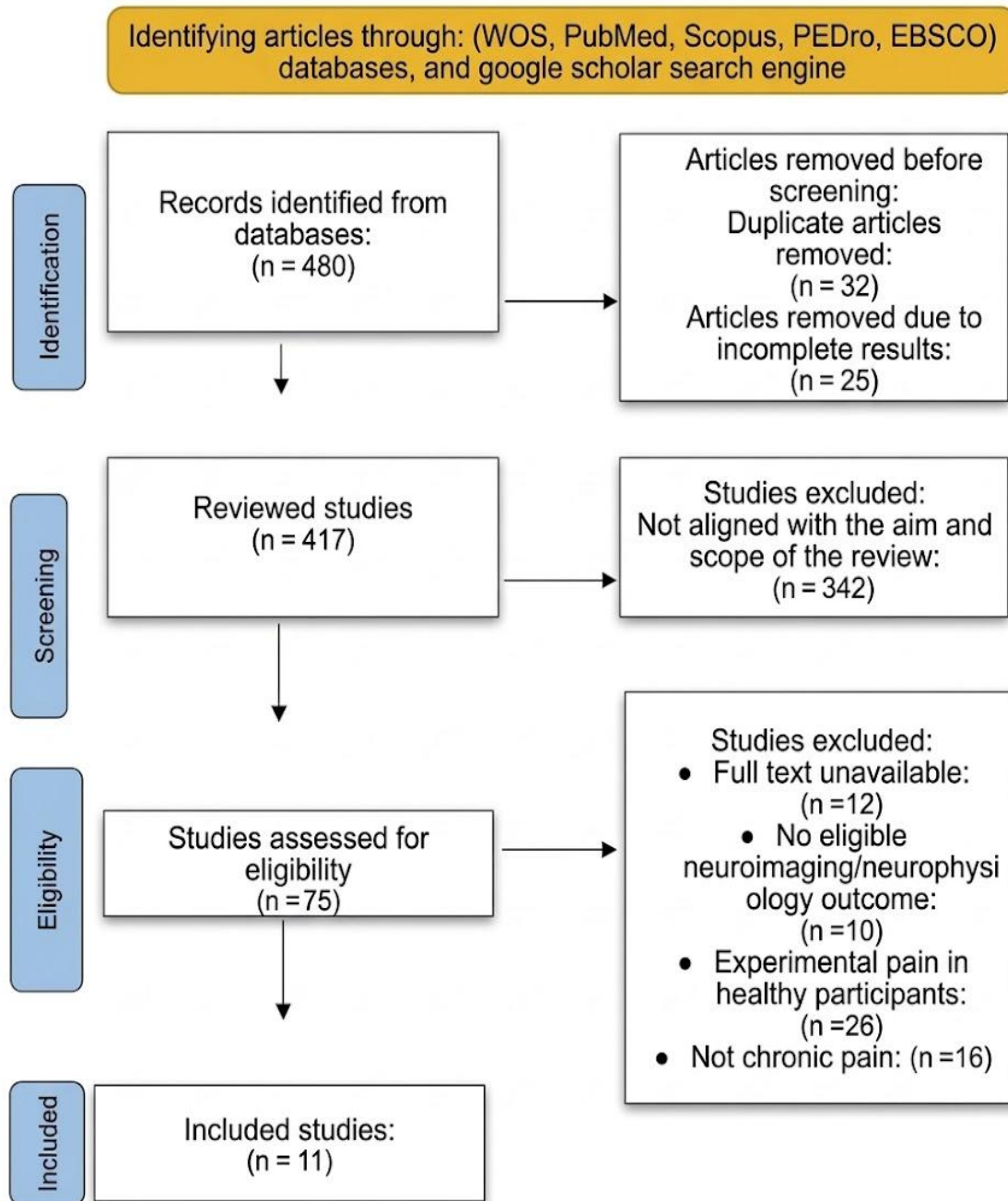


**Figure 2.** The process of searching, reviewing, and selecting articles based on the PRISMA guidelines.

### 3.2. Methodological quality, and risk of bias

All 11 included studies employed observational cross-sectional designs. Across these studies, a total of 805 participants were included, comprising 451 females and 354 males. In terms of sex distribution, two studies included female-only samples and one study included a male-only sample, while the remaining studies recruited mixed-sex populations. Methodological quality scores based on the McMaster Critical Review Form are presented in Table 6. Of the 11 studies, 2 were rated as very good, 5 as good, and 4 as fair. Across the studies, items related to the study objective (Item 1) and

background/literature review (Item 2) were consistently satisfied. In contrast, lower scores were observed for sample size justification (Item 4) and aspects of the study description (Items 8–10), reflecting limited reporting in these domains. Greater variability was noted in Items 13 and 14, which relate to the clinical significance and sample exclusion criteria, with several studies receiving lower scores, suggesting inconsistent reporting of these elements across studies.

**Table 6.** Methodological Quality Assessment (McMaster Scale).

| No. | Author/Year               | 1 | 2 | 3*  | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | Total Score | Quality   |
|-----|---------------------------|---|---|-----|---|---|---|---|---|---|----|----|----|----|----|----|----|----|-------------|-----------|
| 1   | Ching et al., 2018 [33]   | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 0  | 0  | 1  | 1  | 1  | 13          | very good |
| 2   | Freund et al., 2010 [34]  | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 1 | 1 | 0  | 1  | 1  | 0  | 0  | 1  | 1  | 1  | 12          | good      |
| 3   | Gao et al., 2025 [35]     | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 1 | 1 | 0  | 1  | 1  | 0  | 0  | 1  | 1  | 1  | 12          | good      |
| 4   | Gracely et al., 2004 [36] | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 1 | 1 | 0  | 1  | 1  | 0  | 0  | 1  | 1  | 1  | 12          | good      |
| 5   | Kutch et al., 2015 [37]   | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 0 | 0 | 0  | 1  | 1  | 0  | 0  | 1  | 0  | 1  | 9           | Fair      |
| 6   | Niddam et al., 2008 [38]  | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 0  | 1  | 1  | 0  | 0  | 12          | good      |
| 7   | Qiu et al., 2025 [39]     | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 0 | 0 | 0  | 1  | 1  | 0  | 0  | 1  | 0  | 1  | 9           | Fair      |
| 8   | Taylor et al., 2015 [40]  | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 1 | 1 | 0  | 1  | 1  | 1  | 0  | 1  | 1  | 1  | 13          | very good |
| 9   | Wang et al., 2023 [41]    | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 0 | 0 | 0  | 1  | 1  | 0  | 0  | 1  | 1  | 1  | 10          | Fair      |
| 10  | Younger et al., 2010 [42] | 1 | 1 | N/A | 0 | 1 | 0 | 0 | 1 | 1 | 1  | 1  | 1  | 0  | 0  | 1  | 0  | 1  | 10          | Fair      |
| 11  | Smith et al., 2025 [43]   | 1 | 1 | N/A | 0 | 1 | 1 | 1 | 0 | 0 | 0  | 1  | 1  | 1  | 0  | 1  | 1  | 1  | 11          | good      |

Note: 1 = criterion fully met; 0 = criterion not met. Quality categories: Poor (0–8), Fair (9–10), Good (11–12), Very Good (13–14), Excellent (15–16). \* Item 3 (study design) was excluded from the total methodological quality score because all included studies employed the same cross-sectional design. Since this criterion showed no variability across studies, it did not contribute to distinguishing methodological quality and was therefore reported as a descriptive study characteristic rather than a scored quality item.

Table 5 summarizes the results of the JBI Critical Appraisal Checklist used to assess risk of bias in the included studies. The check list evaluates key methodological domains relevant to observational study designs, including the following: clarity of inclusion criteria (Q1), description of study participants and setting (Q2), validity and reliability of exposure measurement (Q3), use of objective criteria for condition measurement (Q4), identification of confounding factors (Q5), strategies to address confounding (Q6), validity and reliability of outcome measurement (Q7), and appropriateness of statistical analysis (Q8). Across the studies, all reports clearly described the inclusion criteria (Q1: Yes) and the study participants and settings (Q2: Yes). In contrast, variability was observed in the handling of confounding factors, with six studies not reporting explicit strategies for confounder control (Q6: No). Overall, the findings indicate variability in the methodological quality across domains, with stronger reporting in the study description and outcome measurement domains, and weaker reporting in the confounding control strategies. These results are descriptively presented to characterize the risk of bias across studies rather than to derive a single aggregate score.

The overall methodological quality of the included studies is summarized in Figure 1, which presents the distribution of JBI risk-of-bias judgments across the eight appraisal domains (Q1–Q8), thereby showing the proportion of studies within each risk-of-bias category.

### 3.3. Study characteristics

Key characteristics of the included studies are summarized in Table 3. The sample sizes ranged from 25 to 175 participants, and the participant ages ranged from 18 to 75 years. Most studies employed a case-control design comparing individuals with chronic pain to pain-free control groups, typically healthy participants. Two studies used alternative comparator groups, including acute versus chronic neck pain, and high versus low pain catastrophizing in fibromyalgia. The included studies covered a range of chronic pain conditions, primarily involving musculoskeletal and related pain syndromes. These included chronic post-hysterectomy pain, complex regional pain syndrome type I, acute and chronic neck pain (including chronic nonspecific neck pain), fibromyalgia, chronic prostatitis, chronic pelvic pain syndrome, myofascial pain syndrome, chronic musculoskeletal pain, chronic ankle pain or ankle instability, chronic temporomandibular myofascial pain, and chronic low back pain. Regarding neuroimaging and assessment methods, functional magnetic resonance imaging (fMRI) was the most frequently used modality, most commonly in the form of resting-state fMRI (rs-fMRI), often complemented by structural MRI (T1-weighted imaging). Pain intensity was most commonly assessed using either numerical rating scales (NRS) or visual analogue scales (VAS). In addition, a subset of studies used validated questionnaires to assess psychological or disability-related factors, including the Pain Catastrophizing Scale (PCS) and the Oswestry Disability Index (ODI). Regarding the motor outcome assessment, only one included study [43] directly evaluated objective motor/postural control using force plate measurements and surface electromyography. The remaining studies primarily assessed self-reported clinical outcomes, including pain intensity, disability, or psychological measures, without direct objective assessment of motor or postural control. Most included studies compared the participants with chronic pain to pain-free healthy controls. However, two studies did not include a healthy control group. Specifically, Gao et al. [35] compared participants with acute neck pain and chronic neck pain, whereas Gracely et al. [36] compared fibromyalgia patients with high versus low pain catastrophizing after controlling for depression. These studies were included because they provided relevant neurophysiological evidence regarding within-condition mechanisms of chronic pain; however, their findings were cautiously interpreted, as they do not permit direct attribution of observed neural alterations to chronic pain relative to pain-free individuals.

## 4. Discussion

This systematic review synthesized evidence on alterations in functional connectivity across limbic, cingulate, cerebellar, and sensorimotor networks in individuals with chronic pain, and examined their associations with motor control and postural control. An important consideration when interpreting the present findings is that the included studies employed different neuroimaging modalities, each providing distinct information about brain organization. Functional MRI primarily reflects the blood oxygen level-dependent (BOLD) activity and functional connectivity, structural MRI characterizes the brain morphology such as cortical thickness and gray matter volume, PET assesses

the regional metabolic or neurochemical activity, whereas MEG measures the temporal dynamics of neuronal activity with high temporal resolution. Because these modalities capture different neurophysiological processes, their findings should be regarded as complementary rather than directly comparable. Consequently, the present review synthesized evidence narratively according to the type of neurophysiological information provided by each modality and did not attempt direct modality-to-modality comparisons.

Across 11 observational cross-sectional studies including 805 participants, the findings consistently indicated that chronic pain is associated with alterations in both brain function and structure within large-scale brain networks implicated in pain processing and movement regulation. However, only a small number of included studies directly assessed the objective motor control or postural performance; therefore, most interpretations regarding motor behavior are based on indirect neuroimaging evidence rather than direct behavioral measurements. Among the included resting-state fMRI studies, altered functional connectivity involving the insular cortex and cingulate regions was commonly reported, often extending to the sensorimotor, prefrontal, and parietal areas. However, these observations should not be interpreted as evidence of modality-specific effects, given the limited number of studies and substantial heterogeneity in study populations, imaging protocols, and analytical approaches.

These alterations were frequently associated with clinical pain measures, such as pain intensity [35,39,41]. For example, reduced connectivity between pelvic floor motor regions and the posterior insula was associated with a greater pain intensity in chronic pelvic pain [39], while a reduced connectivity between the cingulate motor area and insular cortex was associated with lower physical activity in chronic ankle pain or instability [43]. Task-based studies further indicated that during pain- or movement-related contexts, individuals with chronic pain show increased engagement of regions involved in emotion, threat appraisal, and motor inhibition, alongside altered somatosensory responses [41,42,45,46]. Structural neuroimaging studies have demonstrated pain-related neuroplastic alterations in specific brain regions involved in nociceptive processing. For example, chronic myofascial temporomandibular pain has been associated with gray matter volume abnormalities within the trigeminothalamocortical pathway, including the brainstem trigeminal sensory nuclei, thalamus, and primary somatosensory cortex, as well as within the limbic system regions, including the anterior insula, posterior putamen, and globus pallidus. Furthermore, these structural alterations showed region-specific associations with clinical characteristics, including pain severity, pain tolerance, and pain duration [42]. Importantly, functional neuroimaging studies that examined motor outcomes have demonstrated persistent alterations in movement-related brain function in individuals with a history of low back pain who were asymptomatic at the time of assessment. Specifically, altered activation during lumbopelvic postural control tasks was identified in the bilateral angular gyri, posterior cingulate cortices, right precentral gyrus, and left globus pallidus, with these functional alterations associated with postural control deficits and pain-related clinical characteristics [39].

Although the primary conceptual focus of this review was on alterations in functional connectivity within large-scale brain networks, the predefined eligibility criteria also included studies that examined regional brain activation, spontaneous neural activity, and structural neuroplastic changes because these complementary neuroimaging measures provide converging evidence regarding network-level dysfunction and its potential relationship with motor control [33–35]. Accordingly, the synthesis integrates multiple neuroimaging approaches to provide a broader understanding of CNS alterations associated with chronic pain.

Evidence from the included studies indicates that altered connectivity involving the insula and cingulate regions, often in conjunction with sensorimotor cortices, is associated with clinical features of chronic pain. This pattern is consistent with contemporary models proposing that chronic pain involves large-scale network reorganization. However, the resting-state findings included in the present review do not directly demonstrate changes in perception, motivation, or action selection; these interpretations are based on previous task-based and theoretical studies [17,47,48]. A consistent finding across studies is the role of the insula as a functional hub linking interoceptive and salience processing with motor-related systems. For example, a reduced connectivity between pelvic floor motor regions and the posterior insula was associated with greater pain severity in chronic pelvic pain [37], while a reduced connectivity between the cingulate motor area and insula was associated with lower physical activity in chronic ankle instability [41]. These findings are consistent with previous task-based neuroimaging studies in which the insula and cingulate cortex have been associated with salience processing and threat monitoring. However, because the present evidence is primarily derived from resting-state functional connectivity analyses, the observed connectivity alterations cannot, by themselves, confirm these specific functional processes. This interpretation is supported by meta-analytic evidence demonstrating altered insula-centered connectivity with cingulate and default mode network regions in musculoskeletal pain [45]. However, the insular findings were not uniform across chronic pain conditions. For example, in chronic postsurgical pain, the control participants showed increased insular connectivity following pain stimulation, whereas patients exhibited reduced modulation [42], suggesting altered flexibility of salience network responses in pain-related contexts.

The differences across studies may reflect the heterogeneous nature of chronic pain, in which distinct pain mechanisms, clinical characteristics, and temporal profiles may differentially shape network-level adaptations. Accordingly, alterations in the insular connectivity may represent condition-specific patterns of adaptation within salience and interoceptive networks rather than a consistent direction of change across chronic pain populations. This heterogeneity may partly reflect differences among chronic pain conditions, as disorders with distinct etiologies, durations, affected body systems, and symptom profiles may involve different patterns of network adaptation. For example, studies in complex regional pain syndrome have demonstrated altered activation patterns involving insular, cingulate, and opercular regions during experimentally induced pain [45], whereas fibromyalgia has been associated with an enhanced engagement of affective and cognitive pain-processing regions, including the anterior cingulate cortex and secondary somatosensory cortex, particularly in relation to pain catastrophizing [41]. Similarly, chronic neck pain studies have reported alterations involving cingulate, precuneus, and sensorimotor-related regions, thus suggesting disease-specific patterns of network adaptation associated with pain chronicity [40,48]. In contrast, pelvic pain and chronic ankle pain studies have highlighted altered connectivity between pain-related and motor-related regions, thus suggesting that the relationship between neural alterations and motor function may depend on the affected body system and functional demands [41,46]. Therefore, the observed variability across studies should not necessarily be interpreted as inconsistency, but rather as reflecting condition-specific adaptations within distributed pain and sensorimotor networks.

Beyond insular involvement, several studies highlighted alterations in cingulate and default mode network (DMN) regions, particularly the posterior cingulate cortex and precuneus. These regions have previously been associated with self-referential processing and symptom monitoring in task-based and functional neuroimaging studies; however, the resting-state connectivity findings included in the present review cannot directly establish these specific cognitive functions [34]. In chronic non-specific

neck pain, altered spontaneous activity and regional homogeneity in precuneus/PCC were reported, alongside altered functional connectivity involving cingulate and insula-related networks [39]. Adding structural evidence, Gao et al. compared acute versus chronic neck pain and found increased cortical thickness in the prefrontal, cingulate, and precuneus regions and changes in the resting-state neural activity across the prefrontal, sensorimotor, and limbic areas in the chronic stage [35]. When considered together, these findings indicate broader network-level alterations involving the DMN and cingulate systems. Although these regions have been associated with attention, threat processing, and motor planning in previous task-based studies, the resting-state connectivity findings synthesized here do not directly demonstrate these functional roles [35,37,41].

Moreover, several studies indicate that chronic pain is accompanied by altered sensorimotor processing and somatosensory representations, thus providing another axis of convergence with the above network findings. In myofascial pain syndrome, hyperalgesia was accompanied by enhanced activation in somatosensory and limbic regions, including primary/secondary somatosensory cortices and insula-related areas [38]. In chronic myofascial temporomandibular pain, a structural MRI showed an increased gray matter volume in the trigeminothalamic cortical and limbic regions, with decreased gray matter volume in primary somatosensory cortex [42], consistent with long-term neuroplastic changes in pain-relevant somatosensory pathways. Importantly, Smith et al. reported that abnormalities in the sensorimotor function can be present even in young adults with a history of lower back pain when they are asymptomatic, and that these differences were most evident during tasks requiring lumbopelvic postural control [43]. This finding suggests that individuals with a history of lower back pain may exhibit altered sensorimotor brain function even when asymptomatic. However, because the available evidence is cross-sectional, these findings should be interpreted as differences between groups rather than as evidence of persistent alterations over time [40].

A potential framework for interpreting these sensorimotor alterations involves anticipatory postural control, which represents the feedforward regulation of posture through predictive integration of sensory, cognitive, and motor information. Anticipatory postural adjustments (APAs) and anticipatory synergy adjustments are key components of predictive motor control that contribute to postural stability during voluntary movement [46,49]. Although these mechanisms are adaptable and can be modified through training, reflecting the flexibility of neural control processes [50], alterations in limbic–cingulate and sensorimotor network interactions reported in chronic pain may theoretically influence these predictive processes by modifying salience evaluation, threat-related responses, and sensorimotor integration [12,15,17]. However, the included studies did not directly assess APAs or other objective measures of feedforward motor control alongside neuroimaging outcomes. Therefore, the proposed relationship between large-scale brain network alterations and anticipatory motor control should be considered hypothesis-generating rather than evidence of a demonstrated mechanism. Future studies that combine neuroimaging with standardized motor assessments, including electromyography, force plate analysis, and kinematic measures, are needed to determine whether these neural alterations contribute to impaired motor control in chronic pain.

Task-based studies provide further insight into how these network-level alterations may translate into movement-related behavior. In chronic pain, observing or engaging in everyday activities was associated with increased activation in limbic, cingulate, and sensorimotor regions, alongside higher anxiety and perceived pain [40]. In fibromyalgia, higher levels of pain catastrophizing were associated with greater engagement of regions involved in attention, emotion, and motor control, including the anterior cingulate cortex and dorsolateral prefrontal cortex, with additional cerebellar involvement [36].

These findings suggest that cognitive–affective processes may modulate the neural activity during movement-related contexts. When considered alongside connectivity and structural findings, the available evidence is consistent with a network-level account in which alterations in salience-related (insula–cingulate), self-referential (DMN), and sensorimotor networks co-occur in chronic pain, providing plausible—but not definitive—pathways linking pain persistence to altered movement behavior [42,43]. Nevertheless, these observations are derived from heterogeneous neuroimaging methodologies and remain correlational rather than demonstrating modality-specific effects or causal mechanisms.

This review has several strengths, including a comprehensive multi-database search, adherence to PRISMA 2020 guidelines, and the use of structured methodological and risk-of-bias assessments. A narrative synthesis approach, informed by SWiM, was applied where a meta-analysis was not feasible due to heterogeneity across studies. However, several limitations should be considered. All included studies employed cross-sectional designs, which do not allow conclusions regarding the directionality or causality of observed associations. Substantial heterogeneity in pain conditions, neuroimaging modalities, imaging protocols, analytical approaches, and outcome measures limited direct comparability across studies and precluded quantitative synthesis. Consequently, apparent differences across structural MRI, resting-state fMRI, and task-based fMRI should be cautiously interpreted and should not be considered definitive evidence of modality-specific effects.

In addition, the objective motor and postural outcomes were inconsistently reported and variably defined, which increases the indirectness when interpreting relationships between neural findings and motor behavior. Another important limitation is that relatively few included studies directly assessed the objective motor control or postural control. Most investigations relied on functional connectivity, regional brain activation, or structural neuroimaging markers and inferred potential implications for the motor behavior. Therefore, the relationship between brain network alterations and measurable motor impairments remains largely indirect, and conclusions regarding this association should be cautiously interpreted. An additional limitation is that two included studies did not include pain-free control groups but instead compared different chronic pain subgroups (e.g., acute versus chronic pain or high versus low pain catastrophizing) [35,36]. Although these studies provide valuable insights into neurophysiological variability within chronic pain populations, they do not allow direct attribution of observed neural alterations specifically to chronic pain relative to healthy individuals. Therefore, their findings were considered complementary evidence and interpreted with appropriate caution when drawing overall conclusions.

Future research should prioritize longitudinal and interventional designs to examine whether alterations in limbic and salience–sensorimotor connectivity are associated with subsequent changes in motor performance and whether these neural and behavioral measures show concurrent changes following clinical improvement or recovery. Standardization of the neuroimaging and behavioral outcomes is also needed, including the use of well-defined motor tasks alongside objective measures such as electromyography, force plate analysis, and kinematic assessments. In addition, advanced analytical approaches, including mediation and causal modeling frameworks, may help explore whether alterations in salience and affective processing are involved in the relationship between persistent pain and motor function, while acknowledging the correlational nature of existing evidence.

## 5. Conclusions

This systematic review revealed a consistent pattern of brain alterations in individuals with chronic pain, predominantly involving insula-cingulate networks implicated in salience, threat-related processing, and pain modulation, often accompanied by alterations in sensorimotor and default-mode regions. While limbic-cingulate alterations may primarily contribute through pain-related cognitive and affective processes, changes within the sensorimotor and motor-related networks appear more directly relevant to movement regulation, including motor planning, sensorimotor integration, and postural control. Task-based findings suggest altered engagement of regions involved in emotion regulation, threat appraisal, and motor control, whereas structural imaging findings indicate pain-related neuroplastic adaptations in specific brain regions. However, only a small number of included studies directly assessed the objective motor or postural control, and the movement-control differences were therefore demonstrated in only a limited subset of studies. Accordingly, current evidence supports an association between alterations in large-scale brain networks and motor control-related outcomes, but does not yet establish a direct causal relationship or demonstrate uniform motor impairments across chronic pain conditions. Future longitudinal and mechanistic studies that integrate standardized neuroimaging with objective motor assessments are needed to clarify these relationships.

### Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

### Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors gratefully acknowledge the editorial team for their clear guidance and adherence to submission standards, which will help expedite the review and publication process. We also thank all researchers whose work contributed to the foundation of this systematic review.

### Conflict of interest

The authors declare no conflict of interest.

### Authors' contributions

Conceptualization, S.A. and F.R.; Methodology, S.A. and P.F.; Software, P.F.; Validation, P.F. and G.B.; Formal analysis, S.A. and P.F.; Investigation, S.A. and P.F.; Resources, P.F.; Data Curation, P.F.; Writing – Original Draft Preparation, S.A.; Writing – Review & Editing, F.R., S.A. and G.B.; Visualization, P.F.; Supervision, F.R. and G.B.; Project Administration, F.R. All authors have read and agreed to the published version of the manuscript.

## References

1. Murray CJL (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392: 1789–858. [https://doi.org/10.1016/S0140-6736\(19\)31047-5](https://doi.org/10.1016/S0140-6736(19)31047-5)
2. Bendelow G (2013) Chronic pain patients and the biomedical model of pain. *Virtual Mentor* 15: 455–459. <https://doi.org/10.1001/virtualmentor.2013.15.5.msoc1-1305>
3. Jaffal SM (2025) Neuroplasticity in chronic pain: insights into diagnosis and treatment. *Korean J Pain* 38: 89–102. <https://doi.org/10.3344/kjp.24393>
4. Zeng X, Sun Y, Zhiying Z, et al. (2025) Chronic pain-induced functional and structural alterations in the brain: a multi-modal meta-analysis. *J Pain* 28: 104740. <https://doi.org/10.1016/j.jpain.2024.104740>
5. Apkarian AV, Bushnell MC, Treede RD, et al. (2005) Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 9: 463–484. <https://doi.org/10.1016/j.ejpain.2004.11.001>
6. Wiech K, Ploner M, Tracey I (2008) Neurocognitive aspects of pain perception. *Trends Cogn Sci* 12: 306–313. <https://doi.org/10.1016/j.tics.2008.05.005>
7. Fiúza-Fernandes J, Pereira-Mendes J, Esteves M, et al. (2025) Common neural correlates of chronic pain—A systematic review and meta-analysis of resting-state fMRI studies. *Prog Neuropsychopharmacol Biol Psychiatry* 138: 111326. <https://doi.org/10.1016/j.pnpbp.2025.111326>
8. Buckner RL (2013) The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 80: 807–815. <https://doi.org/10.1016/j.neuron.2013.10.044>
9. Moulton EA, Schmahmann JD, Becerra L, et al. (2010) The cerebellum and pain: passive integrator or active participator? *Brain Res Rev* 65: 14–27. <https://doi.org/10.1016/j.brainresrev.2010.05.005>
10. Schmahmann JD (2019) The cerebellum and cognition. *Neurosci Lett* 688: 62–75. <https://doi.org/10.1016/j.neulet.2018.07.005>
11. Ito M (2008) Control of mental activities by internal models in the cerebellum. *Nat Rev Neurosci* 9: 304–313. <https://doi.org/10.1038/nrn2332>
12. Hodges PW, Tucker K (2011) Moving differently in pain: a new theory to explain the adaptation to pain. *Pain* 152: S90–S98. <https://doi.org/10.1016/j.pain.2010.10.020>
13. Tsao H, Galea MP, Hodges PW (2008) Reorganization of the motor cortex is associated with postural control deficits in recurrent low back pain. *Brain* 131: 2161–2171. <https://doi.org/10.1093/brain/awn154>
14. van Dieën JH, Reeves NP, Kawchuk G, et al. (2019) Motor Control Changes in Low Back Pain: Divergence in Presentations and Mechanisms. *J Orthop Sports Phys Ther* 49: 370–9. <https://doi.org/10.2519/jospt.2019.7917>
15. Seminowicz DA, Wideman TH, Naso L, et al. (2011) Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. *J Neurosci* 31: 7540–7550. <https://doi.org/10.1523/JNEUROSCI.5280-10.2011>
16. Pelletier R, Higgins J, Bourbonnais D (2015) Is neuroplasticity in the central nervous system the missing link to our understanding of chronic musculoskeletal disorders? *BMC Musculoskelet Disord* 16: 25. <https://doi.org/10.1186/s12891-015-0480-y>

17. Apkarian AV, Hashmi JA, Baliki MN (2011) Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *Pain* 152: S49–S64. <https://doi.org/10.1016/j.pain.2010.11.010>
18. Moseley GL, Flor H (2012) Targeting cortical representations in the treatment of chronic pain: a review. *Neurorehabil Neural Repair* 26: 646–652. <https://doi.org/10.1177/1545968311433209>
19. Vachon-Preseu E, Tetreault P, Petre B, et al. (2016) Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain* 139: 1958–1970. <https://doi.org/10.1093/brain/aww100>
20. Coombes SA, Misra G (2016) Pain and motor processing in the human cerebellum. *Pain* 157: 117–127. <https://doi.org/10.1097/j.pain.0000000000000337>
21. Kuner R (2010) Central mechanisms of pathological pain. *Nat Med* 16: 1258–1266. <https://doi.org/10.1038/nm.2231>
22. Tracey I, Bushnell MC (2009) How neuroimaging studies have challenged us to rethink: is chronic pain a disease? *J Pain* 10: 1113–1120. <https://doi.org/10.1016/j.jpain.2009.09.001>
23. Kuner R, Flor H (2017) Structural plasticity and reorganisation in chronic pain. *Nat Rev Neurosci* 18: 113. <https://doi.org/10.1038/nrn.2017.5>
24. Hodges PW, Danneels L (2019) Changes in structure and function of the back muscles in low back pain: Different time points, observations, and mechanisms. *J Orthop Sports Phys Ther* 49: 464–76. <https://doi.org/10.2519/jospt.2019.8827>
25. Nijs J, George SZ, Clauw DJ, et al. (2021) Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol* 3: e383–e92. [https://doi.org/10.1016/S2665-9913\(21\)00032-1](https://doi.org/10.1016/S2665-9913(21)00032-1)
26. Wager TD, Atlas LY, Lindquist MA, et al. (2013) An fMRI-based neurologic signature of physical pain. *N Engl J Med* 368: 1388–1397. <https://doi.org/10.1056/NEJMoa1204471>
27. Page MJ, McKenzie JE, Bossuyt PM, et al. (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372: n71. <https://doi.org/10.1136/bmj.n71>
28. Campbell M, McKenzie JE, Sowden A, et al. (2020) Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 368: l6890. <https://doi.org/10.1136/bmj.l6890>
29. Guyatt G, Oxman AD, Akl EA, et al. (2011) GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 64: 383–394. <https://doi.org/10.1016/j.jclinepi.2010.04.026>
30. Wilke J, Groneberg DA (2022) Neurocognitive function and musculoskeletal injury risk in sports: a systematic review. *J Sci Med Sport* 25: 41–45. <https://doi.org/10.1016/j.jsams.2021.07.002>
31. Hadjisavvas S, Themistocleous IC, Papamichael E, et al. (2026) Preseason screening tests and physical assessments as predictors of injury in handball players: a systematic review. *Sports* 14: 234. <https://doi.org/10.3390/sports14060234>
32. Rezazadeh F, Yousefi M, Aali S, et al. (2024) Investigating the effect of hydrotherapy on pain intensity and balance in people with non-specific chronic low back pain: a systematic review. *Stud Med Sci* 35: 919–937. <https://doi.org/10.61186/umj.35.11.919>
33. Ching YY, Wang C, Tay T, et al. (2018) Altered sensory insular connectivity in chronic postsurgical pain patients. *Front Hum Neurosci* 12: 483. <https://doi.org/10.3389/fnhum.2018.00483>
34. Freund W, Wunderlich AP, Stuber G, et al. (2010) Different activation of opercular and posterior cingulate cortex (PCC) in patients with complex regional pain syndrome (CRPS I) compared with healthy controls during perception of electrically induced pain: a functional MRI study. *Clin J Pain* 26: 339–347. <https://doi.org/10.1097/AJP.0b013e3181cb4055>

35. Gao Z, Cui MJ, Wang HJ, et al. (2025) Investigating brain structure and functional alterations in the transition from acute to chronic neck pain: a resting-state fMRI study. *J Pain Res* 18: 579–587. <https://doi.org/10.2147/JPR.S500924>
36. Gracely RH, Geisser ME, Giesecke T, et al. (2004) Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 127: 835–843. <https://doi.org/10.1093/brain/awh098>
37. Kutch JJ, Yani MS, Asavasopon S, et al. (2015) Altered resting state neuromotor connectivity in men with chronic prostatitis/chronic pelvic pain syndrome: A MAPP: Research Network Neuroimaging Study. *Neuroimage Clin* 8: 493–502. <https://doi.org/10.1016/j.nicl.2015.05.013>
38. Niddam DM, Chan RC, Lee SH, et al. (2008) Central representation of hyperalgesia from myofascial trigger point. *Neuroimage* 39: 1299–1306. <https://doi.org/10.1016/j.neuroimage.2007.09.051>
39. Qiu Z, Liu T, Zeng C, et al. (2025) Altered brain dynamics in chronic neck and shoulder pain revealed by hidden Markov model. *Sci Rep* 5: 18018. <https://doi.org/10.1038/s41598-025-03057-w>
40. Taylor AM, Harris AD, Varnava A, et al. (2015) A functional magnetic resonance imaging study to investigate the utility of a picture imagination task in investigating neural responses in patients with chronic musculoskeletal pain to daily physical activity photographs. *PLoS One* 10: e0141133. <https://doi.org/10.1371/journal.pone.0141133>
41. Wang Y, Li Q, Xue X, et al. (2023) Neuroplasticity of pain processing and motor control in CAI patients: A UK Biobank study with clinical validation. *Front Mol Neurosci* 16: 1096930. <https://doi.org/10.3389/fnmol.2023.1096930>
42. Younger JW, Shen YF, Goddard G, et al. (2010) Chronic myofascial temporomandibular pain is associated with neural abnormalities in the trigeminal and limbic systems. *Pain* 149: 222–228. <https://doi.org/10.1016/j.pain.2010.01.006>
43. Smith JA, Tain R, Sharp KG, et al. (2026) Abnormalities in sensorimotor brain function are related to chronicity of low back pain. *Neuroimage* 325: 121651. <https://doi.org/10.1016/j.neuroimage.2025.121651>
44. JBI (2020) Checklist for analytical cross sectional studies. [cited 2026 August 26]. Available from: [https://jbi.global/sites/default/files/2020-08/Checklist\\_for\\_Analytical\\_Cross\\_Sectional\\_Studies.pdf](https://jbi.global/sites/default/files/2020-08/Checklist_for_Analytical_Cross_Sectional_Studies.pdf).
45. Lai P, Chen X, Liu J, et al. (2025) Abnormalities of insular functional connectivity in patients with musculoskeletal pain: A meta-analysis of resting-state fMRI studies. *Brain Res Bull* 224: 111294. <https://doi.org/10.1016/j.brainresbull.2025.111294>
46. Klous M, Mikulic P, Latash ML (2011) Two aspects of feedforward postural control: anticipatory postural adjustments and anticipatory synergy adjustments. *J Neurophysiol* 105: 2275–2288. <https://doi.org/10.1152/jn.00665.2010>
47. Apkarian AV, Baliki MN, Geha PY (2009) Towards a theory of chronic pain. *Prog Neurobiol* 87: 81–97. <https://doi.org/10.1016/j.pneurobio.2008.09.018>
48. Baliki MN, Mansour AR, Baria AT, et al. (2014) Functional reorganization of the default mode network across chronic pain conditions. *PLoS One* 9: e106133. <https://doi.org/10.1371/journal.pone.0106133>
49. Santos MJ, Kanekar N, Aruin AS (2010) The role of anticipatory postural adjustments in compensatory control of posture: 1. Electromyographic analysis. *J Electromyogr Kinesiol* 20: 388–397. <https://doi.org/10.1016/j.jelekin.2009.06.006>

50. Kanekar N, Aruin AS (2015) Improvement of anticipatory postural adjustments for balance control: effect of a single training session. *J Electromyogr Kinesiol* 25: 400–405. <https://doi.org/10.1016/j.jelekin.2014.11.002>.



AIMS Press

© 2026 the Author(s), licensee AIMS Press. This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0>)