



Review

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

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Supplementary

SWiM-aligned synthesis summary (without meta-analysis)

Because meta-analysis was not feasible, we synthesised findings using a structured narrative approach guided by SWiM. Table 1 summarises the prespecified synthesis domains, direction-of-effect coding, and key sources of heterogeneity across included studies.

Table 1. SWiM-aligned synthesis summary (without meta-analysis).

Synthesis domain (grouping)	Direction-of-effect coding used	Participants (studies)	Summary of synthesis findings	Key sources of heterogeneity (examples)	Key studies
Resting-state fMRI (rs-fMRI): functional connectivity / intrinsic activity in cingulate–limbic and related networks.	Altered rs-fMRI measures in chronic pain vs comparator; direction may be ↑/↓ or mixed depending on region/connection.	504 (5)	rs-fMRI studies consistently reported altered connectivity/activity involving insula and cingulate regions, often extending to sensorimotor and prefrontal/parietal nodes; the specific connections/regions and direction varied across studies.	Different pain conditions (postsurgical pain, pelvic pain, neck pain, ankle pain/instability); ROI vs whole-brain; preprocessing/thresholding; connectivity definition.	Ching 2018; Gao 2025; Kutch 2015; Qiu 2025; Wang 2023 [33,35,37,39,41]
Task-based fMRI: evoked activation during pain- or movement-related paradigms.	Altered task-evoked activation in chronic pain vs controls; patterns depend on task and stimulus.	206 (5)	Task-based studies suggested altered engagement of limbic/cingulate and sensorimotor-related regions during painful stimulation or movement-related contexts, consistent with differences in affective/threat appraisal and sensorimotor integration.	Paradigm differences (pressure/electrical/intramuscular pain vs movement imagery vs postural control); stimulus intensity; analysis thresholds; participant characteristics.	Freund 2010; Gracely 2004; Niddam 2008; Taylor 2015; Smith 2025 [34,36,38,40,43]
Structural MRI: cortical thickness / gray matter volume (VBM) in pain-related networks.	Structural differences in chronic pain vs comparator; direction varies by region/metric.	204 (2)	Structural MRI studies reported gray matter or cortical thickness differences across limbic, cingulate, sensorimotor, brainstem, and cerebellar regions; metrics were not directly comparable.	Different structural metrics (thickness vs VBM); different regions/atlasses; different comparators (acute vs chronic vs controls).	Gao 2025; Younger 2010 [35,42]
Associations between neurophysiological measures and pain-related clinical features	Association sign (positive/negative/no clear	546 (7)	Across studies reporting association analyses, more pronounced	Different clinical scales and constructs; varying confounder	Ching 2018; Gao 2025; Gracely

(e.g., intensity/severity/chronicity/catastrophizing).	association) between neuro measures and clinical features.		alterations in connectivity, activation, or structure were frequently linked to greater pain intensity/severity or chronicity and/or higher catastrophizing; models and effect metrics differed substantially.	adjustment; modality-specific metrics; selective reporting of associations.	2004; Kutch 2015; Qiu 2025; Younger 2010; Smith 2025 [33,35–37,39,42,43]
Associations between neurophysiological measures and motor/postural outcomes.	Association sign between neuro measures and motor outcomes (physical activity, motor function, postural control).	252 (2)	Studies that directly assessed movement outcomes suggested links between altered coupling of pain-related and motor-related regions and poorer motor function/physical activity or altered postural control.	Motor outcome definition (activity vs. postural control); ROI definitions; sample characteristics and pain chronicity.	Wang 2023; Smith 2025 [41,43]

Notes: (1) Direction-of-effect coding supports transparent synthesis without pooling; ↑/↓ indicate increased/decreased relative to comparator when reported, and “mixed” indicates variable direction across studies or connections.

(2) Participant totals are domain-specific and may overlap across domains because some studies contributed to more than one domain (e.g., rs-fMRI plus structural MRI).

Certainty of evidence (GRADE)

Table 2 presents the Summary of Findings (SoF) table and GRADE certainty ratings for the pre-specified key outcomes. Across 11 observational cross-sectional studies (total $n = 805$), the certainty of evidence ranged from very low to low across outcomes. Downgrading most commonly reflected limitations related to risk of bias (particularly residual confounding and incomplete reporting/handling of confounders per the JBI appraisal), inconsistency arising from heterogeneity across pain conditions and neurophysiological modalities, and imprecision due to small sample sizes and limited precision of reported estimates. Overall, while the narrative synthesis indicated consistent involvement of cingulate-limbic and related networks in chronic musculoskeletal pain, the observational cross-sectional nature of the evidence and variability in methods limited confidence in the magnitude and generalizability of effects.

Table 2. Summary of findings (SOF) and certainty of the evidence (GRADE).

Outcomes (critical)	Summary of findings (direction of effect)	Participants (studies)	Design	Certainty (GRADE)	Key studies
Resting-state functional connectivity (rs-fMRI) alterations in limbic-cingulate-sensorimotor networks.	Across studies comparing CMP with pain-free controls, rs-fMRI showed altered connectivity patterns involving insula and cingulate regions with extensions to sensorimotor and prefrontal/parietal areas; direction and specific connections varied between studies (e.g., reduced connectivity or reduced modulation).	395 (4 studies)	Observational (cross-sectional)	(⊕⊕⊕⊕ 1-5) VERY LOW	Ching 2018; Kutch 2015; Qiu 2025; Wang 2023 [33,37,39,41]
Task-evoked brain activation differences during pain or movement-related paradigms (fMRI).	During painful stimulation or movement-related tasks, CMP groups showed altered engagement of limbic/cingulate and sensorimotor-related regions compared with controls, consistent with greater affective/threat-related processing and altered sensorimotor integration; patterns varied across paradigms.	177 (4 studies)	Observational (cross-sectional)	(⊕⊕⊕⊕ 1-5) VERY LOW	Freund 2010; Niddam 2008; Taylor 2015; Smith 2025 [34,38,40,43]
Structural MRI alterations (cortical thickness / gray matter volume) in pain-related networks.	Structural MRI studies reported differences in cortical thickness or regional gray matter volume across limbic, cingulate, sensorimotor, brainstem, and cerebellar regions in chronic pain and/or in the transition from acute to chronic pain; findings were not directly comparable across studies.	204 (2 studies)	Observational (cross-sectional)	(⊕⊕⊕⊕ 1-5) VERY LOW	Gao 2025; Younger 2010 [35,42]
Association between	Most studies that tested associations	684 (7 studies)	Observational (cross-	(⊕⊕⊕⊕ 1-5)	Ching 2018; Gao 2025;

neurophysiological measures and pain intensity / severity.	reported that greater pain intensity or severity (or related clinical features) was associated with more pronounced alterations in functional connectivity or brain structure/function measures; effect sizes and models differed substantially.		sectional)	VERY LOW	Kutch 2015; Qiu 2025; Wang 2023; Younger 2010; Smith 2025 [33,35,37,39,41–43]
Association between neurophysiological measures and motor control / postural outcomes.	Two studies directly linked neurophysiological alterations to motor outcomes, suggesting that reduced connectivity between pain-related and motor-related regions was associated with worse motor function/physical activity and altered lumbopelvic postural control.	252 (2 studies)	Observational (cross-sectional)	(⊕⊕⊕⊕ 1-5) VERY LOW	Wang 2023; Smith 2025 [41,43]

Note: GRADE certainty symbols: ⊕ indicates a filled circle and ⊖ indicates an empty circle. Overall certainty of evidence is represented as follows: High ⊕⊕⊕⊕, Moderate ⊕⊕⊕⊖, Low ⊕⊕⊖⊖, and very low ⊕⊖⊖⊖. 1) Risk of bias: All included studies were observational cross-sectional; several did not report explicit strategies to address confounding (JBI domain Q6 rated 'No' in multiple studies). 2) Inconsistency: Considerable clinical and methodological heterogeneity (different pain conditions, imaging modalities, preprocessing/analysis approaches, and outcome definitions) and variable direction of effects across studies. 3) Indirectness: Outcomes are neurophysiological (surrogate) measures and populations included diverse chronic pain conditions; direct applicability to any single CMP subgroup and to clinical outcomes may be limited. 4) Imprecision: Many outcomes were supported by a small number of studies and small-to-moderate sample sizes; no pooled effect estimates were available. 5) Publication bias: Formal assessment (e.g., funnel plot) was not possible; selective reporting cannot be ruled out.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, Line 10-11
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page1- 2, Line 21-53, See the supplementary file PRISMA 2020 for the abstract's checklist.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2-4, Line 55-115
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4, Line 116-130
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 6, Line 192-232
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5, Line 153-181
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5, Line 153-190
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record	Page 7-8, Line 237-

Section and Topic	Item #	Checklist item	Location where item is reported
		and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	255
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7-8, Line 237-255
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Table 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6-7, Line 191-235&Table 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9, Line 280-296
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not Applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7-8, Line 237-255
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not Applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Not Applicable
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not Applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not Applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not Applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not Applicable

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not Applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 10, Line 302-311 AND (Figure 1)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 10, Line 302-311 AND (Figure 1)
Study characteristics	17	Cite each included study and present its characteristics.	Page 14-15, Line 361-388
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 13-14, Line 336-360
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Not Applicable
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 13-14, Line 336-360 (Table 5-Risk of Bias)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Not Applicable
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not Applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not Applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not Applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not Applicable

Section and Topic	Item #	Checklist item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 21-24, Line 391-525
	23b	Discuss any limitations of the evidence included in the review.	Page 25, Line 540-549
	23c	Discuss any limitations of the review processes used.	Page 25, Line 540-549
	23d	Discuss implications of the results for practice, policy, and future research.	Page 25 Line 564-572
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2, Line 32. Page 4, Line 138
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	The review protocol was registered with the International Prospective Register (PROSPERO). All cases are accessible with the registry code: CRD420261369982
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	The review

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			protocol was registered with the International Prospective Register (PROSPERO). All cases are accessible with the registry code: CRD420261369982
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 26, Line 589-604
Competing interests	26	Declare any competing interests of review authors.	Page 26, Line 589-604
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	The review protocol was registered with the International Prospective Register (PROSPERO). All cases are accessible with the registry code: CRD420261369982

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>.



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