

Research Article

The influence of central pain modulation on postoperative outcomes after shoulder surgery: A systematic review

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ABSTRACT

Objective: The aim of this study was to systematically review whether the altered central pain modulation has a significant influence on post-surgical outcomes in patients undergoing shoulder surgery due to musculoskeletal disorders.

Methods: A systematic search of MEDLINE, PEDro, and EMBASE was conducted without time restriction, including observational prognostic studies. Quality in Prognostic Studies Tool was adopted for critical appraisal, and a qualitative synthesis was undertaken. Two authors independently performed study selection, data extraction, and risk of bias assessment; any disagreement was resolved by a third author. A review protocol is published in the PROSPERO registry (CRD42019122303). The data regarding the potential predictors and outcome measures were obtained from the studies.

Results: 11 prospective cohort studies were appraised. Overall, 952 patients were included with a sample size that ranged from 20 to 314. Studies included both arthroscopy and open surgery and presented low to moderate ROB. The prognostic factors investigated were depression, psychological distress, anxiety, catastrophizing, fear avoidance beliefs, self-efficacy and quantitative sensory testing. Only avoidance behaviors and self-efficacy were significantly related to post-surgical pain and function at 12 months after surgery.

Conclusion: Fear avoidance beliefs and inadequate coping strategies seem to be the most correlated factors with the worst pain and function scores. Surgeons and physical therapists should look for patients with signs of altered central pain modulation before surgery as they might be at risk of unfavorable outcome.

Level of Evidence: Level II, Therapeutic Study

Introduction

Shoulder pain is a very frequent and debilitating condition among the general population.¹ The incidence of consultations for shoulder pain in the United Kingdom is 9.5 for every 1,000 patients who refer to the care provided by the health system. It is also estimated that shoulder pain is the third cause of consultations for musculoskeletal problems, as well as accounting for 16% of the total outpatient consultations for orthopedic manipulative therapists.² Rotator Cuff (RC) disorders and osteoarthritis are the most frequent causes of shoulder pain requiring surgical treatment for their management, whether invasive (open surgery) or minimally invasive (arthroscopy), following failure of conservative treatment.^{3,4}

Somestudies^{5,6} have tried to identify the conditions and indicators that could affect the choice and the outcomes of an elective surgical approach instead of conservative treatment and vice versa. It is not clear whether the choice of surgery as the first treatment option is guided by anatomical (eg, the extent of the lesion) or functional (eg, the residual function or the

patient's level of activity) factors, and there is no assurance from the literature if these factors could affect post-surgery outcomes.⁷ Since it seems that these anatomical and functional factors often do not alter the outcome, some evidence tells us that the strongest predictors of surgery failure are low expectations and poor confidence in post-operative physiotherapy.⁵ This change of mind on the weight of the patient's beliefs and expectations, compared to physical and "structural" factors (lesion size, activity level, functionality) in determining outcomes, has gradually stressed the role of altered central modulation of pain in managing post-surgical patients.^{8,9} Previous systematic reviews have shown that psychological factors, including depression, anxiety, catastrophizing and kinesiophobia, are associated with the worse outcomes in the hip,^{8,10} knee^{8,10} and spinal surgery,⁹ but to our knowledge, there is no summary of evidence available regarding their influence on outcomes after shoulder surgery.

The aim of this study is to systematically review whether the presence pre-surgery of altered central pain modulation influences post-surgical outcomes

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in patients undergoing shoulder surgery due to musculoskeletal disorders and which indices of central pain modulation predict poor outcome.

Material and Methods

This systematic review was reported following the indications of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist. A review protocol is published in the PROSPERO registry (CRD42019122303).

An electronic bibliographical search was conducted in MEDLINE, PEDro Database and Embase. In addition, hand-searching was performed on Google Scholar, reference list of studies included and asking in the expert in the field. A combination of Medical Subject Heading terms and text words was used to create search strategies for each database (see Table 1) to include all potential eligible studies. The search was conducted from inception until 15/11/2020.

Table 1. Search Strategy for Each Database

Medline	P	(((((surgery) AND shoulder) OR (“Arthroscopy”[Mesh] AND shoulder)) OR ((shoulder) AND debridement)) OR (“Rotator Cuff Injuries”[Mesh] AND surgery)) OR (((“Rotator Cuff Tear Arthropathy”[Mesh] AND surgery)) OR “Total Shoulder Replacement”) OR “shoulder arthroplasty”) OR “Arthroplasty, Replacement, Shoulder”[Mesh]
	I	“Pain Perception”[MeSH] OR “Pain Threshold”[MeSH] OR “Pain Measurement” [MeSH] OR “Hyperalgesia”[MeSH] OR “Central Nervous System Sensitization”[MeSH] OR “Nociception”[MeSH] OR “Pain Insensitivity” OR “Adaptation, Psychological”[MeSH] OR “Depression”[MeSH] OR “Anxiety”[MeSH] OR “Fear”[MeSH] OR “Hypoalgesia” OR “Altered nociception” OR “Cognitive-emotional Sensitization” OR “Algomerty” OR “Pain Intensity” OR “Pain Sensitivity” OR “Pain Modulation” OR “Pain Modification” OR “Pain Facilitation” OR “Pain Inhibition” OR “Conditioned Pain Modulation” OR “Diffuse Noxious Inhibitory Controls”
	O	“Pain”[MeSH] OR “Activities of Daily Living”[MeSH] OR “Quality of Life”[MeSH] OR pain OR “quality of life” OR “activities of daily living”
	Rational	(P) AND (I) AND (O)
PEDro Database		Title and abstract: Shoulder Title and abstract: surgery
Embase		(pain OR “quality of life” OR “activities of daily living”) AND (“Hypoalgesia” OR “Altered nociception” OR “Cognitive-emotional Sensitization” OR “Algomerty” OR “Pain Intensity” OR “Pain Sensitivity” OR “Pain Modulation” OR “Pain Modification” OR “Pain Facilitation” OR “Pain Inhibition” OR “Conditioned Pain Modulation” OR “Diffuse Noxious Inhibitory Controls”) AND ((surgery AND shoulder) OR (Arthroscopy AND shoulder) OR (shoulder AND debridement) OR (“Rotator Cuff Injuries” AND surgery) OR (“Rotator Cuff Tear Arthropathy” AND surgery) OR “Total Shoulder Replacement” OR “shoulder arthroplasty”)

HIGHLIGHTS

- This is the first study that investigates whether the presence of altered pre-surgical central pain modulation can influence post-surgical outcomes.
- Fear avoidance beliefs and inadequate coping strategies are the most correlated factors with worst pain and function 1 year after shoulder surgery.
- Surgeons and physical therapists should look for patients with signs of altered central pain modulation before surgery as they might be at risk for unfavorable outcome.

Two reviewers will independently review titles, abstracts and full texts to identify articles of interest. A consensus between the two reviewers is necessary for the studies to be included in the review. A third reviewer is available for a final determination if consensus is not achieved by the two initial reviewers.

Inclusion and exclusion criteria

Studies eligible for inclusion needed to be observational studies on an adult population (age > 18 years) on the waiting list or undergoing surgery for musculoskeletal shoulder disorders. To be included, the study needed to have their objective as the determination of the influence of pre-surgical central modulation indices (both direct and indirect such as psychological variables, clinical manifestation of altered central pain modulation like referred pain, etc.) in post-surgical outcomes such as pain, disability and quality of life. Both direct and indirect pain biomarkers related to central pain modulation were considered. Although central pain modulation and psychosocial factors do not necessarily evaluate the same construct, we included the indirect psychosocial variables, as they have been considered as additional signs for the diagnosis of altered central pain modulation.¹¹

We excluded studies published in languages other than English and Italian that consider patients undergoing surgery due to cancer conditions or rheumatologic/inflammatory diseases.

Risk of Bias (ROB) analysis and data synthesis

The ROB of the studies included was assessed using Quality in Prognostic Studies (QUIPS) tool,¹² that is recommended by the Cochrane Collaboration for systematic reviews of prognostic studies. Two authors (TI and DR) independently assessed the ROB, and any disagreement was resolved by a third author (PG).

The results were analyzed by the first researcher (TI) to group potential predictors and outcome measures, and existing evidence regarding the influence of pre-surgical central pain modulation on poor post-surgical outcome was summarized. In this way, a qualitative synthesis was performed, and the results were analyzed trying to

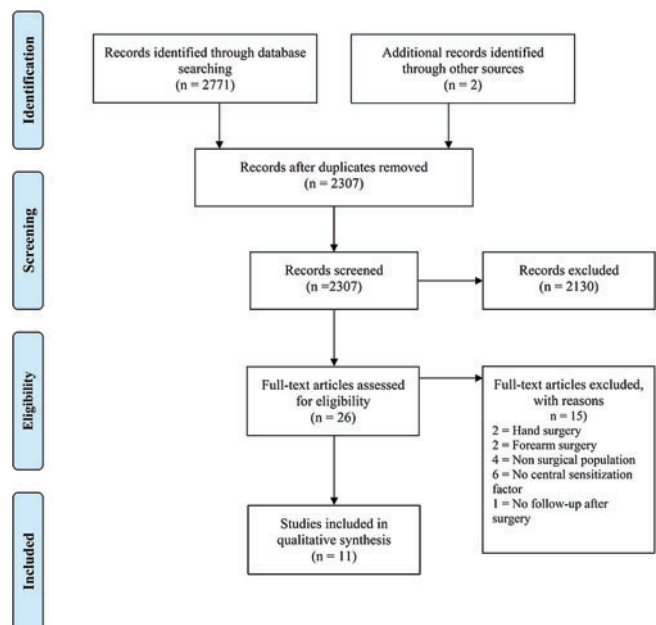


Figure 1. PRISMA Flowchart.

Table 2. Characteristics of Included Studies

Author, Publication Year and Study Design	Sample Characteristics	Prognostic Factors, Measures and Assessment Timing Before Surgery	After Surgery Outcome and Assessment Timing After Surgery	Main Results
Cho et al. 2015 ¹⁹	<i>n</i> = 47 (mean = 57 ± 8 years) Type of Surgery: RC surgery for massive tear	• Depression: HADS (Subscale D) • Anxiety: HADS (subscale A) Timing: 2 weeks	<i>QOL</i> : • WHOQOL-BREF <i>Pain</i> : • VAS <i>Function</i> : • ASES • UCLA Timing: 3-6-12 months	Preoperative HADS-D, HADS-A and PSQI scores did not correlate with the VAS pain score, UCLA or ASES scores at 12 months after surgery: HADS-D: • versus VAS (coeff. -0.074; CI -0.298 to 0.152; <i>P</i> = 0.515) • versus UCLA (coeff. 0.027; CI -0.565 to 0.511; <i>P</i> = 0.920) • versus ASES (coeff. 0.235; CI -1.492 to 1.963; <i>P</i> = 0.785) HADS-A: • versus VAS (coeff. 0.115; CI -0.053 to 0.283; <i>P</i> = 0.174) • versus UCLA (coeff. 0.089; CI -0.491 to 0.313; <i>P</i> = 0.657) • versus ASES (coeff. -0.624; CI -1.913 to 0.665; <i>P</i> = 0.335) PSQI: • versus VAS (coeff. -0.040; CI -0.082 to 0.163; <i>P</i> = 0.664) • versus UCLA (coeff. 0.001; CI -0.295 to 0.293; <i>P</i> = 0.992) • versus ASES (coeff. 0.386; CI -1.330 to 0.558; <i>P</i> = 0.415)
Cho et al. 2017 ²⁰	<i>n</i> = 46 (mean = 65.7 years) Type of Surgery: Total Shoulder Arthroplasty	• Depression: HADS (Subscale D) • Anxiety: HADS (subscale A) Timing: not specified	<i>QOL</i> : • WHOQOL-BREF <i>Pain</i> : • VAS <i>Function</i> : • ASES Timing: 3-6-12 months	HADS-D and HADS-A scores did not correlate with the VAS pain score, ASES score, and WHOQOL-BREF score at 12 months after surgery: HADS-D: • versus VAS (coeff. -0.016; CI -0.276 to 0.244; <i>P</i> = 0.899) • versus ASES (coeff. 0.140; CI -2.030 to 2.309; <i>P</i> = 0.897) • versus WHOQOL-BREF (coeff. -0.815; CI -1.920 to 0.291; <i>P</i> = 0.144) HADS-A: • versus VAS (coeff. -0.010; CI -0.363 to 0.142; <i>P</i> = 0.382) • versus ASES (coeff. 0.787; CI -1.318 to 2.893; <i>P</i> = 0.454) • versus WHOQOL-BREF (coeff. -0.172; CI -1.244 to 0.901; <i>P</i> = 0.748)
Gwilym et al. 2011 ²¹	<i>n</i> = 20 (mean = 55 years) Type of surgery: Arthroscopic subacromial decompression	• Pain Threshold: QST (punctate stimuli threshold) • Presence/absence of Referred Pain Timing: 4 weeks	<i>Pain</i> : • BPI • PainDETECT <i>Function</i> : • OSS Timing: 3 months	• Pre-operative hyperalgesia and referred pain have a significant role (<i>P</i> < 0.005) as a predictor of outcome of the post-operative OSS. • No statistically significant relationships between pre-operative PainDETECT scores and mechanical pain thresholds with post-operative OSS (Pearson correlation coefficient = 0.371, <i>P</i> = 0.13 and Pearson correlation coefficient = -0.03, <i>P</i> = 0.92)
Jain et al. 2018 ²²	<i>n</i> = 50 (mean = 59 years) Type of Surgery: RC open surgery	• Fear Avoidance Beliefs: FABQ (subscale Physical Activity) Timing: not specified	<i>Function/Pain</i> : • SPADI Scale Timing: 3, 6, 12, 18 months	• The FABQ physical activity score predicted SPADI such that those with higher FABQ physical activity scores (more fear avoidance behavior) had higher SPADI scores (worse shoulder pain and function). This difference was most pronounced at 3 months of follow-up (<i>P</i> = 0.001)
Kadum et al. 2018 ¹⁴	<i>n</i> = 63 (mean = 71 years) Type of Surgery: Total Shoulder arthroplasty (TSA)	• Pain Sensitivity: electrical pain threshold (EPT) Timing: Before 6 weeks	<i>Pain</i> : • VAS <i>Function</i> : • quickDASH Timing: 3-12 months	• There is a correlation between preoperative EPT and 12 months Quick DASH • Linear regression analysis showed that when the preoperative EPT is high the 12-month QuickDASH score is low (coeff. = -2.20; CI = -3.1 to -1.3 <i>P</i> = 0.0001).
Koorevaar et al. 2016 ¹⁵	<i>n</i> = 315 (mean = 52 years) Type of Surgery: Elective shoulder surgery	• Depression, anxiety, distress, somatization: 4DSQ Timing: 2-3 weeks	<i>Function</i> : • DASH • Patient perceived improvement of pain and function (1 to 7 scale) Timing: 12 months	Distress, depression, anxiety and somatisation before surgery, after adjustment for age, gender and DASH score preoperatively, predicted less of an improvement in DASH score. When additionally adjusted for postoperative symptoms of psychological disorders, the regression coefficients dropped considerably, and all significant associations disappeared: • Distress (coeff. 0.30; CI -6.09 to 6.7; <i>P</i> = 0.93) • Depression (coeff. -4.68; CI -14.72 to -5.36; <i>P</i> = 0.36) • Anxiety (coeff. -6.25; CI -13.84 to 1.30; <i>P</i> = 0.10) • Somatization (coeff. -3.00; CI -10.52 to 4.52; <i>P</i> = 0.43)
Ravindra et al. 2018 ¹⁰	<i>n</i> = 93 (Mean = 56.4 years) Type of surgery: Shoulder Arthroscopy	• Psychological impairment: WORC (emotion), SF-36 Timing: not specified	<i>Function</i> : • ASES • WORC (composite), SF-36 <i>Pain</i> : • VAS Timing: 2 weeks, 3-6-12 months	• None significant correlation between WORC composite and VAS (coeff. corr = -0.245; <i>P</i> = 0.069) at 2 weeks, 3 and 6 months • Less WORC emotion is correlated with more VAS (coeff = -0.277; <i>P</i> = 0.02) at 12 months
Potter et al. 2015 ²³	<i>n</i> = 70 (mean = 61 years) Type of surgery: RC arthroscopy	• Psychological Distress: Distress Risk Assessment Method Timing: not specified	<i>Function</i> : • ASES • Simple Shoulder Test <i>Pain</i> : • VAS Timing: 12 months	Distress is not correlated to VAS for pain, the Simple Shoulder Test, and the American Shoulder and Elbow Surgeons score 1 year after arthroscopic RC repair: Non-distressed vs distressed (mean postoperative values): • VAS 1.0 (95% CI, 0.5-1.4) versus 1.9 (95% CI, 1.0-2.8) (<i>P</i> = 0.10) • Simple Shoulder Test 11 (95% CI, 10.0-11.0) versus 9 (95% CI, 8.1-10.4) (<i>P</i> = 0.06) • ASES 88 (95% CI, 84-92) versus 80 (95% CI, 72-88) (<i>P</i> = 0.08)

Table 2. Characteristics of Included Studies (Continued)

Author, Publication Year and Study Design	Sample Characteristics	Prognostic Factors, Measures and Assessment Timing Before Surgery	After Surgery Outcome and Assessment Timing After Surgery	Main Results
Thorpe et al. 2018 ¹⁷	n = 124 Type of surgery: RC repair with or without subacromial decompression and arthroscopic subacromial decompression only	<ul style="list-style-type: none"> • Fear avoidance beliefs: TSK • Pain Catastrophizing: PCS • Self-Efficacy: PSEQ • Depression, stress, anxiety: DASS Timing: 1 week	Function: <ul style="list-style-type: none"> • ASES Timing: 3, 12 months	Less psychological values (TSK, PCS, PSEQ, DASS) are correlated with less function (ASES) at 3 and 12 months. The differences are bigger than MCID (12 to 17). <ul style="list-style-type: none"> • Cluster with better psychologic function (mean and standard deviations): ASES before surgery = 54.3 (18.0); ASES 3 months = 71.6 (16.3); ASES 12 months = 86.2 (17.6) • Cluster with poorer psychological function (mean and standard deviations) ASES before surgery = 39.5 (15.2); ASES 3 months = 52.2 (18.4); ASES 12 months = 74.9 (19.7)
Valencia et al. 2014 ¹⁸	n = 78 Type of surgery: shoulder or clavicle arthroscopy	<ul style="list-style-type: none"> • Pain sensitivity QST → CPM (conditioned pain modulation), temporal summation of supra-threshold heat pain response (SHPR) • Thermal pain threshold • Depressive symptoms: PHQ-9 • Pain Catastrophizing: PCS Timing: 24/48 hours	Function: <ul style="list-style-type: none"> • DASH Pain: <ul style="list-style-type: none"> • BPI Timing: 3-6 months	<ul style="list-style-type: none"> • Minor hypersensitivity to SHPR (3 months) is correlated to better function (DASH) and less pain (BPI) at 6 months (coeff. = -0.34; P = 0.004).
Woollard et al. 2017 ¹³	n = 46 (mean = 46.5) Type of surgery: arthroscopy subacromial decompression	<ul style="list-style-type: none"> • Fear avoidance beliefs: FABQ • Depression: CES-D • Anxiety: BAI • Timing: not specified 	Function/pain: <ul style="list-style-type: none"> • DASH • WORC Timing: 6 months	<ul style="list-style-type: none"> • FABQ total score (OR1.40.95, 95% CI: 0.91-0.98) and the FABQ_work sub-scale (OR1.40.92, 95% CI: 0.87-0.97) were predictors of outcomes (P < 0.005)

4DSQ, Four-Dimensional Symptom Questionnaire; ASES, American Shoulder and Elbow Surgeons' Scale; BAI, Beck Anxiety Inventory; BPI, Brief Pain Inventory; CES-D, Clinical Epidemiologic Studies Depression Scale; CI, Confidence Interval; DASH, Disabilities of the Arm, Shoulder, and Hand Questionnaire; DASS, Depression, Anxiety and Stress Scale; FABQ, Fear Avoidance and Beliefs Questionnaire; FPQ-II, Fear of Pain Questionnaire; HADS, Hospital Anxiety and Depression Scale; MCID, Minimal Clinically Important Difference; OSS, Oxford Shoulder Score; PCS, Pain Catastrophizing Scale; PHQ, Patient Health Questionnaire; PSEQ, Pain Self-Efficacy Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QOL, Quality of Life; QST, Quantitative Sensory Testing; RC, Rotator Cuff; SPADI, Shoulder Pain and Disability Index; STAI, State-Trait Anxiety Inventory; TSK, Tampa Scale of Kinesiophobia; TSK-11, Shortened Version of the Tampa Scale of Kinesiophobia; UCLA, University of California Los Angeles Scale; VAS, Visuo-Analog Scale; WHOQOL-BREF, World Health Organization Quality of Life Scale Abbreviated Version.

Table 3. Quality Assessment of Included Studies with Quality in Prognostic Studies (QUIPS) Tool

	Risk of Bias						Overall risk
	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting	
Cho et al. 2015 ¹⁹	Moderate	High	Moderate	Low	High	Low	Moderate
Cho et al. 2017 ²⁰	Moderate	High	Moderate	Low	High	Low	Moderate
Gwilym et al. 2011 ²¹	Moderate	Moderate	Low	Low	High	Low	Moderate
Jain et al. 2018 ²²	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Kadum et al. 2018 ¹⁴	Low	Moderate	Low	Low	Moderate	Low	Low
Koorevaar et al. 2016 ¹⁵	Moderate	High	Low	Low	Low	Low	Low
Ravindra et al. 2018 ¹⁶	Moderate	High	Low	Moderate	Moderate	Low	Low
Potter et al. 2015 ²³	Moderate	Moderate	Low	Low	High	Low	Moderate
Thorpe et al. 2018 ¹⁷	Low	Moderate	Low	Low	Low	Low	Low
Valencia et al. 2014 ¹⁸	Low	Moderate	Low	Low	Low	Low	Low
Woollard et al. 2017 ¹³	Low	High	Low	Low	Moderate	Moderate	Moderate

correlate the central sensitization variables with post-surgical outcome types, based on the ROB of the studies. A second researcher was involved in case of doubt.

Results

Selection process and data extraction

The literature search retrieved 2,771 records. After removing duplicates (464 studies), we screened the title and abstract of 2,307 references and selected 26 papers for full-text analysis. Finally, only 11¹³⁻²³ prospective cohort studies met the inclusion criteria. The study selection process is summarized in the

PRISMA flowchart (see Figure 1), and we summarized data extracted from studies in Table 2.

ROB of the studies included

Five studies were found to beat low ROB,^{17-19,21,22} all from moderate^{17,21,22} to high^{18,19} risk in attrition bias; as in all of these studies, there is a clear description of how the data of the missing subjects are treated. Six studies were found to be at moderate ROB,^{13-16,20,23} most of which did not report the ways in which the confounding prognostic factors were managed.^{13-15,20} Each of the studies reported an adequate description of drop-outs, so that all studies were judged to be at moderate^{15-17,20,22} or high^{13,14,18,19,23} risk

Table 4. Measures Used to Detect Prognostic Factors

Prognostic Factor	Number of Studies	Measures
Psychological Characteristics		
Depressive symptoms (included psychological distress)	8	HADS 4DSQ WORC DRAM DASS PHQ-9 CES-D
Anxiety	5	HADS 4SDQ DASS BAI
Pain catastrophizing	2	PCS
Fear avoidance beliefs	3	FABQ TSK
Self-efficacy	1	PSEQ
Clinical Manifestations of Altered Central Pain Modulation		
Presence of referred pain	1	Dichotomous (yes/no)
Quantitative Sensory Testing (QST)		
Hyperalgesia (punctate stimuli)	3	VAS BPI
Temporal summation of suprathreshold heat pain response	1	VAS

4DSQ, Four-Dimensional Symptom Questionnaire; BAI, Beck Anxiety Inventory; CES-D, Clinical Epidemiologic Studies Depression Scale; DASS, Depression, Anxiety and Stress Scale; FABQ, Fear Avoidance and Beliefs Questionnaire; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PHQ, Patient Health Questionnaire; PSEQ, Pain Self-Efficacy Questionnaire; TSK, Tampa Scale of Kinesiophobia; VAS, Visuo-Analog Scale.

of attrition bias. The assessment of ROB of the studies included is shown in Table 3.

Synopses of the results

Studies included were all prospective cohort design. Overall, 952 patients were included: the sample size for each study ranged from 20¹⁵ to 314.¹⁸ Studies included both arthroscopy^{15,18-23} and open^{13,14,16,17} surgery. Prognostic factors and measures used to detect it are shown in Table 4. Results are listed below following the emerging biopsychosocial index (prognostic factor) of altered central pain modulation associated with outcomes. Prognostic factors, post-surgical outcomes and synopsis of the results are shown in Table 5.

Depressive symptoms

Seven studies^{13,14,18-20,22,23} evaluated the presence of pre-surgical depressive symptoms as potential predictor in patients undergoing shoulder arthroplasty,¹⁴ RC repair¹³ and shoulder arthroscopy.^{19,20,22} Pain was investigated in 6 studies^{13,14,19,20,22,23} with low to moderate ROB; only Ravindra et al. 2018¹⁹ found a significant correlation between depressive symptoms and pain at 12 months. Three other studies^{13,14,20} that measured pain at 12 months found no significant correlation. All studies included a 6-month analysis in which the correlation was not significant. Function was investigated in 6 studies^{13,14,18,20,22,23} with low to moderate ROB, but none of them found a significant correlation with depressive symptoms. Only Cho et al. 2017¹⁴ evaluated the correlation between depressive symptoms and quality of life, but this was not significant at 12 months of follow-up.

Anxiety

Five studies^{13,14,18,21,23} investigated anxiety as a potential predictor of altered central pain modulation in patients undergoing shoulder

arthroplasty,¹⁴ RC repair,¹³ subacromial decompression²³ and elective shoulder surgery.¹⁸ Pain relief was evaluated in three studies^{13,14,23} with moderate ROB, but there was no significant correlation between pain and pre-surgery anxiety levels at 3 months^{13,14}, 6 months^{13,14,23} and 12 months.^{13,14} Five studies^{13,14,18,21,23} considered function as the post-surgical outcome. Only Thorpe et al. 2018²¹ found a statistically significant correlation by assessing anxiety and function at 3 and 12 months (baseline): this measure was analyzed in clusters with avoidance behaviors, catastrophizing and self-efficacy. It was thus possible to identify a group with better and one with worse psychological function. The cluster with the worst psychological function reported significant worst function after surgery. The study was at low ROB. The other 4 studies^{13,14,18,23} found no significant correlation between anxiety and post-surgical function. No correlation was found between pre-surgical anxiety levels and quality of life^{13,14} after surgery.

Pain catastrophizing

Two studies^{21,22} with low ROB investigated the presence of pain catastrophizing as the potential predictor of altered central pain modulation in patients undergoing RC surgery²¹ and shoulder or clavicle arthroscopy.²² The correlation with pain levels after surgery was only investigated by Valencia et al. 2014²², who did not find any statistically significant correlation; only Thorpe et al. 2018²¹ found a statistically significant correlation between catastrophizing and function.

Fear avoidance beliefs

Three studies^{16,21,23} with low to moderate ROB investigated the influence of fear avoidance beliefs as potential predictors of altered central pain modulation in patients with both open¹⁶ and arthroscopic RC repair with and without subacromial decompression.^{21,23} All studies reported a significant correlation between avoidance behavior, pain¹⁶ and function^{16,21,23} at 3 months^{16,21} and 6 months.²³

Self-efficacy

Only one study²¹ with low ROB investigated the influence of reduced self-efficacy before surgery, finding significant correlation with function at 3 and 12 months after RC surgery.

Clinical manifestation of altered central pain modulation

Only one study¹⁵ with moderate ROB investigated the correlation between the presence of pre-surgical referred pain as potential predictor and function after subacromial decompression, reporting a significant correlation at 3 months.

Quantitative sensory testing (QST)

Three studies^{15,17,22} evaluated the role of altered central pain modulation in predicting outcomes by performing QST in patients undergoing shoulder arthrodesis,¹⁷ subacromial decompression¹⁵ and shoulder and clavicle arthroscopy.²² A significant correlation was found between pain after surgery and the absence of painful hypersensitivity, which is evaluated as the temporal summation of thermal stimuli (hot and cold) above-threshold. A significant correlation was found between function after surgery and the presence of pre-surgical hyperalgesia in two studies^{15,17} out of three. However, reduced painful hypersensitivity was positively correlated with greater function at 3 and 6 months.²²

Discussion

The objective of this review was to investigate the influence of pre-surgical indices of the central pain modulation on post-surgical outcome measures in patients awaiting shoulder surgery due to musculoskeletal disorders. The review showed that among

Table 5. Synopses of the Results

Pre-Surgical Prognostic Factor	Post-Surgical Outcome	Studies	Risk of Bias	Correlation PF/Outcome			
Psychological Characteristics							
Depressive symptoms (included psychological distress)	Pain	+ Ravindra 2018 ¹⁶	Low	No			
		- Cho 2015 ¹⁹	Moderate				
		- Cho 2017 ²⁰	Moderate				
		- Potter 2015 ²³	Moderate				
		- Valencia 2014 ¹⁸	Low				
		- Woollard 2017 ¹³	Moderate				
	Function	- Cho 2015 ¹⁹	Moderate				
		- Cho 2017 ²⁰	Moderate				
		- Koorevaar 2016 ¹⁵	Low				
Quality of life	- Potter 2015 ²³	Moderate					
	- Valencia 2014 ¹⁸	Low					
	- Woollard 2017 ¹³	Moderate					
Anxiety	Pain	- Cho 2015 ¹⁹	Moderate	No			
		- Cho 2017 ²⁰	Moderate				
		- Woollard 2017 ¹³	Moderate				
	Function	+ Thorpe 2018 ¹⁷	Low				
		- Cho 2015 ¹⁹	Moderate				
		- Cho 2017 ²⁰	Moderate				
	Quality of life	- Koorevaar 2016 ¹⁵	Low				
		- Woollard 2017 ¹³	Moderate				
		- Cho 2015 ¹⁹	Moderate				
Pain catastrophizing	Pain	- Valencia 2014 ¹⁸	Low	No			
		- Valencia 2014 ¹⁸	Low				
	Function	+ Thorpe 2018 ¹⁷	Low				
Fear avoidance beliefs	Pain	+ Jain 2018 ²²	Moderate	Yes			
		+ Jain 2018 ²²	Moderate				
	Function	+ Thorpe 2018 ¹⁷	Low				
		+ Woollard 2017 ¹³	Moderate				
		+ Thorpe 2018 ¹⁷	Low				
Self-efficacy	Function	+ Thorpe 2018 ¹⁷	Low	Yes			
		Clinical Manifestations of Altered Central Pain Modulation					
		Presence of referred pain	Function		+ Gwilym 2011 ²¹	Moderate	Yes
					Quantitative Sensory Testing (QST)		
		Hyperalgesia (punctate stimuli)	Function		+ Gwilym 2011 ²¹	Moderate	Yes
+ Kadum 2018 ¹⁴	Low						
- Valencia 2014 ¹⁸	Low						
Temporal summation of suprathreshold heat pain response	Pain	+ Valencia 2014 ¹⁸	Low	Yes			
	Function	+ Valencia 2014 ¹⁸	Low	Yes			

+, significant prognostic factor; -, non-significant prognostic; PF, Prognostic Factor.

all the potential predictors investigated, only the presence of fear avoidance beliefs and inadequate coping strategies (less self-efficacy) before surgery are significantly correlated to worse outcomes after surgery in terms of pain and function. However, only one study²¹ investigated self-efficacy, while the evidence regarding the correlation between avoidance behaviors and outcomes after surgery comes from a larger number of studies. This evidence seems to be in agreement with other studies that have shown how the fear of pain creates a vicious circle that leads to avoiding painful activities, consequently increasing the fear of pain itself, influencing the outcomes (this model is described as fear-avoidance model).^{24,25}

Depression, anxiety and pain catastrophizing do not seem to influence post-surgical outcomes in patients undergoing shoulder surgery. As for QST, the review revealed some uncertainty on the correlation

between a decreased pain threshold to electrical,¹⁷ thermal²² and pressure stimuli¹⁵ before surgery and reduced pain and function after surgery. However, this evidence comes from a small number of studies with conflicting results, which increases the uncertainty of these conclusions.

Compared to a large number of evidence and theoretical models that demonstrate a clear influence of the psychological characteristics,^{25,26} the results of the present review regarding their poor correlation in post-surgical patients are in line with what was also reported in the study by Baert et al.,²⁷ in which they investigated the influence of altered central pain modulation in patients undergoing knee arthroplasty. At the same time, they appear to be in contrast with the results of studies focusing on conservative treatment,^{28,29} in which QST are potential predictors of the development of chronic pain.

The uncertainty that has emerged from this review on the prognostic value of many indices of altered central pain modulation may be due to some intrinsic factors of the studies themselves. First of all, the strong heterogeneity between the outcome measures was used, especially for psychological indices. As we can see from Table 4, depression and psychological distress, for example, were taken into account as prognostic factors in eight studies^{13,14,18-23} and seven different outcome measures were used, which make it difficult to compare results.

Another aspect that may have contributed to this uncertainty on the prognostic values is the selection of study participants: in some studies, the number of participants was small¹⁵ and often only a few participants had a baseline value for prognostic factors that is far from the norm, which significantly decreases the possibility of finding a predictive correlation of the prognostic index itself. Moreover, in the literature, it is well known that the correlation between the psychological construct and pain or function is often influenced by other psychological factors³⁰ such as emotions, optimism and behavioral factors. Of the included studies, none specifically considered these aspects as possible contributing factors.

The results of the present review, however, show that there is a significant correlation trend between emotional-behavioral characteristics that, if managed in the pre-surgical period, can improve the outcomes of surgery and the consequent conservative treatment. In light of the significant correlation found with avoidance behaviors, the use of cognitive-behavioral strategies such as patient education to pain neurophysiology and gradual load exposure³¹ in order to reduce the avoidance of functional activities could be used as a pre-surgical therapeutic strategy to improve outcome after shoulder surgery. Some evidence³²⁻³⁴ supports the use of these strategies in patients with altered central modulation of pain. Given the importance of some factors in influencing the outcomes of patients undergoing shoulder surgery, future research should move towards the design, management and implementation of prospective cohort studies of greater methodological quality, especially the enrollment of participants, the management of confounding factors and the use of more homogeneous outcome measures. Moreover, given the correlation shown by some QSTs, such as the assessment of the pain threshold, conducting studies centered on them could be scientifically relevant, since the limited number of publications in literature.

Our work has some strengths and limits. The strengths of this systematic review are its methodological rigor with standardised methods to find, select and assess methodological quality of the studies included. The limits of this work are essentially the absence of a quantitative analysis (meta-analysis) that would have been difficult to implement due to substantial heterogeneity in terms of outcome measures and characteristics of the studies included. Search strategies, even if comprehensive and based on PICO approach, may have not detected some studies of interest especially from some grey literature sources.

Among all the prognostic factors investigated, avoidance behaviors seem to be most correlated with worse outcomes at one year in terms of pain and function. The clinical manifestations of altered central pain modulation and the QST showed a significant correlation, even if the number of published studies is too limited to draw accurate conclusions. Future research should focus on constructing methodologically better studies, especially in terms of the selection of participants and the use of more homogeneous outcome measures, since there is strong heterogeneity among those used in the various

studies published to date; from a clinical point of view, surgeons and physical therapists should look for patients with signs of altered central pain modulation before surgery as they might be at risk of an unfavorable outcome.

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