

# Abnormal Brain Structure and Function in People with Shoulder Pain: A Systematic Review of Neuroimaging Studies

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**Background:** Shoulder pain (SP) is a prevalent musculoskeletal disorder. Emerging evidence suggests maladaptive brain plasticity in individuals with SP. This systematic review summarized structural and functional brain abnormalities in individuals with SP and explored their associations with clinical outcomes.

**Methods:** PubMed, Web of Science, EBSCO, and EMBASE were searched from inception to June 2025. The risk of bias was assessed using JBI checklist, and the evidence was graded using the GRADE approach.

**Results:** Five cross-sectional studies were included. These studies demonstrated low to moderate risk of bias. Individuals with SP demonstrated lower volume and density of thalamus grey matter compared to healthy controls. Besides, lower grey matter (volume, density or thickness) was observed in regions such as the amygdala, prefrontal, postcentral, and temporal cortices. Functional neuroimaging studies reported both increased and decreased functional connectivity, as well as abnormalities in regional homogeneity (ReHo) and amplitude of low-frequency fluctuation (ALFF) in brain areas including thalamus, prefrontal, anterior cingulate, middle temporal, orbitofrontal, and sensorimotor cortices. These structural and functional brain changes were associated with higher pain intensity, lower pain threshold, longer pain duration, poor shoulder function and psychological outcomes. However, the overall certainty of evidence was rated as very low due to the small number of studies and methodological heterogeneity.

**Conclusion:** This systematic review provides preliminary, hypothesis-generating evidence on brain abnormalities in individuals with SP. Very low-certainty evidence suggests that SP may be associated with structural and functional abnormalities in brain regions involved in pain processing, emotion, and sensorimotor integration. Further longitudinal studies are needed to validate the findings.

**Keywords:** shoulder pain, magnetic resonance imaging, neuroimaging, brain alterations, central nervous system

## Introduction

Shoulder pain (SP) is the third most prevalent musculoskeletal complaint in primary care, with an estimated prevalence of 1.0%–4.8%.<sup>1</sup> The most common cause of SP is rotator cuff-related SP, which includes subacromial impingement syndrome, rotator cuff tendinitis, and rotator cuff tears, accounting for 80% of shoulder conditions.<sup>2,3</sup> Other shoulder pathologies include adhesive capsulitis, bursitis, bicipital tendinitis, osteoarthritis, and labral lesions.<sup>4</sup> Common clinical features include limited range of motion, weakness, and pain.<sup>5</sup> Pain and functional impairment of shoulder negatively affect daily activities, quality of life, and psychosocial well-being.<sup>6</sup> Emerging evidence suggested that damage of shoulder structures may not necessarily correlate with intensity and duration of SP.<sup>7,8</sup> Previous reviews have reported widespread mechanical hyperalgesia, referred pain, and impaired conditioned pain modulation in individuals with SP,<sup>9,10</sup> suggesting that hypersensitivity of the central nervous system plays a role beyond peripheral mechanisms. However, these reviews primarily summarized behavioral and

psychophysical evidence without directly examining objective brain changes using neuroimaging techniques. Therefore, it is crucial to synthesize evidence regarding abnormalities on brain images in individuals with SP to better understand mechanisms underlying SP.

As neuroimaging technology advances, it is possible to investigate the complex pain perception and modulation in various musculoskeletal pain conditions.<sup>11</sup> Several non-invasive modalities, such as magnetic resonance imaging (MRI), magnetoencephalography (MEG), positron emission tomography (PET), single-photon-emission computed tomography (SPECT/CT), functional near-infrared spectroscopy (fNIRS), and electroencephalogram (EEG), have been used to assess the structure and function of the brain.<sup>12</sup> In recent years, MRI has been extensively used in pain research because it offers high spatial resolution for imaging both cortical and deep brain structures, is non-invasive and free of ionizing radiation, and is widely available.<sup>13</sup> Numerous studies have revealed abnormal brain structure and function in musculoskeletal pain conditions, including lower back pain,<sup>14,15</sup> neck pain,<sup>16</sup> and knee osteoarthritis.<sup>17</sup> The structural and functional abnormalities in the brain have been identified in regions involved in emotional regulation, attention, memory, and self-referential processing, including the prefrontal cortex,<sup>18</sup> amygdala,<sup>19</sup> and insula.<sup>20</sup> Sensorimotor brain regions such as the precentral cortex<sup>21</sup> and cerebellum<sup>22</sup> also exhibit abnormalities. Although there are some common pain-processing brain regions,<sup>23</sup> various musculoskeletal pain conditions present unique patterns of brain abnormalities.<sup>24</sup>

Recent research has examined the potential abnormalities of specific brain regions in individuals with SP, such as the thalamocortical pathway<sup>25</sup> and prefrontal cortex.<sup>26</sup> Neuroimaging studies often exhibit heterogeneity in imaging techniques, analytical methods, and patient populations (eg, distinct diagnoses such as rotator cuff-related SP or adhesive capsulitis, which involve different pathophysiological mechanisms)<sup>27,28</sup> This methodological heterogeneity underscores the need for a systematic review to synthesize the existing evidence. However, no systematic reviews have summarized the brain abnormality pattern in individuals with SP. This review aimed to: (1) summarize evidence regarding structural and functional abnormalities in the brain of individuals with SP; and (2) determine the relationships between brain abnormalities and clinical outcomes. Understanding the potential brain abnormalities may help clinicians develop more targeted interventions for SP, such as neuromodulation.

## Materials and Methods

### Protocol

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol has been registered with PROSPERO (CRD42023454587).

### Search Strategy

The electronic databases of PubMed, Web of Science, EBSCO, and EMBASE were searched from inception to June 2025. The search strategy followed the PECO principle (Population: human adults; Exposure: SP; Comparison: healthy control; Outcome: the structural and functional abnormalities of the brain detected by brain imaging techniques such as MRI, fNIRS, EEG, MEG, PET and SPECT/CT, and the correlations between brain abnormalities and clinical outcomes such as pain intensity, pain duration, muscle strength, range of motion, and psychological outcomes). The reference lists of the included studies were also searched. Additionally, forward citation tracking was performed for the included studies using PubMed and Web of Science. The detailed search strategy is presented in [Appendix S1](#).

### Selection Strategy

All citations retrieved from each database were imported into Endnote. After duplicates were removed, three reviewers (B.F. and C.S.L.) independently screened the titles and abstracts for eligibility. Subsequently, the full texts were retrieved and assessed according to the inclusion and exclusion criteria. In case of disagreements between the three reviewers, a third reviewer (H.T.L.) was consulted to reach a consensus.

Studies were selected if they included: (1) participants with SP of any chronicity, including acute SP (duration of < 1 month), subacute SP (duration of 1–3 months), chronic SP (duration of > 3 months) and mixed chronicity;<sup>29</sup> (2) one or more brain imaging techniques for assessing brain structure or function; and (3) were published as full-text original

research reports. Studies were excluded if they: (1) were in vitro, animal or cadaveric studies; (2) had no comparison with a control group; (3) SP that did not originate from disorders within the shoulder joint (eg, pain due to neck problems, myofascial pain, fibromyalgia, complex regional pain syndrome, or other neurological disorders such as stroke); or (4) were study protocols, editorials, commentaries, opinion-based papers, reviews, or meta-analyses.

## Data Extraction and Data Synthesis

Two independent reviewers (B.F. and C.S.L.) extracted data using a standardized form that included: (1) study characteristics (authors, year of publication, study design); (2) participants' characteristics (sample size, age, sex, diagnosis, duration of symptoms, dominant hand, pain side); (3) characteristics of controls (sample size, age, sex, dominant hand); (4) methods used to assess brain structure or function (eg, functional magnetic resonance imaging (fMRI), etc); (5) outcome measures (eg, brain structure/region, brain function/activity, etc); and (6) clinical outcomes (eg, pain intensity, pain duration, shoulder function, and psychological outcomes, etc) for assessing the correlation with brain findings. Extracted data was synthesized through qualitatively description and summary tables according to brain structure, brain function, and clinical relationships.

## Assessments of Risk of Bias and Certainty of Evidence

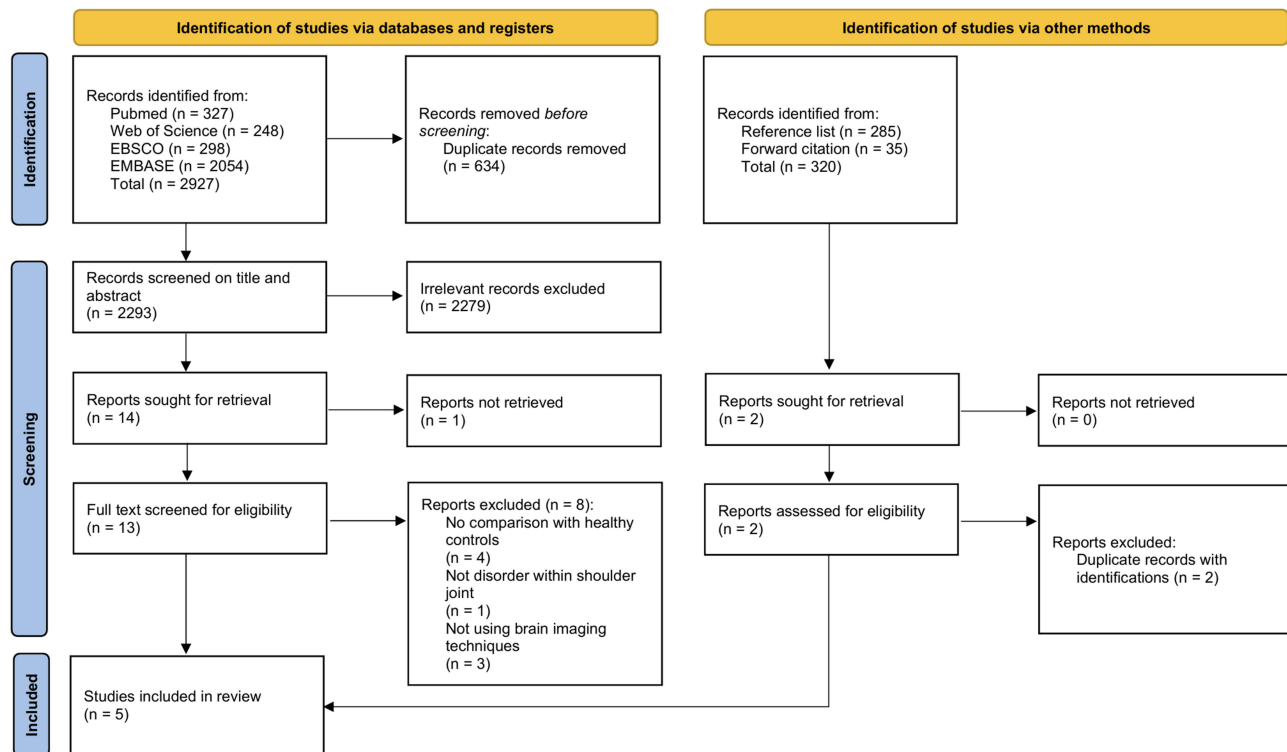
Two reviewers (B.F. and S.Q.C.) independently assessed the risk of bias using the Joanna Briggs Institute (JBI) checklist for analytical cross-sectional studies or JBI checklist for cohort studies.<sup>30</sup> This consists of eight questions regarding eligibility criteria, study sample, exposure measures, condition criteria, confounding factors, outcome measures, and statistical analysis. Each item is rated as either: yes, no, unclear, or not applicable. To determine the risk of bias of the included studies, an answer of “yes/no/unclear” was scored as “2/0/1”, respectively, and the percentage of the score in the total score was calculated. Items rated as “not applicable” were not included in the total score calculation. Scores of 75% or above, 55%–75%, and 55% or below were considered as low, moderate, and high risk of bias, respectively.<sup>31</sup> Scoring disagreements were resolved by consensus between the two reviewers or, if necessary, by a third reviewer (H.T.L). The intraclass correlation coefficient (ICC), using two-way mixed effects analysis for absolute agreement, was calculated using IBM SPSS Statistics 27.0 for Windows (IBM Corp., Armonk, NY, USA) to determine the inter-rater agreement between the two reviewers.

The certainty of evidence for brain findings and their correlations with clinical outcomes were determined using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE).<sup>32,33</sup> Outcomes were rated as having high, moderate, low, or very low certainty evidence according to the GRADE criteria.<sup>32,33</sup> The certainty of evidence was downgraded by one level (serious) or two levels (very serious) based on the following domains: (1) risk of bias: downgraded when the evidence was derived from more than 50% (serious) or 75% (very serious) of studies classified as having a moderate or high risk of bias (assessed using the JBI checklist); (2) inconsistency: downgraded when results were inconsistent across more than 50% (serious) or 75% (very serious) of the studies regarding the direction or magnitude of effect, or methodological heterogeneity; (3) indirectness: downgraded when more than 50% (serious) or 75% (very serious) of the included studies differed significantly from the primary review question in terms of populations or outcome measures; (4) imprecision: downgraded by one level (serious) when the total sample size contributing to an outcome was less than 400,<sup>34</sup> or by two levels (very serious) when the outcomes was based on a single study; and (5) publication bias: downgraded by a maximum of one level when there was clear evidence of selective reporting.

## Results

### Study Selection

A total of 2,927 articles were retrieved from the databases. After the removal of duplicates, 2,293 titles and abstracts were screened, with 14 included for full-text screening. The full text of one potential study was not available despite contacting the corresponding author who did not reply. Of the 13 remaining articles, five met the inclusion criteria. The reasons for exclusion were: (1) no comparison with healthy controls (n = 4); (2) disorder unrelated to the shoulder joint (n = 1); (3) no brain imaging (n = 3). The detailed screening flow diagram is shown in [Figure 1](#).



**Figure 1** The detailed screening flow diagram.

## Study Characteristics

The characteristics of the included studies are summarized in Table 1. The five included studies used a cross-sectional design. It is noteworthy that the healthy control groups in Li et al 2020<sup>35</sup> and Wei et al 2022<sup>36</sup> shared identical demographic characteristics, indicating potential overlap in control participants. Therefore, a total of 345 unique participants (199 individuals with SP and 146 healthy controls) were included in these studies after accounting for the shared healthy control cohort (n = 24) between Li et al<sup>35</sup> and Wei et al<sup>36</sup>. The non-unique total number of participants was 369. The sample size per study ranged from 39 to 104. Their mean age ranged from 43.2 to 76.3 years. The diagnoses of SP included rotator cuff-related SP,<sup>37</sup> adhesive capsulitis,<sup>25,26</sup> and SP for which the specific diagnosis was not reported in the original studies.<sup>35,36</sup> Among the five studies, only one study reported a mean pain duration of  $6.38 \pm 6.05$  months for SP participants,<sup>35</sup> and the remaining four studies did not report the mean pain duration for SP group.<sup>25,26,36,37</sup>

All included studies used MRI to compare brain structure and function between individuals with SP and healthy controls.<sup>25,26,35–37</sup> Four studies assessed the structural differences in grey matter (measured as volume, density, cortical thickness, asymmetry index of cortical surface area, and asymmetry index of cortical thickness),<sup>25,26,36,37</sup> and one study assessed the structural differences of white matter<sup>37</sup> (measured as fractional anisotropy reflecting the integrity and orientation of white matter).<sup>38</sup> All five studies assessed brain function using resting-state fMRI.<sup>25,26,35–37</sup> For the resting-state analyses, all five studies examined functional connectivity,<sup>25,26,35–37</sup> which reflects functional synergy across brain regions,<sup>39</sup> two studies measured regional homogeneity (ReHo),<sup>26,35</sup> which represents the functional coordination of local brain regions,<sup>40</sup> and one study measured the amplitude of low-frequency fluctuation (ALFF),<sup>25</sup> which reflects the intensity of regional spontaneous neural activity.<sup>41</sup>

Four included studies explored the correlation between brain abnormalities and clinical outcomes.<sup>25,26,35,36</sup> Specifically, four assessed pain intensity,<sup>25,26,35,36</sup> one examined pain threshold,<sup>25</sup> three measured pain duration,<sup>26,35</sup> two assessed shoulder function,<sup>35,36</sup> one examined pain vigilance and awareness,<sup>25</sup> and one assessed depressive symptoms.<sup>26</sup>

Regarding correction for multiple comparisons, all the five included studies applied appropriate correction methods (such as threshold-free cluster enhancement with family-wise error correction, false discovery rate, and Gaussian random

**Table 1** Study Characteristics

Study (Authors, Publication Years, Study Design)	Participants Characteristics		Brain Imaging Method	Brain Imaging Outcomes	Clinical Outcomes Measured
	Participants with Shoulder Pain (Sample Size, Age, Sex, Diagnosis, Duration of Symptoms, Dominant Hand, Pain Side)	Healthy Controls (Sample Size, Age, Sex, Dominant Hand)			
Conboy et al 2021 <sup>37</sup> Cross-sectional study	n = 21 Mean age = 76.3 ± 7.68 years Male = 18; Female = 3 Rotator cuff tear Duration of symptoms = NR Dominant hand: 18 right-handed; 3 left-handed Pain side: 11 right side; 4 left side; 6 bilateral side	n = 18 Mean age = 74.9 ± 6.59 years Male = 12; Female = 6 Dominant hand: NR	Structural MRI	<ul style="list-style-type: none"> <li>● Grey matter density</li> <li>● Cortical thickness</li> <li>● Fractional anisotropy of white matter</li> </ul>	NR
			fMRI	<ul style="list-style-type: none"> <li>● Functional connectivity</li> </ul>	
Li et al 2023 <sup>37</sup> Cross-sectional study	n = 52 Mean age = 45.4 ± 10.3 years Male = 26; Female = 26 Adhesive capsulitis Duration of symptoms = NR Dominant hand: all right-handed Pain side: 24 right side; 20 left side; 8 bilateral side	n = 52 Mean age = 43.2 ± 6.7 years Male = 26; Female = 26 Dominant hand: all right-handed	Structural MRI	<ul style="list-style-type: none"> <li>● Grey matter volume</li> </ul>	Pain intensity: numerical rating scale Pain threshold: using electrical stimulation Pain vigilance and awareness questionnaire
			fMRI	<ul style="list-style-type: none"> <li>● Functional activity (ALFF)</li> <li>● Functional connectivity</li> </ul>	
Li et al 2020 <sup>37</sup> Cross-sectional study	n = 37 Mean age = 53.65 ± 5.45 years Male = 20; Female = 17 Shoulder pain without specified diagnosis Duration of symptoms = 6.38 ± 6.05 months Dominant hand: all right-handed Pain side: NR	n = 24* Mean age = 55.83 ± 4.72 years Male = 10; Female = 14 Dominant hand: all right-handed	fMRI	<ul style="list-style-type: none"> <li>● Functional activity (ReHo)</li> <li>● Functional connectivity</li> </ul>	Pain intensity: visual analog scale Shoulder function: Constant-Murley score Pain duration
Wei et al 2022 <sup>36</sup> Cross-sectional study	n = 37 Mean age = NR Male = 22; Female = 15 Unilateral shoulder pain without specified diagnosis Duration of symptoms = NR Dominant hand: all right-handed Pain side: 15 right side; 22 left side	n = 24* Mean age = 55.83 ± 4.72 years Male = 10; Female = 14 Dominant hand: all right-handed	Structural MRI	<ul style="list-style-type: none"> <li>● Asymmetry index of cortical surface area</li> <li>● Asymmetry index of cortical thickness</li> </ul>	Pain intensity: visual analog scale Shoulder function: Constant-Murley score
			fMRI	<ul style="list-style-type: none"> <li>● Functional connectivity</li> </ul>	
Li et al 2024 <sup>26</sup> Cross-sectional study	n = 52 Mean age = 48.1 ± 10.2 years Male = 26; Female = 26 Adhesive capsulitis Duration of symptoms = NR Dominant hand: NR Pain side: NR	n = 52 Mean age = 47.3 ± 7.5 years Male = 26; Female = 26 Dominant hand: NR	Structural MRI	<ul style="list-style-type: none"> <li>● Grey matter volume</li> </ul>	Pain intensity: numerical rating scale Depression: hospital anxiety and depression scale Pain duration
			fMRI	<ul style="list-style-type: none"> <li>● Functional activity (ReHo)</li> <li>● Functional connectivity</li> </ul>	

**Notes:** \*The healthy control groups in Li et al<sup>35</sup> and Wei et al<sup>36</sup> shared identical demographic characteristics, indicating potential overlap in control participants. To avoid double-counting, their 24 participants were counted only once.

**Abbreviations:** MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; NR, no report; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity.

field theory) for the analysis examining structural and functional differences between individuals with SP and healthy controls. However, for the correlation analyses between brain imaging measures and clinical outcomes, only one study (Li et al 2024) explicitly reported using Bonferroni correction.<sup>26</sup> The remaining three studies that examined clinical correlations did not report applying correction for multiple comparisons.<sup>25,35,36</sup> The methodological characteristics of the included studies were shown in [Appendix S2](#).

## Risk of Bias Assessments

Table 2 shows the JBI score of each article. The scores ranged from 62.5% to 81.25%. There was no “not applicable” answer for any items in the included studies. Three studies showed low risk of bias<sup>25,26,37</sup> and two studies<sup>35,36</sup> showed moderate risk of bias. The ICC for the inter-rater reliability was 0.75. All discrepancies identified during the initial stage were subsequently resolved through discussion involving a third reviewer. The results of the certainty of evidence assessment using GRADE are shown in [Appendix S3](#).

## Syntheses of Results

### Abnormalities in Brain Structure

#### Grey Matter

The results of structural abnormalities are shown in Table 3. Among the four studies that compared the differences in grey matter between individuals with SP and healthy controls,<sup>25,26,36,37</sup> two studies reported significant lower grey matter volume in bilateral thalamus,<sup>25</sup> left amygdala,<sup>26</sup> and right ventromedial prefrontal cortices<sup>26</sup> in individuals with SP. One study reported significantly lower grey matter density in the left thalamus, left postcentral gyrus, left anterior intra-parietal sulcus, left inferior parietal lobule, and right temporal-parietal junction in individuals with SP compared to healthy controls.<sup>37</sup> One study found significantly smaller cortical thickness in the right temporal-parietal junction, right superior temporal sulcus, and right inferior temporal cortex in individuals with SP compared to healthy controls.<sup>37</sup> Another study examined the asymmetry index of cortical surface area and the asymmetry index of cortical thickness and reported no significant differences in the precentral and postcentral cortex in individuals with unilateral left or right SP compared to healthy controls.<sup>36</sup> In summary, although two studies with low risk of bias consistently reported smaller volume and density of thalamus grey matter in individuals with SP, the certainty of evidence was very low due to the small sample size, heterogeneous measures and the observational study design. Very low-certainty evidence also supported grey matter structural abnormalities in other brain regions that are responsible for sensory integration, emotion, and cognitive processing, such as the postcentral cortex, amygdala, ventromedial prefrontal cortices, and parietal and temporal cortices.

#### White Matter

Only one included study compared the white matter structure between individuals with and without SP by calculating fractional anisotropy.<sup>37</sup> This study found lower fractional anisotropy of white matter in the bilateral inferior frontal occipital fasciculus, bilateral inferior longitudinal fasciculus, right superior longitudinal fasciculus, and right optic radiations in individuals with SP<sup>37</sup> despite the very low-certainty of evidence.

### Abnormalities in Brain Function

The results of resting-state fMRI are presented in Table 3. Of the five studies that assessed functional connectivity, heterogeneous findings were reported, showing both greater and lower intensity of functional connectivity in various brain regions.<sup>25,26,35–37</sup> Individuals with SP demonstrated significantly lower functional connectivity between the motor network

**Table 2** Results of Risk of Bias Assessment Using Joanna Briggs Institute Checklist

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total Score	Risk of Bias
Conboy et al 2021 <sup>37</sup>	2	2	1	2	1	2	1	2	81.25%	Low
Li et al 2023 <sup>25</sup>	2	2	0	2	1	2	1	2	75%	Low
Li et al 2020 <sup>37</sup>	2	2	0	0	1	2	1	2	62.5%	Moderate
Wei et al 2022 <sup>36</sup>	2	2	0	0	1	2	1	2	62.5%	Moderate
Li et al 2024 <sup>26</sup>	2	2	0	2	1	2	1	2	75%	Low

**Notes:** 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?

**Table 3** Summary of Magnetic Resonance Imaging (MRI) Findings of the Included Studies That Compared Brain Structure/Function Between Individuals with Shoulder Pain and Controls

Study	Diagnosis of Shoulder Pain	Brain Imaging Method	Brain Imaging Outcomes	Main Finding
<b>Brain structures: Grey matter</b>				
Conboy et al 2021 <sup>37</sup>	Rotator cuff tear	Structural MRI	Density	↓: left postcentral gyrus, left anterior intra-parietal sulcus, left inferior parietal lobule, right temporal-parietal junction around the superior temporal sulcus and left thalamus
Li et al 2023 <sup>25</sup>	Adhesive capsulitis	Structural MRI	Volume	↓: bilateral thalamus
Li et al 2024 <sup>26</sup>	Adhesive capsulitis	Structural MRI	Volume	↓: left amygdala and right ventromedial prefrontal cortices
Conboy et al 2021 <sup>37</sup>	Rotator cuff tear	Structural MRI	Cortical thickness	↓: right temporal-parietal junction, right superior temporal sulcus, and right inferior temporal cortex
Wei et al 2022 <sup>36</sup>	Unilateral shoulder pain without specified diagnosis	Structural MRI	Cortical thickness	No difference between left-sided and right-sided shoulder pain
Wei et al 2022 <sup>36</sup>	Unilateral shoulder pain without specified diagnosis	Structural MRI	Cortical surface area	No difference between left-sided and right-sided shoulder pain
<b>Brain structures: White matter</b>				
Conboy et al 2021 <sup>37</sup>	Rotator cuff tear	Diffusion-weighted MRI	Fractional anisotropy	↓: left and right inferior frontal occipital fasciculus, left and right inferior longitudinal fasciculus, right superior longitudinal fasciculus and right optic radiations
<b>Brain function: Functional connectivity</b>				
Conboy et al 2021 <sup>37</sup>	Rotator cuff tear	fMRI	Functional connectivity	↓: between motor network and right middle temporal visual cortex No difference in strength of intrinsic functional connectivity of the motor network
Li et al 2023 <sup>25</sup>	Adhesive capsulitis	fMRI	Functional connectivity	↑: between left thalamus and left postcentral gyrus
Li et al 2020 <sup>35</sup>	Shoulder pain without specified diagnosis	fMRI	Functional connectivity	↓: between right orbitofrontal cortex and right rectus gyrus; between right orbitofrontal cortex and right superior frontal gyrus
Wei et al 2022 <sup>37</sup>	Unilateral shoulder pain without specified diagnosis	fMRI	Functional connectivity	↑: between left postcentral and right cingulate gyrus between left postcentral and left paracentral lobule between right postcentral and left caudate between right postcentral and left paracentral lobule between right postcentral and left postcentral between right precentral and right cingulate gyrus between right precentral and right precuneus between right precentral and left paracentral
Li et al 2024 <sup>26</sup>	Adhesive capsulitis	fMRI	Functional connectivity	↑: between right ventromedial prefrontal cortices and right anterior cingulate cortex
<b>Brain function: Functional activity</b>				
Li et al 2023 <sup>25</sup>	Adhesive capsulitis	fMRI	ALFF	↑: left thalamus and bilateral anterior cingulate cortex
Li et al 2020 <sup>35</sup>	Shoulder pain without specified diagnosis	fMRI	ReHo	↑: left middle temporal gyrus ↓: right orbitofrontal cortex
Li et al 2024 <sup>26</sup>	Adhesive capsulitis	fMRI	ReHo	↓: right ventromedial prefrontal cortices

**Note:** ↓ = reduce; ↑ = increase.

**Abbreviations:** MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity.

and right middle temporal visual cortex,<sup>37</sup> between the right orbitofrontal cortex and right rectus gyrus,<sup>35</sup> and between the right orbitofrontal cortex and right superior frontal cortex.<sup>35</sup> Other studies showed significantly greater functional connectivity in the left postcentral gyrus with the left thalamus,<sup>25</sup> right cingulate gyrus,<sup>36</sup> left paracentral lobule,<sup>36</sup> and right postcentral gyrus;<sup>36</sup> in the right postcentral gyrus with the left caudate<sup>36</sup> and left paracentral lobule;<sup>36</sup> in the right precentral gyrus with the right cingulate cortex,<sup>36</sup> right precuneus,<sup>36</sup> and left paracentral lobule;<sup>36</sup> and between the right ventromedial prefrontal cortices and right anterior cingulate cortex<sup>37</sup> when compared to healthy individuals. Among the five studies examining functional connectivity abnormalities, only one reported directional variations in functional connectivity, showing that individuals with SP presented a negative correlation in functional activity between the motor network and right middle temporal visual cortex, rather than a positive correlation observed in healthy controls.<sup>37</sup> Two studies found varied patterns of ReHo between groups.<sup>26,35</sup> Individuals with SP demonstrated lower ReHo in the right orbitofrontal cortex<sup>35</sup> and right ventromedial prefrontal cortices,<sup>26</sup> while there was greater ReHo in the left middle temporal gyrus in individuals with SP.<sup>35</sup> Only one study found a greater ALFF in the left thalamus and bilateral anterior cingulate cortex in individuals with SP.<sup>25</sup> In summary, very low-certainty evidence supported heterogenous brain functional abnormalities (such as the thalamus, ventromedial prefrontal cortices, anterior cingulate cortex, middle temporal cortex, orbitofrontal cortex, and precentral and postcentral cortex) in individuals with SP.

### Correlations with Clinical Outcomes

#### Pain Intensity

Two included studies revealed a significant association between pain intensity and brain structural abnormalities in individuals with SP.<sup>25,36</sup> (Table 4). Higher pain intensity was associated with smaller grey matter volume of bilateral thalamus ( $r = -0.32$ ,  $p = 0.02$ )<sup>25</sup> and a smaller asymmetry index of the cortical surface area in the precentral cortex for left SP ( $r = -0.57$ ,  $p = 0.01$ ).<sup>36</sup> However, it should be noted that these studies did not report applying correction for multiple comparisons in their correlation analyses<sup>25,36</sup> and the risk of false-positive findings is increased. Functionally, higher pain intensity was associated with greater functional connectivity between right ventromedial prefrontal cortex and right anterior cingulate cortex ( $r = 0.44$ ,  $p = 0.005$ ).<sup>26</sup> However, the certainty of evidence was very low as only one cross-sectional study reported the correlation.

#### Pain Threshold

**Table 4** Correlations Between Brain Abnormalities and Clinical Outcomes

Study	Brain Imaging Method	Brain Imaging Outcomes	Correlations with Clinical Outcomes				
			Pain Intensity	Pain Threshold	Pain Duration	Shoulder Function	Psychological Factors
<b>Brain structure</b>							
Li et al 2023 <sup>37</sup>	Structural MRI	Grey matter volume	Bilateral thalamus ( $r = -0.32$ , $p = 0.02$ )	Bilateral thalamus ( $r = 0.56$ , $p < 0.001$ )	NR	NR	NR
Wei et al 2022 <sup>36</sup>	Structural MRI	Asymmetry index of cortical surface area	Precentral regions (left-sided shoulder pain; $r = -0.57$ , $p = 0.01$ )	NR	NR	Precentral regions (left-sided shoulder pain; $r = 0.47$ , $p = 0.03$ ) Postcentral regions (left-sided shoulder pain; $r = 0.46$ , $p = 0.03$ )	NR
Li et al 2024 <sup>26</sup>	Structural MRI	Grey matter volume	NR	NR	Ventromedial prefrontal cortices ( $r = 0.47$ , $p = 0.004$ )	NR	Ventromedial prefrontal cortices ~ depression symptoms ( $r = 0.58$ , $p < 0.001$ )

(Continued)

Table 4 (Continued).

Study	Brain Imaging Method	Brain Imaging Outcomes	Correlations with Clinical Outcomes				
			Pain Intensity	Pain Threshold	Pain Duration	Shoulder Function	Psychological Factors
<b>Brain function</b>							
Li et al 2023 <sup>25</sup>	fMRI	ALFF	No correlation	No correlation	NR	NR	Anterior cingulate cortex ~ pain vigilance and awareness questionnaire (r = 0.35, p = 0.01)
		Functional connectivity	Functional connectivity (between left thalamus and left postcentral gyrus) (No correlation)	Functional connectivity (between left thalamus and left postcentral gyrus) (r = NR, p = NR)	NR	NR	NR
Li et al 2020 <sup>35</sup>	fMRI	ReHo	Left middle temporal gyrus and right orbitofrontal cortex (No correlation)	NR	Left middle temporal gyrus and right orbitofrontal cortex (No correlation)	Left middle temporal gyrus and right orbitofrontal cortex (No correlation)	NR
Wei et al 2022 <sup>36</sup>	fMRI	Functional connectivity	NR	NR	NR	Functional connectivity (between right precentral gyrus and right cingulate gyrus) (right-sided shoulder pain; r = 0.53, p = 0.04)	NR
Li et al 2024 <sup>26</sup>	fMRI	Functional connectivity	Functional connectivity (between right ventromedial prefrontal cortices and right anterior cingulate cortex) (r = 0.44, p = 0.005)	NR	Functional connectivity (between right ventromedial prefrontal cortices and right anterior cingulate cortex) (No correlation)	NR	Functional connectivity (between right ventromedial prefrontal cortices and right anterior cingulate cortex) ~ depression symptoms (No correlation)
		ReHo	No correlation	NR	No correlation	NR	NR

**Abbreviations:** MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; NR, no report; ALFF, amplitude of low-frequency fluctuation; ReHo, regional homogeneity.

There was only one study reporting that lower pain thresholds were related to a smaller grey matter volume of the bilateral thalamus in people with SP (r = 0.56, p < 0.001)<sup>25</sup> and associated with functional connectivity between the left thalamus and left postcentral gyrus (not reporting the direction of the association),<sup>25</sup> without correction for multiple comparisons in the correlation analyses. The certainty of evidence was very low.

#### Pain Duration

One structural MRI study revealed that longer pain duration was correlated with greater grey matter volume in the ventromedial prefrontal cortices (r = 0.47, p = 0.004).<sup>26</sup> However, the certainty of evidence was also very low.

#### Shoulder Function

Very low-certainty evidence from one MRI study showed that<sup>36</sup> poorer shoulder function of individuals with left SP was correlated with a smaller asymmetry index of the cortical surface area in the precentral (r = 0.47, p = 0.03) and postcentral cortex (r = 0.46, p = 0.03). Additionally, functional MRI analyses demonstrated worse shoulder function of

individuals with right SP was associated with lower functional connectivity linking the right precentral gyrus and right cingulate gyrus ( $r = 0.53$ ,  $p = 0.04$ ).<sup>36</sup> However, the risk of false-positive findings was increased due to the lack of correction for multiple comparisons and the certainty of evidence was very low.

### Psychological Factors

Two included studies found brain structural and functional abnormalities were related to psychological factors, such as depressive symptoms,<sup>26</sup> and pain vigilance and awareness.<sup>25</sup> Greater grey matter volume in the ventromedial prefrontal cortices was associated with more severe depressive symptoms ( $r = 0.58$ ,  $p < 0.001$ ).<sup>26</sup> More severe pain vigilance and awareness was reported to be correlated with greater ALFF within the anterior cingulate cortex ( $r = 0.35$ ,  $p = 0.01$ ) without correction for multiple comparisons.<sup>25</sup> Again, the certainty of evidence was very low.

## Discussion

This systematic review was the first to synthesize evidence regarding brain abnormalities in individuals with SP compared to healthy controls. The overall certainty of evidence was rated as very low due to the small number and heterogeneity of studies. Very low-certainty evidence suggests possible structural and functional alterations in brain regions responsible for pain processing, emotional regulation, and sensorimotor integration compared with healthy controls. These brain abnormalities may be associated with higher pain intensity, lower pain threshold, longer pain duration, as well as poor shoulder function and psychological outcomes.

### Pain Processing

This review found that individuals with SP have less grey matter in the thalamus compared to healthy controls,<sup>25,37</sup> which is correlated with higher pain intensity and lower pain thresholds (uncorrected for multiple comparison, with increased risk of false positives).<sup>25</sup> Additionally, greater spontaneous activity of thalamus and functional connectivity between postcentral cortex and thalamus have been observed in individuals with SP.<sup>25</sup> The thalamus serves as an important relay station of nociceptive signal transmission, integrating sensory input and regulating pain perception.<sup>42</sup> Overactivation of the thalamus may lead to excitatory toxicity and subsequent atrophy.<sup>25,43,44</sup> Therefore, the observed smaller thalamic grey matter in those with SP raises the possibility of maladaptive plasticity resulting from shoulder nociceptive inputs.<sup>45</sup> These structural abnormalities may disrupt the role of thalamus in modulating sensory signals, which leads to the amplification of pain signals and contributes to central sensitization.<sup>46,47</sup> Indeed, central sensitization has been identified in individuals with SP,<sup>9</sup> which may involve the maladaptive plasticity of the thalamus. These findings raise the possibility that the thalamus could be a potential treatment target in future neuromodulation studies.

Although these abnormalities in the thalamus are relatively consistent across two MRI studies,<sup>25,37</sup> one study measured grey matter volume (Li et al 2023)<sup>25</sup> and the other measured grey matter density (Conboy et al 2021).<sup>37</sup> Therefore, the certainty of evidence remains very low, given the heterogenous methodologies, small sample sizes, and the cross-sectional study design. Further high-quality, prospective MRI studies with larger sample sizes and long follow-up are needed to confirm the causal relationships between the thalamic abnormalities and clinical outcomes of SP, as well as its role and potential as a biomarker and therapeutic target.

The findings of the thalamic abnormalities are consistent with previous systematic reviews reporting lower grey matter volume of the thalamus in individuals with complex regional pain syndrome<sup>48</sup> and low back pain.<sup>49</sup> In contrast, greater thalamus grey matter volume has been observed in individuals with temporomandibular pain.<sup>50</sup> These differences may be due to the specific locations of pain, supporting the previous observation that pain-related brain abnormalities are location-specific.<sup>51</sup>

### Emotional Regulation

Functional MRI studies may indicate functional reorganization in brain regions involved in the emotional and cognitive dimensions of pain in individuals with SP. Specifically, this review identified functional abnormalities in the cingulate cortex, including greater spontaneous activity;<sup>25</sup> greater functional connectivity with the ventromedial prefrontal cortex;<sup>26</sup> and enhanced functional connectivity with precentral and postcentral gyrus.<sup>36</sup> The cingulate cortex is a key region mediating

the affective-motivational and cognitive-evaluative components of pain experience, and it plays an essential role in encoding the emotional distress of pain.<sup>52-54</sup> Overactivation of the cingulate cortex may amplify the perceived threat of pain, driving catastrophic cognition and avoidance behaviour towards pain.<sup>52,55</sup> This is consistent with the observed correlations between anterior cingulate cortex activity and pain vigilance and awareness in the individuals with SP (uncorrected for multiple comparison, with increased risk of false positives).<sup>25</sup> The activation of the cingulate cortex has been observed across various musculoskeletal pain conditions, including low back pain<sup>56,57</sup> and fibromyalgia.<sup>58</sup>

Structural and functional abnormalities were also reported in the ventromedial prefrontal cortex, orbitofrontal cortex, and amygdala,<sup>26,35</sup> which are the brain regions responsible for emotion regulation in pain conditions.<sup>59,60</sup> Interestingly, longer pain duration and more severe depressive symptoms appeared to be correlated with greater grey matter volume in the ventromedial prefrontal cortices of individuals with SP,<sup>26</sup> which seemed to contradict the finding of lower grey matter volume of the ventromedial prefrontal cortices in those with SP compared with healthy controls.<sup>26</sup> Ventromedial prefrontal cortices are also involved in descending antinociceptive pathways.<sup>61</sup> Antinociceptive compensatory reorganization of the brain was found in response to nociceptive stimulation,<sup>62</sup> indicating the possibility that such compensation may mitigate the grey matter volume reduction of ventromedial prefrontal cortices within the SP group, although the overall grey matter volume in the SP group was lower than healthy controls. However, more studies are warranted to clarify this.

These results should be interpreted with considerable caution given the small number of studies, heterogenous methodologies, cross-sectional study design, and very low certainty of evidence. These findings raise the possibility that addressing emotional problems may be beneficial in SP management, such as mindfulness and cognitive behavioral therapy.<sup>63-65</sup> However, whether these interventions can modulate these brain regions and improve outcomes in individuals with SP remains to be investigated in future high-quality studies.

## Sensorimotor Integration

This review found structural and functional reorganization within the sensorimotor networks of individuals with SP, although the certainty of evidence is very low.<sup>25,36,37</sup> Studies have reported greater functional connectivity between the sensorimotor cortex and both the thalamus and cingulate cortices,<sup>25,36</sup> as well as lower grey matter density in the postcentral cortex and temporal-parietal junction.<sup>37</sup> Importantly, abnormalities in the structure and function of the sensorimotor cortex appeared to be associated with impaired shoulder function (uncorrected for multiple comparison, with increased risk of false positives).<sup>36</sup> Similar reviews in other pain conditions reported evidence for grey matter abnormalities in the postcentral gyrus of those with low back pain<sup>57</sup> and abnormal motor cortex function in those with temporomandibular pain.<sup>50</sup> Abnormalities in these brain regions, which are responsible for multisensory integration and motor planning, may support the sensorimotor impairments observed in individuals with SP.<sup>66</sup> Conboy et al 2021 also used behavioural testing conducted to demonstrate the sensory integration impairment and disruption of movement perception in individuals with SP.<sup>37</sup> Individuals with SP are found to modify their movement patterns and avoid pain-provoking activities due to fear-avoidance belief.<sup>67,68</sup> Evidence indicates that immobilization can lead to cortical reorganization,<sup>69-71</sup> supporting the hypothesis that maladaptive abnormalities in sensorimotor networks may reflect cortical plasticity in response to a pain-induced protective movement strategy.

These observations should be viewed as hypothesis-generating, due to limited number of studies, cross-sectional study design, and methodological heterogeneity. These results may suggest that maladaptive changes in sensorimotor networks might correlate to functional impairment in those with SP. They could provide a theoretical rationale for exploring whether interventions targeting sensorimotor reorganization, such as graded motor imagery,<sup>72</sup> could be beneficial in individuals with SP.

## Limitations and Future Research

This study has several limitations. Firstly, there are only five included studies with potentially overlapping cohorts and small sample sizes, and most identified abnormalities in the various brain regions were only reported by a single study. Therefore, the generalizability of these results was limited, and should be interpreted with caution. Secondly, there was significant heterogeneity in the analytical metrics (such as voxel-based morphometry and surface morphology) and patient populations (such as rotator cuff tears, adhesive capsulitis, and SP without specified diagnosis) of the included studies, which precluded direct results comparisons across these studies. The clinical heterogeneity limits the generalizability of our findings to the

entire SP population. Future work should prioritize standardizing imaging protocols and data analysis frameworks to enable comparisons across studies. Thirdly, dominant hand and symptom duration of included participants were not reported in some studies. These variables are related to interpreting potential lateralization effects and the influence of pain chronicity on brain changes. Future studies should prioritize standardized reporting of these characteristics to enable comparisons. Fourthly, three included studies did not use correction for multiple comparisons in clinical correlation analysis, thereby increasing the risk of false positives. Consequently, the observed associations between brain alterations and clinical outcomes should be regarded as hypothesis-generating rather than definitive. Fifthly, all included studies used a cross-sectional design, which prevents the determination of causal association between brain abnormalities and pain. It remains unclear whether the observed neural abnormalities in individuals with SP are the cause or results of pain. Therefore, the translational implications of MRI findings require cautious interpretation. Future large-sample prospective studies are needed to clarify the causal relationship between neural abnormalities and pain progression.

## Conclusions

Very low-certainty evidence suggests that SP may be associated with structural and functional brain abnormalities in regions involved in pain processing, emotional regulation, and sensorimotor integration. These abnormalities appeared to correlate with pain intensity, pain threshold, pain duration, shoulder function, and psychological outcomes. However, given the methodological heterogeneity, small sample sizes, and the cross-sectional design of the included studies, these findings should be considered preliminary and hypothesis-generating. The causal association and clinical translational potential of these results remain to be clarified. The findings suggest a potential rationale for future high-quality longitudinal and interventional studies to confirm these observations and to explore whether targeting neuroplasticity (such as targeting the thalamus) could be beneficial in SP management.

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## Disclosure

All authors have no conflicts of interest to declare.

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