Tooth, C., Maricot, A., Verschueren, J., Gard. S., Tassignon, B. (2026). Structural and Functional Brain Differences Related to Recurrent Shoulder Instability: A Systematic Review. *JOSPT Open*. Advance publication. https://doi.org/10.2519/josptopen.2026.0157

Structural and functional brain differences related to recurrent shoulder instability: a systematic review

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PROSPERO registration number: CRD42023486507

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023486507

Number of words: 5450 words

Funding

No funding was received by the authors or their immediate families for performing the study. The authors declare no conflict of interest.

Author contributions

C.T. conceptualized the study and contributed to defining the research objectives. She conducted data extraction from the selected studies and wrote the initial draft of the manuscript. **A.M.** carried out the systematic literature search in PubMed, Web of Science, and Embase, screened articles based on inclusion and exclusion criteria, independently assessed the quality of the included studies, and extracted relevant data. He also assisted in writing the initial draft of the manuscript. **J.V.** provided critical revisions to the manuscript. **S.G.** assisted in data analysis and synthesis, contributed intellectual input to the discussion section, and provided critical revisions to the manuscript. **B.T.** supervised the study, ensured methodological rigor, contributed to the study design and conceptual framework, provided intellectual input in the discussion section, and critically revised the manuscript.

Patient involvement

Study participants were not involved in the design, conduct, interpretation, or translation of the current research.

Data sharing

All data relevant to the study are included in the article or are available as supplementary files.

Competing interests

The authors, their immediate families, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article.

Abstract

Objective

To explore (i) structural and functional brain changes associated with recurrent shoulder instability, and (ii) their associations with clinical outcomes.

Design

Systematic review of observational and case-control studies.

Literature Search

A comprehensive search was conducted in PubMed, Web of Science, and Embase for articles published up to December 2023. Reporting was guided by the PERSiST and PRISMA 2020 guidelines.

Study Selection Criteria

Peer-reviewed observational and case-control studies were eligible if they included individuals with recurrent shoulder instability and assessed structural or functional brain changes using neuroimaging.

Data Synthesis

The internal validity of included studies was evaluated using the NIH Quality Assessment Tool for Observational and Cross-Sectional Studies and the Tool for Case-Control Studies. Outcomes were synthesized qualitatively due to heterogeneity in imaging protocols and outcome measures.

Results

Seven studies met the inclusion criteria, involving 100 patients with recurrent shoulder instability and 70 healthy controls. Structural brain differences assessed via voxel-based morphometry (VBM) were not significant in three studies, and were significant in one. Six studies reported consistent patterns of neuroplasticity in functional brain outcomes, with increased functional connectivity in the primary sensorimotor cortex, dorsolateral prefrontal cortex, and anterior insula. Four studies identified significant correlations between brain connectivity measures and clinical scores, suggesting a link between sensorimotor and emotional regulation networks and functional outcomes in recurrent shoulder instability.

Conclusion

Functional, rather than structural, brain alterations appeared to be involved in recurrent shoulder instability. These findings support the relevance of central mechanisms in recurrent shoulder instability and require confirmation through longitudinal designs and larger cohorts.

Key words*:* neuroplasticity; imagery; motor control; pain; upper extremity

1. Introduction

Glenohumeral (shoulder) instability affects about 2% of the general population[1, 2]. Despite generally favourable rehabilitation outcomes following surgical and non-surgical treatment[3, 4], recurrent shoulder instability persists in up to 13% of affected patients[3, 5, 6]. This persistence is especially noted in young and female patients[7, 8]. In the sports context, rates of shoulder instability (4 per 100,000 athlete exposures) have been estimated at 35.6 in wrestling, 35.4 in football (soccer), and 28.6 in ice hockey. In rugby, shoulder dislocations and injuries represent about 14% of all injuries sustained and have the highest recurrence rate among injuries reported[9]. Shoulder instability is often misdiagnosed or underdiagnosed[2, 10]. The financial impact of shoulder dislocations, particularly recurrent cases, is considerable. The average cost of a single emergency department visit in the United States for shoulder dislocation was $2207, and shoulder stabilisation surgery $7807 in 2020[11].

Shoulder instability is associated with substantial physical and psychological deficits. Physical impairments include (chronic) pain, muscle weakness, and decreased range of motion, which can severely impact daily activities and athletic performance[7]. Different tests and questionnaires can assess these aspects and the repercussions on daily living activities. In clinical practice, the most used are the apprehension test[12-15], the Oxford Shoulder Instability Score[16, 17], the Western Ontario Shoulder Instability Index[18], the Rowe score[19], Subjective Shoulder Value[20] or the Simple Shoulder Test[21]. Psychologically, individuals with recurrent shoulder dislocations may experience anxiety, depression, and reduced quality of life due to the fear of re-injury and ongoing discomfort[22].

According to Lewis et al.[2], shoulder instability and apprehension (defined as anxiety and resistance in patients with a history of glenohumeral instability[23]) can be attributed to three different causes: (1) muscle patterning dysfunction, (2) structural defects resulting from a traumatic injury or (3) structural defects acquired through atraumatic processes. However, neuromuscular deficits following peripheral joint injuries, such as shoulder dislocations, are increasingly viewed as neurophysiological dysfunctions rather than merely local injuries[24].

Chronic neuromuscular alterations, partly due to the loss of afferent feedback mediated by mechanoreceptors, have been observed in the ankle and the knee[25-29]. The brain's fundamental role in the perception and modulation of musculoskeletal dysfunctions and associated (chronic) pain has been associated with clinical outcomes such as joint instability, altered muscle pattern recruitment, and pain[20, 30, 31]. These factors could increase the likelihood of re-injury and chronic instability due to altered motor control[25, 32]. Similarly, it is plausible that people with SI may experience structural or functional adaptations in somatosensory and motor brain areas, which could be related to developing recurrent shoulder instability. However, despite this understanding, conventional physiotherapy practices often do not integrate these insights into treatment and management[31, 33].

The 2022 Bern Consensus Group on Shoulder Injury Prevention, Rehabilitation and Return to Sport emphasised the importance of integrating neuroplasticity principles into shoulder injury rehabilitation[34]. Consolidating current knowledge by providing a comprehensive overview of brain structure and function among people with shoulder instability could inform clinical practice. A previous systematic review focused exclusively on functional cortical adaptations related to shoulder instability. We update and expand these findings by integrating recent evidence on functional and structural brain adaptations, and their associations with clinical outcomes.

2. Methods

This systematic review was developed, executed, and written following the PERSiST[35] and PRISMA 2020 Statement[36] guidelines. The PRESS Guideline Statement[37] and the PRISMA-S guidelines[38] were used to strengthen the literature search and its reporting. The protocol was registered in the PROSPERO database (CRD42023486507).

2.2 Search strategy and selection criteria

We used the PICO framework (Population – Intervention – Comparison – Outcome) to formulate the review question: "Which cerebral neural differences are related to shoulder instability? Three databases (PubMed, Web of Science and Embase) as well as the reference list of included studies were systematically searched. The systematic literature search was finalised on the 17th of July 2025. No filters were applied. Grey literature (study registries and other online sources) was not searched. Table 1 outlines our search strategy.

Primary research, comparative analyses and re-analysis of published data were included. Meta-analyses, systematic reviews, and narrative reviews were excluded. Articles written in English, French or Dutch were included. Eligible studies involved patients with shoulder instability and recurrent shoulder instability. Shoulder instability was defined as symptomatic glenohumeral joint instability in one or more directions[39]. Recurrent shoulder instability is the occurrence of repeated instability events of either a subluxation or a dislocation[40].

2.3 Eligibility assessment

We conducted a two-stage selection process in which two reviewers (AM and AD) independently assessed the remaining articles using Rayyan's web application (https://rayyan.ai/). Duplicates were removed through Rayyan's automated duplicate removal tool. One author (AM) manually checked for any additional duplicates. We included studies investigating structural and functional brain outcomes in patients with shoulder instability older than 18 years.

Research on other injuries (e.g. no instability, muscle tears, fractures), animals or cadavers, or not investigating brain function and structure were excluded. During the first selection stage, articles were screened on title and abstract using the PICO framework, study design and language. The remaining articles were reviewed on full-text independently and included according to the same criteria. If no full text was available, the corresponding author was contacted. Conflicts were

resolved through discussion, and a third reviewer (BT) was contacted if consensus could not be reached.

2.4 Quality assessment

The internal validity of included studies was appraised using the 'Quality Assessment Tool for Observational and Cross-Sectional Studies' and the 'Quality Assessment Tool for Case-Control Studies' according to their study design[41]. Two reviewers (AM and AD) independently rated the quality of the included studies and resolved differences through discussion.

Each response, denoted as 'Yes,' 'No,' or 'Other' (indicating 'could not determine', 'not applicable', 'not reported'), was converted to scores: 0, 2, or 1, respectively. A higher score indicates poorer quality. A cumulative score was assigned to each study, with those scoring 75% or higher than the possible highest score classified as poor quality, scores between 55% and below 75% as fair quality, and studies scoring less than 55% considered good.

2.5 Data extraction

Two reviewers independently extracted the following characteristics (AM and CT): author, publication year, study design, inclusion criteria, participant characteristics, sample size, methods for quantifying brain outcomes. The reviewers reported summary and spread measures of the primary outcomes, when available, and the statistical analysis methods from each study. Specific outcomes that describe structural & functional brain outcomes were extracted. Structural brain outcomes refer to measures that quantify the brain's anatomical and physical properties. Functional outcomes were brain activations associated with task performance and functional connectivity during task performance. If secondary outcome measures were computed, correlations between brain outcomes and clinical tests or questionnaires, they were also extracted.

3. Results

Out of 2209 articles, 1519 articles were screened after duplicates were removed. After the first round of screening, 28 articles remained and were assessed for full-text eligibility. Ultimately, seven articles were included[23, 42-47]. Figure 1 depicts the PRISMA flowchart detailing the study selection process. All extracted data are reported in Supplementary Material.

3.1 Quality assessment

Six of the seven included articles (85%) were considered fair regarding their overall quality assessment[23, 42, 43, 45-47]. One study[44] was rated as at low risk of bias. None of the included studies reported a sample size justification. All studies were unclear on whether brain changes occurred before the onset of recurrent shoulder instability and if exposure measures were consistently applied, compromising internal validity. There was a low risk of bias for defining the study population and differentiating patients from controls. Five out of six case-control studies (83.3%) had an increased risk of bias by not adjusting the statistical analysis for key potential confounding variables as they were not mentioned or not measured[23, 42, 43, 45-47]. One study blinded assessors for the health status of participants[42]. The quality assessments are depicted in figures 2a to 2d.

3.2 Brain neuroimaging findings

Across all studies, a pooled total of 100 patients with recurrent shoulder instability (male:female, 4:1) and 70 healthy controls (male:female, 2:1,) participated. fMRI was used in all studies. The most common analysis methods were voxel-based morphometry (VBM)23, 42, 47 and functional connectivity analysis[23, 42, 46]. An overview of the extracted data is provided in Supplementary Material.

Structural brain differences

VBM analysis was used in 3 studies to investigate differences in brain anatomy[23, 42, 46]. There were no significant differences in grey matter density using VBM between patients with recurrent shoulder

instability and healthy controls[23, 42]. Zanchi et al. (2017)[46] reported higher fractional anisotropy values in the left internal capsule and adjacent thalamic regions in patients with shoulder instability compared to healthy controls, suggesting subtle alterations in white-matter microstructure.

Functional brain connectivity

Functional connectivity was assessed using an independent component analysis approach[23, 42, 47], which decomposes fMRI data into independent components, reflecting spatially independent components, each associated with a distinct time course. Functional connectivity analyses were performed in 3 cross-sectional studies[23, 42, 47]. Significant differences between patients with shoulder instability and healthy controls were found in the motor cortex, somatosensory and prefrontal cortex, ventral anterior cingulate cortex, posterior cinculate, precuneus and the anterior insula[23, 42, 47]. Patients with shoulder instability had increased connectivity in several brain areas: the bilateral primary sensorimotor area, dorsolateral prefrontal cortex, anterior insula, and dorsal anterior cingulate cortex. Specifically, Smode increased by 148% in the right hemisphere (IC 12) and 144% in the left hemisphere (IC 17)[23]. Patients with recurrent shoulder instability had reduced bilateral visual network in the parietal region compared to healthy controls (-185% Smode IC 30)[23]. Decreases in functional connectivity were found in the ventral anterior cingulate cortex, posterior cingulate and precuneus[47].

Brain activity related to shoulder outcomes

Brain activation patterns were investigated in five studies[23, 44, 45, 47]. The studies applied three main tasks to induce brain activation patterns: visual apprehension stimulation[23, 45, 47], passive shoulder motions[44, 45], and active shoulder tasks[43, 44].

Visual apprehension stimulation

Significantly higher apprehension-related activation was present ($p < 0.05$) while watching the apprehension videos in the right hippocampus (amygdala), right pre-central gyrus (MNI coordinates:

x:58, y:10, z:42) and left hippocampus in patients with shoulder instability compared to healthy controls[45].

When assessing the right shoulder of healthy participants compared to the right shoulder of participants with recurrent shoulder instability, patients had reduced activity in the left pre-central gyrus, right pre-central gyrus (MNI coordinates: x:34, y:-26, z:52), right inferior parietal lobule, left inferior parietal lobule, left fusiform gyrus, right fusiform gyrus, left post-central gyrus, right superior occipital gyrus, right superior parietal lobule, left paracentral lobule, straight gyrus, right middle orbital gyrus, left middle frontal gyrus, left posterior cingulate cortex, right inferior temporal gyrus, left thalamus[45].

There was reduced cortical activation in patients with shoulder instability during visual apprehension stimulation in the left motor cortex, left premotor cortex, somatosensory cortex, lateral occipital cortex, and middle temporal gyrus/para-hippocampal gyrus[47].

Passive shoulder motions

Internal and external rotation of the humerus in 90° abduction44, 45 was induced at a frequency of 1 Hertz. During these passive motion tasks, there were statistical differences in brain activation patterns in patients with shoulder instability compared to healthy controls[44, 45].

Healthy controls had more brain activation in the right superior frontal gyrus, right medial temporal pole, left inferior temporal gyrus[56, 57], right post-central gyrus, right pre-central gyrus[44, 45], left angular gyrus and the left middle temporal gyrus[45], left precentral gyrus (premotor area), left superior temporal gyrus, left caudate nucleus, right cerebellum lobule VI, right caudate nucleus & right insula[56].

Significantly higher brain activity was measured in the right superior temporal gyrus, right inferior parietal lobule, left rolandic operculum, right inferior frontal gyrus, left superior temporal gyrus, left precentral gyrus, left precuneus, right middle frontal gyrus, right precentral gyrus, right calcarine

gyrus, right angular gyrus, left posterior-medial frontal gyrus, left insula in patients with shoulder instability compared to healthy controls[44].

Active shoulder tasks

There were no statistical differences in cortical activation between movement type (abduction/forward flexion) and no significant interaction between group and movement type[43]. These tasks entailed isometric flexion, abduction or external rotation44 and dynamic flexion or abduction[43]. In patients with recurrent shoulder instability compared to healthy participants, significantly increased brain activity was observed during active shoulder tasks in the following brain regions at the cluster level: primary motor cortex, pre-central gyrus, inferior frontal gyrus, superior temporal gyrus, left rolandic operculum, right angular gyrus, right inferior parietal lobule, supramarginal gyrus, right calcarine gyrus, left precuneus, left posterior-medial frontal gyrus, right inferior frontal gyrus, right middle frontal gyrus43, 44. At the voxel level the primary motor cortex of the left hemisphere stayed statistically significant[43].

During dynamic forward flexion and abduction compared to the shoulder in resting state, patients had increased activation in the primary motor cortex, supramarginal gyrus, inferior frontal gyrus, pre-central gyrus and middle frontal gyrus[43]. In the parahippocampal gyrus and perirhinal cortex, patients with recurrent shoulder instability showed significantly lower activation compared to controls ($p < 0.05$)[43]. All clusters were in the left hemisphere.

3.3 Association between functional brain outcomes and clinical test scores

Four studies explored the relationship between functional brain outcomes (i.e., brain activity, functional connectivity) and clinical test scores[23, 42, 45, 47]. In patients with shoulder instability, apprehension videos induced significant increases in apprehension score (measured by a Visual Analog Scale: VAS_{ap}) compared to controls ($p < 0.01$)[23]. There was a significant negative correlation between task-positive minus task negative Smodes and visual apprehension ($r = -0.47$; $p = 0.02$),

indicating that connectivity of brain networks (IC 12, 17, 30) become more active with apprehension in patients with SI[23].

There were significant correlations between brain functional connectivity and clinical test scores in patients with anterior shoulder instability ($p < 0.05$). VAS_{ap}, WOSI and ROWE scores were positively correlated with functional connectivity in the bilateral anterior insula, anterior and posterior cingulate cortex, somatosensory area and somatosensory cortex. ROWE score was positively associated with functional connectivity measurements in the anterior midcingulate cortex and visual and attentional areas. Post hoc GLM analysis also revealed significant correlations ($p < 0.05$, $r > 0.75$) between brain activation in the bilateral frontal pole and left inferior temporal gyrus and ROWE score, as well as between bilateral pre-central and post-central gyrus and bilateral superior parietal lobe and SSV score[45].

In patients with a history of traumatic unidirectional shoulder instability and who underwent surgery (Bankart labral repair or Latarjet-Patte procedure), post-hoc GLM analysis found positive correlations between right-occipital cortex and right-frontal pole activities before surgery and SST scores post-surgery ($p < 0.05$)[47].

3.4 Association between structural brain outcomes and clinical test scores

One study assessed the relationship between clinical test score and whole-brain white matter structural outcomes[46]. Structural brain alterations were assessed in patients with a history of traumatic anterior glenohumeral instability and apprehension. Significant negative correlations ($p < 0.05$) were found between SST and fractional anisotropy ($r = -0.25$; range = -0.72; -0.11). No significant correlation was found between the other clinical test scores and structural brain outcomes.

3.5 Association between functional brain adaptations and structural shoulder changes

In patients with traumatic shoulder instability at one year after a stabilisation surgery (Bankart and Latarjet procedures), all returned to their sports activities without being re-injured one year after surgery. Compared to one-year post-surgery, significant alterations were observed in brain activation before surgery. A significant increase in brain activation was found at baseline in the lateral occipital cortex ($p < 0.001$), middle temporal gyrus and parahippocampal gyrus ($p < 0.05$), pre-central gyrus ($p < 0.05$) and post-central gyrus ($p < 0.05$)[47].

One study[44] investigated the association between glenoid bone defects and brain activity during shoulder motions. No significant whole-brain correlations were found during passive shoulder motion ($p < 0.05$). Exploratory and region-of-interest analyses revealed a negative association ($p = 0.001$, $r = -0.79$ [-0.93;-0.43]) between glenoid defect size and activity in the right cerebellum. During active shoulder motions, greater glenoid bone loss was positively associated ($p < 0.05$) with increased activation in a widespread cortical network, including motor, premotor, parietal, and subcortical regions. There were no significant negative correlations between glenoid bone defect and brain activity.

4. Discussion

The objective was to synthesise current evidence on structural and functional brain adaptations associated with shoulder instability. Building on the work of Livett et al.[48] this systematic review extends the scope by incorporating studies on structural brain adaptations and examining associations between neuroimaging findings and clinical outcomes. This broader scope not only strengthens the neurobiological interpretation of the findings but also enhances the clinical relevance of central nervous system adaptations in shoulder instability. Three main messages emerge. First, functional brain differences in brain regions responsible for motor planning,

sensorimotor processing, visual processing, emotional regulation, executive functions, higher cognitive control, memory, language processing and object recognition are consistently observed in patients with recurrent shoulder instability[23, 42, 46]. Second, evidence for structural reorganisation is limited and inconsistent[23, 42, 46, 47]. Third, significant associations between clinical test scores and functional brain outcomes suggest potential clinical relevance, although conclusions must remain cautious given the small number of studies and participants.

Brain neuroimaging findings: Structural adaptations

Evidence for structural brain changes in patients with recurrent shoulder instability is sparse and inconsistent23, 42, 46, 47. One study reported structural changes, showing increased fractional anisotropy in the left internal capsule and parts of the thalamus compared with healthy controls46. These regions are involved in sensorimotor signal transmission and integration49, 50, and the observed changes may reflect structural plasticity in response to altered afferent input or increased motor control demands associated with instability[51]**.** However, the majority of included studies using voxel-based morphometry reported no adaptations in the grey or white matter structure[23, 42, 47].

Findings in shoulder instability differ from those reported in lower limb ligament injuries (i.e., anterior cruciate ligament injury, chronic ankle instability)25, 28, 52, where more consistent adaptations in whole brain white and grey matter microstructure have been described26, 32. These differences may relate to chronicity, prolonged altered sensory input, changes in proprioception, and compensatory motor strategies that the brain adopts to maintain optimal function despite instability. However, they may also reflect methodological limitations in the shoulder instability literature. The included studies are characterised by small sample sizes and heterogeneity in eligibility criteria, which may obscure potential differences in brain structure. For instance, Cunningham's study[42] included only patients with anterior shoulder instability, whereas Zanchi's study[47] required that antero-inferior instability be of traumatic origin, a criterion not specified in the other two studies23, 42.

Current evidence, therefore, does not demonstrate structural brain reorganisation in patients with shoulder instability. However, preliminary diffusion tensor imaging findings suggest that selective microstructural plasticity cannot be excluded. This underscores the complexity of the brain's response to different types of joint instability and warrants further investigation.

Brain neuroimaging findings: Functional brain connectivity

Increased connectivity was observed in regions associated with shoulder sensory perception, motor control, executive functions (such as working memory, cognitive flexibility and attention), emotion processing and risk evaluation in patients with shoulder instability23, 42, 46. These findings suggest a redistribution of neural resources across the cognitive, sensory, motor and emotional domains to maintain shoulder function and mitigate the impairments caused by recurrent shoulder instability. This interpretation is further supported by the observed reduced connectivity in regions related to visual processing and motor coordination compared to healthy controls[23], which may partly explain some of the functional shoulder function deficits found in these patients39, 53-55. Neuroplastic differences in somatosensation might alter a patient's perceptions and proprioception, increasing the risk of placing the joints in non-physiological positions and suffering from a new injury[56]. Unwarranted neuroplasticity may place the athlete in a vicious circle further increasing instability and the risk of re-injury.

Comparisons with previous work (Livett et al. 2022) indicate agreement regarding the presence of functional cortical changes associated with shoulder instability[48]. However, the overall moderate to high risk of bias of the included studies and variability in experimental designs, limits definitive conclusions on the exact role of functional adaptations in recurrent shoulder instability.

Similar patterns of altered functional connectivity have been reported in other joints with chronic instability such as chronic ankle instability and anterior cruciate ligament deficiency. In these populations, increased engagement of sensorimotor and cognitive networks has been interpreted as reflecting adaptations to altered proprioceptive input and motor control demands[25, 27, 28, 56, 57]. While

these observations suggest that supraspinal adaptations may be a common feature of joint instability, extrapolation to shoulder instability should be made cautiously. The clinical relevance of such adaptations remains speculative and requires confirmation in shoulder-specific, longitudinal studies.

Brain activity related to shoulder outcomes

Functional brain adaptations in recurrent shoulder instability appear to be strongly task dependent. Tasks involving threats of apprehension, cognitive engagement, or emotional processing elicit more pronounced differences between patients and controls than passive movements. During visual apprehension or anticipation of potentially destabilising shoulder positions, patients with recurrent shoulder instability show increased activity in brain regions associated with movement planning, multisensory integration, and visual processing[45, 47]. Specifically, on the injured side, there is increased activity in regions tied to object recognition, while the opposite side is more active in areas related to spatial navigation and memory43, 45. This pattern suggests the brain compensates for reduced activity when preparing or imagining shoulder movements perceived as threatening.

In contrast, passive shoulder motions do not elicit differences in brain activation between patients and controls[43-45]. Passive tasks involve limited cognitive engagement and minimal emotional load, which may explain the absence of detectable functional differences. This contrast highlights that altered brain processing is most evident when patients are challenged cognitively or emotionally[58-60].

During active and dynamic shoulder movements, increased activation has been observed in motor-related regions, including the primary motor cortex and premotor areas, in patients with recurrent shoulder instability[24, 56]. This pattern potentially indicates a less efficient motor function, requiring more neural resources to plan and execute movements. In comparison, healthy controls tend to show greater engagement of regions related to spatial processing and memory. This difference suggests that while recurrent shoulder instability patients rely more on motor areas to compensate for deficits, healthy individuals use memory and spatial processing to support movement.

Association between functional brain outcomes and clinical test scores

Four studies specifically explored correlations between brain function and clinical outcomes, providing preliminary insights into the clinical relevance of supraspinal changes. Haller et al.[23] as well as Shitara et al.[45] reported significant correlations between functional connectivity and measures of apprehension, pain and shoulder function, assessed via the VASap, WOSI and Rowe score. An increased functional connectivity correlating with an increased feeling of unpleasantness during tasks.

Moreover, Cunningham et al.[42] demonstrated significant correlations between VAS pain, WOSI and Rowe scores with brain connectivity in areas such as the anterior and posterior cingulate cortex, prefrontal cortex, and somatosensory cortices. These brain regions are dedicated to movement conception, motor control, pain regulation, memory and spatial orientation. The correlations suggest that patients with higher functional connectivity in these areas tend to report better clinical outcomes, reinforcing the notion that brain adaptations play a crucial role in managing and potentially mitigating shoulder instability and that those aspects has to be considered in the rehabilitation process[34].

However, the variability in functional brain adaptations observed across different clinical test scores also indicates the need for a more nuanced approach in rehabilitation strategies. By understanding how specific brain networks are involved in the perception and modulation of shoulder instability symptoms, clinicians can design more targeted interventions that address both the physical and neurological aspects of the condition.

Association between structural brain outcomes and clinical test scores

Only one study assessed this association and found significant but weak negative correlations between the Simple Shoulder Test score and fractional anisotropy, a measure of white matter integrity[46]. This suggests that there may be a potential link between structural brain changes and

clinical outcomes. However, the weak correlation could be due to various factors, including the heterogeneity of patient population, and the specific clinical tests used.

Association between functional brain adaptations and structural shoulder changes

Functional brain adaptations likely interact in response with structural changes in the shoulder joint itself as a compensatory mechanism. These adaptations are observed in areas involved in sensory perception, motor control, and cognitive processing, which help mitigate the functional impairments caused by shoulder instability to maintain overall functionality despite the instability[23, 44, 47]. Functional brain adaptations can be linked to structural changes in the shoulder through their impact on clinical outcomes23, 42, 46.

Longitudinal evidence is scarce, but one study[47] assessed patients with traumatic shoulder instability before and one year after stabilisation surgery, and found significant alterations in brain activation. These findings suggest that pre-surgical brain adaptations might provide prognostic information on surgical success and shoulder stability post-surgery, which could be valuable for identifying patients at risk of poorer outcomes and guiding rehabilitation strategies pre- and post-operatively.

Implications for clinical practice

The shoulder is the joint most affected by instability and dislocation, with high injury and recurrence rates in young and female athletes[40]. This systematic review highlights significant differences in brain functional connectivity, particularly in areas associated with emotion regulation, memory, and movement planning. From a clinical perspective, these changes underline the importance of addressing neuroplastic changes in treatment strategies.

Rehabilitation strategies that involve active engagement, variable sensory input, and cognitively demanding tasks may better reflect the contexts in which altered brain processing has been observed. Such approaches are consistent with contemporary motor learning principles and current recommendations for shoulder prevention[32, 61]. Virtual reality could also be employed to simulate environments that introduce novel challenges to facilitate motor learning[62]. This tool could aid in

engaging cognitive and motor systems in ways that traditional therapies might not, allowing for a more comprehensive approach to the modulation of neuroplastic changes. However, given the limited and heterogenous neuroimaging evidence these implications are speculative rather than recommendation for clinical practice.

Limitations and future research

There were relatively few studies included and not all studies were of high quality. Considerable heterogeneity in the outcome measures, inclusion criteria and clinical tests used across studies makes it difficult to compare results and draw conclusions about brain adaptations in patients with recurrent shoulder instability. Alternatively, these adaptations may be attributed to changes in interoceptive signalling, reflecting the brain's interpretation of altered internal and external sensory input[63]. Such changes in afferent input from the shoulder joint could elicit task-specific but transient functional alterations, which are detectable using neuroimaging but may not represent lasting neuroplastic changes. Many studies lacked comprehensive clinical (physical) tests, which are crucial for a thorough assessment of shoulder instability.

Future research should focus on the functional and structural aspects of shoulder instability, including larger sample sizes, using clinical tests, and comprehensive assessments. There is also a clear need for the development of standardised inclusion criteria partly based on clinical tests to improve the consistency and comparability of research findings.

5. Conclusion

There were no structural brain adaptations in people with recurrent shoulder instability. There were functional brain changes, characterised by altered functional connectivity and brain activation patterns, primarily in brain areas related to motor control, sensory perception, and emotional processing.

Key points

Findings

- Functional, but not structural, brain differences were observed in patients with recurrent shoulder instability.
- Increased functional connectivity was consistently found in brain areas related to motor control, sensory integration, and emotion regulation.
- Functional brain outcomes (connectivity and activation) show significant correlations with clinical measures (VASap, WOSI, Rowe), indicating that brain adaptations are reflected in shoulder instability symptoms.

Implications

- These findings suggest that neuroplastic changes may serve as compensatory mechanisms to maintain function in recurrent shoulder instability patients.
- Integrating motor learning and sensory-cognitive strategies into rehabilitation could improve outcomes and reduce the risk of recurrence.

Caution

The small number of included studies, variability in inclusion criteria, and lack of longitudinal data limit the generalizability of the findings. Further high-quality research is needed, particularly in young and female populations who are at higher risk.

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Tables

Table 1: Search strategy

1.	((shoulder* instabil*) OR (shoulder* dislocat*) OR (shoulder* stabil*) OR (shoulder* sublux*) OR (shoulder* unstab*) OR (shoulder* luxation) OR (glenohumeral instabil*) OR (glenohumeral dislocat*) OR (glenohumeral stabil*) OR (glenohumeral sublux*) OR (glenohumeral unstab*) OR (GHJ instabil*) OR (GHJ stabil*) OR (GHJ sublux*) OR (GHJ unstab*))
2.	((Brain) OR ("central nervous system") OR (grey matter) OR (motor cortex) OR (motor area) OR (locomotor region) OR (neuroplasticity) OR (neurocognition) OR (cognitive process) OR (cognitive performance) OR ("cognitive function") OR (executive function) OR (neural excitability) OR (neural activity) OR (neuronal activity) OR (brain activity) OR (cortical activity) OR (subcortical activity) OR (neuroimaging) OR (functional connectivity) OR (electroencephalography) OR (transcranial magnetic stimulation) OR (magnetoencephalography) OR (motor evoked potential))
3.	((fracture*) OR (concussion) OR ("Brain injury") OR ("Spinal cord injury") OR (cancer) OR ("nerve injury") OR ("cerebral palsy"))
4.	#1 AND \#2 NOT \#3

Table 2 (shortened version): Summary of findings

Authors (year)	Structural and functional brain adaptations	Clinical test scores	Association between brain outcomes and clinical test scores	Associations between functional and structural brain changes	Association between functional brain and structural shoulder changes
Cunningham et al., 2015 42	*Structural* No significant ≠ between groups ($p < 0.05$) Significant ≠ in brain networks between patients & controls: $p < 0.01$	Apprehension videos: patients > controls ($p < 0.01$) Control videos: no significant ≠ between groups ($p > 0.05$), but both ↑ (patients: $p < 0.001$, controls: $p < 0.01$)	*FC analyses:* VAS, WOSI and ROWE x IC1, IC2, IC3, IC4 (bilateral anterior insula, anterior, posterior cingulate cortex, somato-sensory area & cortex): $p < 0.05$ Final VAS, ROWE x s-mode of IC5, IC6, IC7 ($p < 0.05$) ROWE x IC5, IC6, IC7 component strength (anterior midcingulate cortex, visual & attentional areas): $p < 0.05$ *Post hoc GLM:* Rowe x bilateral frontal pole, left inferior temporal gyrus: $p < 0.05$ SSV x bilateral precentral & postcentral gyrus & bilateral superior parietal lobe ($p < 0.05$)		
Haller et al., 2014 23	*Structural* No significant ≠ between groups ($p < 0.05$) *Functional* <u>FC analyses:</u> Patients > controls ($p < 0.05$): Bilateral primary sensorimotor area, dorsolateral prefrontal cortex, anterior insula, dorsal anterior cingulate cortex Patients < controls ($p < 0.05$): Visual network		All: $r = -0.47$, $p = 0.02$ Control: $r = -0.63$, $p = 0.05$ Patients: $r = -0.31$, $p = 0.27$		

	(parietal region) Task-related brain activation : Patients > controls ($p < 0.05$): left primary sensorimotor area & dorsolateral prefrontal cortex				
Howard et al., 201943	*Functional* Active shoulder movements No significant ≠ in cortical activation between flexion and abduction: $p < 0.05$ No significant interaction effect for movement type*patient group ($p < 0.05$) Active moment vs. no movement (regardless of movement used): $p < 0.05$ (with FWE) Patients > controls: primary motor cortex, supramarginal gyrus, middle & inferior frontal gyrus, precentral gyrus Controls > patients:parahippocampal gyrus, perirhinal cortex				
Shitara et al., 201545	*Functional* Motor imagery: active task vs. sitting RSI > controls ($p < 0.001$): right hippocampus and amygdala Controls > RSI: ($p < 0.001$): left precentral & postcentral gyrus, left posterior cingulate cortex, right rectal gyrus, right superior occipital gyrus, right superior & inferior parietal lobule, right middle orbital gyrus, left paracentral lobule Motor imagery: passive apprehension task vs. sitting RSI > controls ($p < 0.001$): right precentral gyrus, left hippocampus Controls > RSI ($p < 0.001$): lft precentral &		Significant positive correlations ($r > 0.75$, $p < 0.05$) between brain activity (all the previously mentioned areas and apprehension intensity)		

	postcentral gyrus, left & right inferior parietal lobule, left paracentral lobule, right inferior temporal gyrus, right precentral gyrus, left thalamus, left & right fusiform gyrus, left middle frontal gyrus Passive shoulder apprehension task Controls > RSI ($p < 0.001$): right superior frontal gyrus, right medial temporal pole, left middle & inferior temporal gyrus, right precentral & postcentral gyrus, left angular gyrus				
Shitara et al., 202244	*Functional* Passive shoulder motion Controls > RSI in every brain region ($p < 0.05$) Isometric shoulder contraction Brain activity RSI > Controls ($p < 0.05$): bilateral superior temporal and precentral gyri, right angular gyrus, middle frontal gyrus, inferior frontal & parietal lobules, calcarine gyrus, left precuneus, rolandic operculum, middle cingulate cortex, insula lobe				*Passive shoulder motion* No significant correlation during passive motion task ($p > 0.05$) *Isometric contraction* Significant correlation with right cerebellum activity: $p = 0.001$, $r = -0.79$ (95%CI: -0.93; -0.43) Significant correlation with activity in the left pre-SMA, middle, frontal & precentral gyrus, anterior cingulate cortex, superior & inferior parietal lobules, middle temporal gyrus, bilateral precuneus, superior frontal & medial gyri, caudate nuclei
Zanchi et al., 201747	*Structural* No significant ≠ between groups ($p < 0.05$) *Functional* Apprehension videos Baseline > 1 year follow-up in: left motor & premotor cortex, somatosensory cortex, lateral occipital cortex ($p < 0.001$), para-hippocampal gyrus ($p < 0.05$)		SST-scores x right-occipital cortex & right-frontal pole ($p < 0.05$)		
Zanchi et al.,	*Structural*		SST and FA: $r = -0.25$ (-0.72; -0.11), $p < 0.05$	Significant correlation S-	

201746	<u>TBSS Analyses</u> Significant ↑in FA in: left internal capsule ($p < 0.05$) and Thalamus ($p < 0.05$)		No significant correlations for the other scores: $p > 0.05$	mode values of ICA component and FA of left internal capsule x partial thalamus ($p < 0.01$) Significant ≠ ($r = -0.24$, $p < 0.05$) between controls and patients with RSI: **Hypo**activation in the ventral anterior cingulate cortex, posterior cingulate cortex and precuneus **Hyper**activation in the anterior insula, motor and somatosensory cortex	

621

Supplementary Material 1: Summary of findings

Haller et al., 2014 23	Prospective	Inclusion (I) SI (II) Positive apprehension test (III) Normal or corrected-to-normal visual acuity Exclusion (I) Major medical disorders (cancer, cardiac illness), sustained head injury, psychiatric or neurologic disorder, or alcohol or drug abuse. (II) Use of psychotropics, stimulants and β-blockers	Inclusion (I) Healthy volunteers Exclusion (I) Any history of shoulder injury or SI or hyperlaxity (> 85° ER) (II) Major medical disorders (cancer, cardiac illness), sustained head injury, psychiatric or neurologic disorder, or alcohol or drug abuse. (III) Use of psychotropics, stimulants/β-blockers	SI N = 15 (all m.) Age = 27.5±6.4 yr. 9 RH (+ right-RSI); 6 LH(+left RSI) Control N = 10 (all m.) Age = 29.0±4.7 yr.	fMRI 3-T scanner FMRI task Two active conditions (apprehension and control videos) + a resting condition Clinical tests scores and questionnaires VAS(ap)	• Brain structure: VBM analysis of gray matter &TBSS analysis of white matter • Brain function: ➢ FC analysis of whole brain between patients & controls (s-mode values) ➢ Task-related brain activity: apprehension videos • Correlations: pearson r ➢ Smodes & VAS_{ap} • Clinical test scores: ➢ Visual apprehension (VAS_{ap})	**Brain neuroimaging findings – structural brain ≠** No significant ≠ between groups ($p < 0.05$) **Brain neuroimaging findings – functional brain ≠** *FC analyses:* Patients > controls ($p < 0.05$): Bilateral primary sensorimotor area, dorsolateral prefrontal cortex, anterior insula, dorsal anterior cingulate cortex Patients < controls ($p < 0.05$): Visual network (parietal region) *Task-related brain activation :* Patients > controls in left primary sensorimotor area & dorsolateral prefrontal cortex **Clinical test scores** • Apprehension videos: patients > controls ($p < 0.01$) • Control videos: no significant ≠ between groups ($p > 0.05$), but both ↑ (patients: $p < 0.001$, controls: $p < 0.01$) **Correlations between task-related brain activation & clinical test scores** • All: $r = -0.47$, $p = 0.02$ • Control: $r = -0.63$, $p = 0.05$ Patients: $r = -0.31$, $p = 0.27$
Howard et al., 201943	Cross-sectional	Inclusion	Inclusion (I) No history of	SI	fMRI	• Brain function: ➢ Task-related brain activity: forward flexion, abduction	**Brain neuroimaging findings – Task-related brain activation**

		(I) Polar Type II/III SI (II) Diagnostic based on patient history, clinical examination, imaging (RX/MRI) & arthroscopy <u>Exclusion</u> (I) Collagen disorders (II) Previous significant surgery (II) Previous trauma (IV) MRI exclusion factors (V) Neuromuscular conditions (VI) Multiple sclerosis (VII) Any other possibly cofounding brain pathology	shoulder pathology <u>Exclusion</u> (I) Collagen disorders (II) Previous significant surgery (III) Previous trauma (IV) MRI exclusion factors (V) Neuromuscular conditions (VI) Multiple sclerosis (VII) Any other possibly cofounding brain pathology	N = 16 (15 f.; 1 m.) Age = 24.2±6.0 yr. 12 RH (+ right RSI); 4 LH (+ left RSI); <u>Control</u> N = 16 (15 f.; 1 m.) Age = 23.8±5.1 yr. 4 LH; 12 RH	1.5 T scanner <u>fMRI task</u> Movements of forward flexion, abduction and a resting condition <u>Clinical tests scores and questionnaires</u> • OSIS • WOSI	or rest with family-wise error correction (FWE) • Clinical test scores: ➢ Shoulder function (OSIS) ➢ Degree of disability in ADL (WOSI)	*Active shoulder movements* • No significant ≠ in cortical activation between flexion and abduction: $p < 0.05$ • No significant interaction effect for movement type*patient group ($p < 0.05$) *Active moment vs. no movement (regardless of movement used):* • $p < 0.05$ (with FWE) <u>Patients > controls:</u> • Primary motor cortex • Supramarginal gyrus • Middle & Inferior frontal gyrus • Precentral gyrus <u>Controls > patients:</u> • Parahippocampal gyrus- • Perirhinal cortex
Shitara et al., 201545	Cross-sectional study	<u>Inclusion</u> (I) Experience of more than 1 traumatic dislocation (II) Positive apprehension test (III) Positive relocation test (IV) Experience of an isolated, right-sided RSI identified as a	<u>Inclusion</u> (I) Healthy volunteers (II) Right-handed	<u>SI</u> N = 14 (3 f.; 11 m.) Age = 28.2±8.6 yr. [16-44]	<u>fMRI</u> 3-T scanner <u>Motor imagery task</u> Imagery- and memory-induced apprehension with pictures (control condition, kettle condition and ABER condition) <u>Passive shoulder</u>	• Brain function: ➢ Task-related brain activity: motor imagery, passive shoulder task • Correlations: pearson r • Clinical test scores: ➢ NRS(ap)	**<u>Brain neuroimaging findings – Task-related brain activation</u>** *Motor imagery: active task vs. sitting* <u>RSI > controls ($p < 0.001$)</u> • Right hippocampus and amygdala <u>Controls > RSI: ($p < 0.001$)</u> • Left precentral & postcentral gyrus • Left posterior cingulate cortex • Right rectal gyrus • Right superior occipital gyrus

		Bankart lesion by MRA or arthroscopy (V) Right-handed <u>Exclusion</u> (I) Non-traumatic, multidirectional shoulder instability (II) History of a dislocation within a month prior to participation in the study (III) < 16 yr. (IV) Other joint instability with apprehension (V) Neuropsychiatric disorders (VI) MRI exclusion factors	<u>Exclusion</u> (I) Any joint instability with apprehension (II) Neuropsychiatric disorders (III) MRI exclusion factors	<u>Control</u> N = 12 (4 f.; 8 m.) Age = 23.2±3.2 yr. [20-29]	<u>motion task</u> – Passively rotated in internal (0°–20°) and external motion (0°–90°) with 90° abduction at 1 Hz		• Right superior & inferior parietal lobule • Right middle orbital gyrus • Left paracentral lobule *Motor imagery: passive apprehension task vs. sitting* <u>RSI >controls (p < 0.001)</u> • Right precentral gyrus • Left hippocampus <u>Controls > RSI (p < 0.001)</u> • Left precentral & postcentral gyrus • Left & right inferior parietal lobule • Left paracentral lobule • Right inferior temporal gyrus • Right precentral gyrus • Left thalamus • Left & right fusiform gyrus • Left middle frontal gyrus *Passive shoulder apprehension task* <u>Controls > RSI (p < 0.001)</u> • Right superior frontal gyrus • Right medial temporal pole • Left middle & inferior temporal gyrus • Right precentral & postcentral gyrus • Left angular gyrus **<u>Correlations between task-related brain activation & shoulder apprehension</u>** Significant positive correlations (r > 0.75, p < 0.05) between brain activity (all the previously mentioned areas and

							apprehension intensity)
Shitara et al., 202244	Cross-sectional study	Inclusion (I) Repeated traumatic dislocation (II) Positive apprehension and relocation tests (III) Isolated, right-sided RSI associated with a Bankart lesion identified on MRA or arthroscopy. (IV) Right-handed Exclusion (I) < 16 yo, (II) Nontraumatic SI (III) Multidirection SI (IV) History of neuropsychiatric disorders (V) MRI exclusion factors (VI) History of shoulder dislocation within 1 month before study participation	Inclusion (I) Healthy volunteers (II) Right-handed Exclusion (I) < 16 yo, (II) History of neuropsychiatric disorders (III) MRI exclusion factors (e.g. cardiac pacemaker)	SI N = 13 (2f.; 11m.) Age: 27.8 ± 9.2 yr. Control N = 12 (4f.; 8m.) Age, 23.2 ± 3.2 yr.	fMRI 3-T scanner Passive shoulder motion task Passively rotated in internal (0°–20°) and external motion (0°–90°) with 90° abduction at 1 Hz Voluntary shoulder muscles contraction task Isometric flexion, abduction, or external rotation of the right shoulder at 0° abduction	• Brain function: ➢ Task-related brain activity: passive shoulder motion & isometric contraction • Shoulder structure: glenoid bone loss • Correlations: pearson r	**Brain neuroimaging findings – Task-related brain activation** *Passive shoulder motion* • Controls > RSI in every brain region ($p < 0.05$) *Isometric shoulder contraction* Brain activity RSI > Controls ($p < 0.05$) • Bilateral superior temporal and precentral gyri • Right angular gyrus • Middle frontal gyrus • Inferior frontal & parietal lobules • Calcarine gyrus • Left precuneus • Rolandic operculum, • Middle cingulate cortex • Insula lobe **Correlations between task-related brain activation & glenoid bone defects** *Passive shoulder motion* No significant correlation during passive motion task ($p > 0.05$) *Isometric contraction* • Significant correlation with right cerebellum activity: $p = 0.001$, $r = -0.79$ (95%CI: -0.93; -0.43) • Significant correlation with activity in: ➢ Left pre-SMA

							➢ Middle, frontal & precentral gyrus ➢ Anterior cingulate cortex ➢ Superior & inferior parietal lobules ➢ Middle temporal gyrus ➢ Bilateral precuneus ➢ Superior frontal & medial gyri ➢ Caudate nuclei
Zanchi et al., 201747	Longitudinal cohort	<u>Inclusion</u> (I) Male patients (II) History of traumatic unidirectional (anteroinferior) SI (III) Positive apprehension sign whether painful or not (IV) Radiologic evidence of their instability <u>Exclusion</u> (I) Pain at rest (II) Preoperatively radiological signs of dislocation arthropathy (III) Hyperlaxity (> 85° ER) (IV) Abnormal visual acuity, (V) History of major medical disorders,	/	<u>SI</u> N = 13 (all m.) Age: 30.03 ± 7.64 yr. 13 RH (10 right-RSI and 3 left-RSI) Bankart labral repairs (N=3); open Latarjet (N=6); arthroscopic Latarjet procedure (N=4)	<u>fMRI</u> 3T scanner <u>fMRI task</u> Two active conditions (6 apprehension videos and 6 controls videos) + a rest condition <u>Clinical tests scores and questionnaires</u> • VAS(p) • SST • SSV • ROWE • WOSI	• Brain structure: VBM analysis of gray matter & TBSS analysis of white matter • Brain function: Task-related brain activity: apprehension videos • Correlations: pearson r • Clinical test scores: ➢ Pain intensity ➢ Shoulder performance in ADL ➢ Shoulder function ➢ Shoulder stability and motion ➢ Degree of disability in ADL	**<u>Brain neuroimaging findings – structural brain ≠</u>** No significant difference between groups (p <0.05) **<u>Brain neuroimaging findings – Task-related brain activation</u>** *Apprehension videos* Baseline > 1 year follow-up in: • Left motor & premotor cortex • Somatosensory cortex • Lateral occipital cortex (p < 0.001) • Para-hippocampal gyrus (p < 0.05) **<u>Correlations between post-hoc GLM activation with clinical test scores</u>** • SST-scores x right-occipital cortex & right-frontal pole (p < 0.05)

		head injury, psychiatric/ neurologic disorders, alcohol/drug abuse, (VI) Use of psychotropics, stimulants/β-blockers on a regular basis					
Zanchi et al., 201746	Cross-sectional study	<u>Inclusion</u> (I) Patient presenting to a specialised shoulder surgery consultation with a history of traumatic anterior glenohumeral instability (II) Positive apprehension test (III) Radiologic evidence based on MRA or CT scan, (IV) Pain VAS scores ≤ 3 <u>Exclusion</u> (I) Pain at rest (II) Acute event of instability (within 6 previous months) (III) History of drug/alcohol abuse (IV) Major medical	<u>Inclusion</u> (I) Healthy volunteers, (II) No history of shoulder injury, SI or hyperlaxity (> 85° ER or > 105° hyperabduction) (III) Elbow against waist, or hyper-abduction > 105° <u>Exclusion</u> (I) History of drug or alcohol abuse (II) Major medical disorders (III) Use of psycho-tropics, stimulants or β -blockers	<u>SI</u> N = 14 (m:14) Age: 27.3 ± 2.0 yr. 4 LH (+ left-RSI); 10 RH (+right-RSI) <u>Control</u> N = 10 (all m.) Age: 29.6 ± 1.3 yr.	<u>fMRI</u> 3T scanner <u>Clinical tests scores and questionnaires</u> • VAS(ap) • SST • SSV • ROWE • WOSI	• Brain structure: fractional anisotropy • Brain function: functional connectivity • Correlations: pearson r ➢ Between FA and clinical tests scores ➢ Between functional and structural brain changes • Clinical test scores: ➢ Pain intensity ➢ Shoulder performance in ADL ➢ Shoulder function ➢ Shoulder stability and motion ➢ Degree of disability in ADL	•

		disorders (V) Use of psychotropics, stimulants or β - blocker					

Caption: ADL : activities of daily living ; RH= right-handed ; LH= left-handed ; FC= functional connectivity ; GLM = General linear model ; IC = independent component ; VAS(ap)= visual analog scale for apprehension ; VAS (p) = visual analog scale for pain ; NRS (ap) = Numeric rating scale for apprehension ; MRA = Magnetic Resonance Arthrography ; M = male ; F = female ; SI = shoulder Instability ; SST= Simple Shoulder Test ; SSV = subjective Shoulder Value ; WOSI = Western Ontario Shoulder Instability ; FA = fractional anisotropy ; VBM = voxel-based morphometry ; TBSS = Tract-based spatial statistics ; Yr = year

Supplementary Material 2 : Apprehension-related activation in patients with shoulder instability during visual apprehension stimuli

Apprehension-related brain activation in patients with shoulder instability							
Brain areas with increased activity			*T-score*	*p-value (FWE, cluster level)*	*Coordinates (MNI)*		
					x	*y*	*z*
Motor control regions							
Right pre-central gyrus44			3.65	< 0.001	58	10	42
Memory and emotion-related regions							
Right hippocampus, amygdala44			4.32	< 0.001	14	-6	-12
Left hippocampus44			3.59	< 0.001	58	-28	-20
Brain areas with decreased activity	*voxels*	*-Log10(p)*	*Z-max*	*p-value*	*Coordinates (MNI)*		
					x	*y*	*z*
Motor control regions							
Pre-central gyrus46	779	1.63	2.97	< 0.05	-46	2	48
Sensory processing regions							
Post-central gyrus46	709	1.39	3.04	< 0.05	16	-20	68
Visual processing regions							
Lateral occipital cortex46	3064	7.22	3.06	< 0.001	46	-58	16
Memory and emotion-related regions							
Middle temporal & para-hippocampal gyrus46	863	1.9	3.14	< 0.05	-44	-60	10

Apprehension-related brain activation between patients with recurrent shoulder instability and healthy controls			
Brain area with reduced activity	*T-score*	*Coordinates (MNI)*	
		x	*y*	*z*
Motor control regions				
Left pre-central gyrus44	3.93/5.88	-40/-36	-18/-14	58/56
Right pre-central gyrus44	4.23	34	-26	52
Left paracentral lobule44	3.48/4.96	-8/-4	-38/-38	66/64
Sensory processing regions				
Left post-central gyrus44	3.71/4.05	-42/-46	-16/-30	50/48
Right inferior parietal lobule44	3.69/5.09	26/26	-56/-56	52/52
Left inferior parietal lobule44	4.07	-46	-58	56
Visual processing regions				
Right superior occipital gyrus44	3.78	20	-98	22
Right superior parietal lobule44	3.61	36	-64	62
Left fusiform gyrus44	3.91	-28	-68	-10
Right fusiform gyrus44	3.82	38	-42	-24
Higher cognitive control and executive function regions				
Right middle orbital gyrus44	3.57	6	40	-14
Left middle frontal gyrus44	3.83	-24	30	54
Emotion and limbic system regions				
Straight gyrus	3.89/3.59	16/4	24/38	-12/18
Left posterior cingulate cortex44	3.91	-10	-50	28
Left thalamus44	3.95	-24	-26	4
Language processing and object recognition				
Right inferior temporal gyrus44	4.33	62	-24	-22

BA = Brodmann Area, FWE = Family-Wise Error, MNI = Montreal Neurological Institute, RSI = recurrent shoulder instability

Supplementary Material 3: Apprehension-related activation in patients with shoulder instability during passive movements

Apprehension-related activation in patients with shoulder instability compared to healthy controls					
Brain areas with decreased activity	*T-score*	*p-value (FWE, cluster level)*	*Coordinates (MNI)*		
			x	*y*	*z*
Motor control regions					
Right pre-central gyrus 44, 45 (M1)	3.80/5.27	< 0.001/< 0.05	32/50	-30/-2	74/48
Left precentral gyrus – premotor area (M1)45 [46]	5.99	< 0.05	44	-14	56
Right cerebellum (lobule VI) 45	5.09	< 0.05	30	-54	-26
Sensory processing regions					
Right post-central gyrus44	3.37	< 0.001	30	-42	74
Language processing and object recognition-related regions					
Left superior temporal gyrus45	5.90	< 0.05	-62	-14	6
Left inferior temporal gyrus44, 45	3.80/5.94	< 0.001/< 0.05	-54/-52	-56/-14	-4/-26
Left middle temporal gyrus44	3.55	< 0.001	-62	-32	-6
Left angular gyrus44	3.72	< 0.001	-48	-62	42
Higher cognitive control and executive function regions					
Right superior frontal gyrus44	4.86	< 0.001	24	-10	74
Emotion and memory-related regions					
Right medial temporal pole44	4.24	< 0.001	38	6	-26
Left caudate nucleus45	5.55	< 0.05	-10	18	12
Right caudate nucleus45	5.07	< 0.05	16	2	20
Right insula45	4.64	< 0.05	44	-6	-6

FWE = Family-Wise Error, MNI = Montreal Neurological Institute, RSI = recurrent shoulder instability

Supplementary Material 4: Apprehension-related activation in patients with shoulder instability during active movements

Apprehension-related activation in patients with shoulder instability compared to healthy controls						
Brain areas with increased activity	*Cluster size*	*T-score*	*p-value (FWE, at cluster level)*	*Coordinates (MNI)*		
				x	*y*	*z*
Motor control regions						
Primary motor cortex43	430	5.22	< 0.05	38	-26	56
Pre-central gyrus43	769	4.54	< 0.05	-40	-2	52
Left pre-central gyrus45	/	5.41	< 0.05	-14	-26	60
Right pre-central gyrus45	/	4.98	< 0.05	58	8	32
Language and speech processing regions						
Inferior frontal gyrus43	769	4.87	< 0.05	-44	12	22
Left superior temporal45	/	5.42	< 0.05	-44	-36	20
Right superior temporal gyrus45	/	6.94	< 0.05	64	-34	10
Left Rolandic operculum (area OP2)45	/	6.05	< 0.05	-38	-28	20
Sensory processing and spatial awareness regions						
Right angular gyrus45	/	4.33	< 0.05	62	-50	34
Right inferior parietal lobule45	/	6.87	< 0.05	54	-48	46
Supramarginal gyrus43	430	4.24	< 0.05	-56	-36	44
Visual processing regions						
Right calcarine gyrus (area 18) 45	/	4.68	< 0.05	10	-96	10
Left precuneus (area 7A) 45	/	5.17	< 0.05	-16	60	66
Higher cognitive control and executive function regions						
Left posterior-medial frontal gyrus45	/	3.75	< 0.05	-8	-20	50
Right inferior frontal gyrus45	/	5.44	< 0.05	32	6	32
Right middle frontal gyrus43, 45	769/-	4.22/4.98	< 0.05/< 0.05	48/40	-22/34	-20/46
Brain areas with decreased activity						

Memory and emotion-related regions						
Parahippocampal gyrus43	719	4.93	< 0.05	28	-24	0
Perirhinal cortex43	719	3.73	< 0.05	48	-22	-20

FWE = Family-Wise Error, MNI = Montreal Neurological Institute, RSI = recurrent shoulder instability

Figures

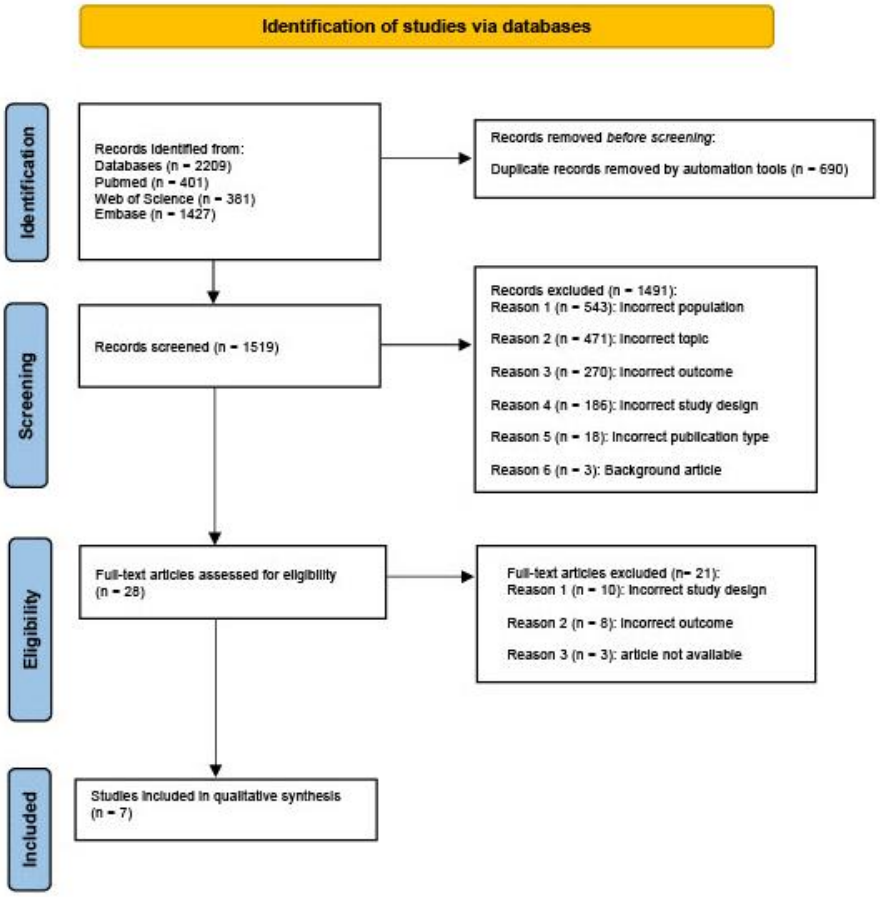

Figure 1 – PRISMA flowchart: *The figure depicts the process of study identification, screening, eligibility assessment, and inclusion, including reasons for exclusion at each stage.*

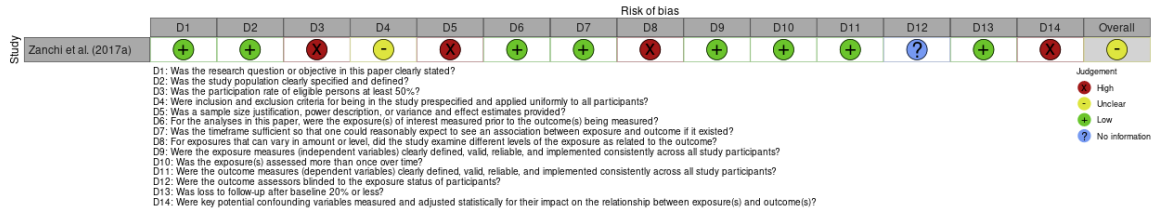

Figure 2a – Individual risk of bias assessment of the included cohort studies.

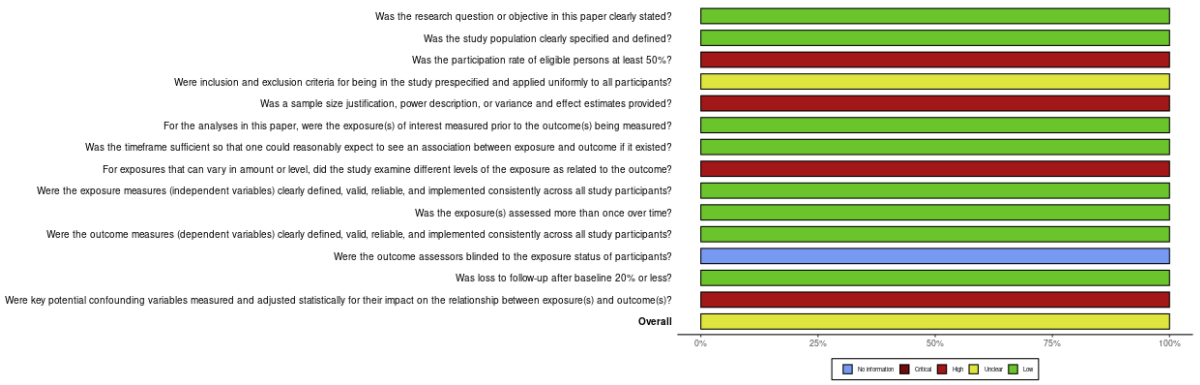

Figure 2b – Risk of bias assessment across the included cohort studies.

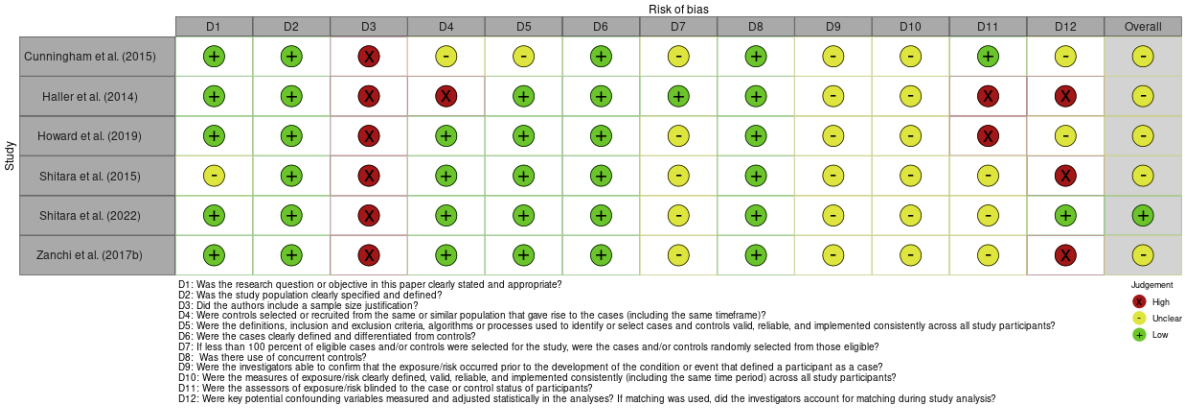

Figure 2c – Individual risk of bias assessment of the included case-control studies.

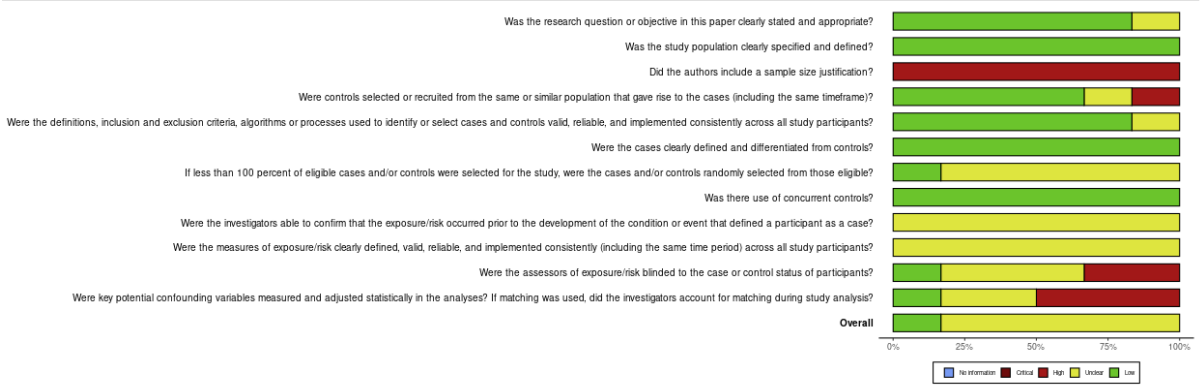

Figure 2d – Risk of bias assessment across the included case-control studies.