REVIEW ARTICLE

Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature

Suzie Noten, MSc*,†; Filip Struyf, PhD*; Enrique Lluch, PhD, MSc†,‡; Marika D'Hoore, PT, MSc*; Eveline Van Looveren, PT, MSc*; Mira Meeus, PhD*,†,§

*Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp; †Pain in Motion International Research Group, Antwerp, Belgium; ‡Department of Physical Therapy, University of Valencia, Valencia, Spain; §Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

■ **Abstract**

Background: Shoulder pain is a common health problem in which changes in shoulder structure cannot always explain the patient's perceived pain. Central sensitization (CS) might play a role in a subgroup of these patients.

Methods: The literature was systematically reviewed to address the role of CS in patients with shoulder pain. Electronic databases PubMed and Web of Knowledge were searched for relevant studies.

Results: Eighteen full-text articles were included, methodological quality was scored, and information was extracted. Studies were clustered on those studying patients with musculoskeletal (MSK) shoulder pain and those studying patients with hemiplegic shoulder pain (HSP). In particular, quantitative sensory testing revealed hyperalgesia for pressure pain in the MSK group, whereas these results were inconsistent in patients with HSP. Conditioned pain modulation was reduced in patients with MSK shoulder pain, but functioned normally in the HSP group.

Conclusion: This review has shown that great progress has been made toward a better understanding of neurophysiologic pain mechanisms in patients with shoulder pain. The presence of generalized mechanical hyperalgesia, allodynia, and impaired conditioned pain modulation in patients with MSK shoulder pain indicates the involvement of the central nervous system. Widespread somatosensory abnormalities observed in patients with HSP could suggest a central origin for their shoulder pain and predispose patients with HSP to develop CS, although results are inconsistent. Additional research is required adopting different assessment methods (especially dynamic methods) to establish the role of CS in patients with shoulder pain. ■

Key Words: central sensitization, pain processing, shoulder, chronic pain, systematic review

INTRODUCTION

Shoulder pain is the third most common musculoskeletal condition, with incidence rates up to 2.5%.[1,2] Although more than half of all patients with shoulder pain recover completely within 1 year after injury,[3–5] the remaining report persistent shoulder pain.[6] It is suggested in the literature that central sensitization (CS) might play a role in these persistent complaints in (some) patients with shoulder pain.[7]

Address correspondence and reprint requests to: Mira Meeus, PhD, Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp, Campus CDE – Building S, Universiteitsplein 1, 2610 Wilrijk, Belgium. E-mail: mira.meeus@uantwerpen.be.

Submitted: May 9, 2016; Revised June 21, 2016; Revision accepted: July 8, 2016

DOI. 10.1111/papr.12502

Central sensitization is defined as an increased functioning of neurons and circuits in nociceptive pathways that leads to pain from innocuous stimuli or an excessive perception of pain from low-level painful stimuli. Continuous nociceptor input eventually results in neuronal plasticity of the peripheral and central nervous system.[8] Sensitivity of the tissues can be altered within the injured area (primary hyperalgesia), but also in the adjacent, uninjured tissue (secondary hyperalgesia); the latter is indicative for CS or central hypersensitivity.[9] Central hypersensitivity has already been found in various chronic pain populations including those with chronic whiplash,[10] fibromyalgia,[11] carpal tunnel syndrome,[12] osteoarthritis,[13] tension-type headache,[14] temporomandibular joint pain,[15] and subacromial impingement syndrome.[7]

All of these studies found an involvement of central pain processing mechanisms in those pain populations. Despite that there is no gold standard for assessing CS, quantitative sensory testing and paradigms such as conditioned pain modulation and exercise-induced endogenous analgesia are regularly used to evaluate the presence of CS.

Although a more research has already been carried out on the above-mentioned chronic pain syndromes, the role of CS in shoulder pain patients has been poorly investigated. Shoulder pain is a prevalent health presentation with complex underlying factors. The exact pathology is not always clear; muscles and joints do not always seem to be the main cause of the persistent problem, and biomedical approaches are not always successful. Shoulder pain can be related to a musculoskeletal problem, but is also a common disorder after a stroke.[16] Poststroke shoulder pain is usually studied and treated as peripheral nociceptive or neuropathic pain, but evidence for the effectiveness of therapeutic interventions is lacking.[17] It can improve during rehabilitation,[18] but it may also be a durable or persistent problem.[19]

Given the evidence of alterations in the central and peripheral nervous system in many other chronic pain populations,[8,9,20] CS might explain why some patients with shoulder pain—both musculoskeletal or poststroke—do not respond to regular treatment procedures directed to the shoulder. Therefore, the primary aim of this review was to investigate whether there is evidence for abnormal central pain processing in patients with shoulder pain of musculoskeletal or neurologic origin.

METHODS

This systematic review is reported following the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses).[21]

Eligibility Criteria and Study Selection

To be included in the present systematic review, articles had to evaluate signs of CS (I), as contributor to the pain (O), in patients with shoulder pain (P). The comparison (C) was not defined to obtain all articles regarding the presence of CS in patients with shoulder pain. All original study designs were included (S). Articles were eligible for this systematic review if they fulfilled the following inclusion criteria: central pain processing was assessed; in human adults (> 18 years) suffering from shoulder pain; the article reported original research in full text; and the article was published in English, French, or Dutch. Studies were excluded if only primary hyperalgesia or peripheral sensitization was assessed, as these are not indicative for CS.[22]

Information Sources and Search Strategy

PubMed and Web of Knowledge were searched to identify relevant articles concerning CS in adults with shoulder pain. The last search took place on May 27, 2015. Three groups of key words which were related to "central sensitization," "shoulder pain," and "pain" were stipulated for the search. Key words from the different groups were combined. The construct of the search strategy is presented in Table 1. In addition, the reference lists from relevant articles were checked to obtain as much information as possible. Literature was independently searched and screened by EVL and MD, who have Bachelor's degrees in Physiotherapy and Rehabilitation Sciences. They were trained by MM, who obtained the degree of PhD with the dissertation regarding chronic pain and CS and has published several systematic reviews in this domain.

Data Items and Collection

Information was extracted from each included study about design and purpose of the study; characteristics of study participants (including number of participants, mean age, sex, and diagnosis); inclusion and exclusion criteria; methods of assessing the presence of CS; outcome measures; and main results.

Table 1. Search Strategy

Keywords Group 1	Group 2	Group 3
Central nervous system sensitization (MeSH) OR	Shoulder pain (MeSH) OR	Pain (MeSH)
Central hypersensitivity OR	Frozen shoulder OR	
Sensitization OR	Adhesive capsulitis OR	
Neural inhibition OR	(shoulder [MeSH] AND pain [MeSH])	
Pain inhibition (MeSH) OR		
Pain processing OR		
Central sensitivity OR		
Nociception (MeSH) OR		
Hyperalgesia (MeSH) OR		
Algometry OR		
Central hyperexcitability OR		
Pain modulation OR		
Pain threshold (MeSH) OR		
Quantitative sensory testing OR		
Windup OR		
Postsynaptic potential summation (MeSH) OR		
Temporal summation OR		
Spatial summation OR		
Conditioned pain modulation OR		
Diffuse noxious inhibitory controls OR		
Heterotopic noxious counter stimulation OR		
Counterirritation		

Risk of Bias in Individual Studies

Methodological quality was assessed independently by 2 researchers (EVL and MD), who were blinded from each other's results. After rating the selected articles, the results of both researchers were compared and differences were analyzed in a consensus meeting. In cases of disagreement, the reviewers screened the articles a second time and the points of difference were discussed until a consensus was made. When consensus could not be reached, a third opinion was provided by the last author (MM). Several checklists were used to assess the methodological quality of the articles depending on the study design. Quality assessment of case–control studies or cohort studies was performed using the Dutch Cochrane Checklist (http://dcc.cochrane.org). Cross-sectional studies were judged with the same checklist used for case–control studies, but the questions regarding comparability of groups and blinding were dropped. Randomized controlled trials (RCTs) were evaluated with the PEDro scale (http://www.pedro.org.au/wp-content/uploads/PEDro_scale.pdf).

Level of Evidence

After pooling the results, the overall quality of evidence for each outcome was rated with the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[23]

RESULTS

Study Selection and Study Characteristics

The selection process of the articles is represented in Figure 1. After screening, 18 full-text articles were included in this systematic review. Of the 18 selected articles, 15 were observational studies (9 case–control,[7,17,24–30] 3 cohort,[31–33] and 3 cross-sectional[34–36]) and 3 were RCTs. The characteristics of the included studies are presented in Table 2.

Methodological Quality

The methodological quality ratings of the reviewed studies are presented in Table 3. There was 91% of agreement (117 of 129 items). After a second review and a comparison of the 12 differences, the reviewers reached a consensus for all items. The level of evidence of the 10 observational studies was determined for each relevant outcome starting as low-quality evidence according to the GRADE system. For most outcomes of the observational studies, the quality of evidence remained low. These studies showed limitations of the study design and inconsistency of the study results. Limitations were mainly due to not accounting for confounders and outcome measures being self-reported measures. Most cohort studies showed a lack of follow-up.

The level of evidence of the 3 RCTs[37–39] was determined starting as high-quality evidence according to the GRADE system. The methodological quality was low, according to the PEDro classification. Two RCTs failed to get half of the maximum score[38,39] and were downgraded to a moderate level of evidence.

Study Population

Most studies included patients with chronic shoulder pain[7,17,24–26,28,29,34,36–39]; 1 study included patients in the acute phase,[31] while the rest of the studies did not specifically define the duration of shoulder pain.[27,30,32,35] The population of patients in the different studies could be distinguished in 2 major groups: patients with musculoskeletal (MSK) shoulder pain and patients with a history of stroke suffering from hemiplegic shoulder pain (HSP).

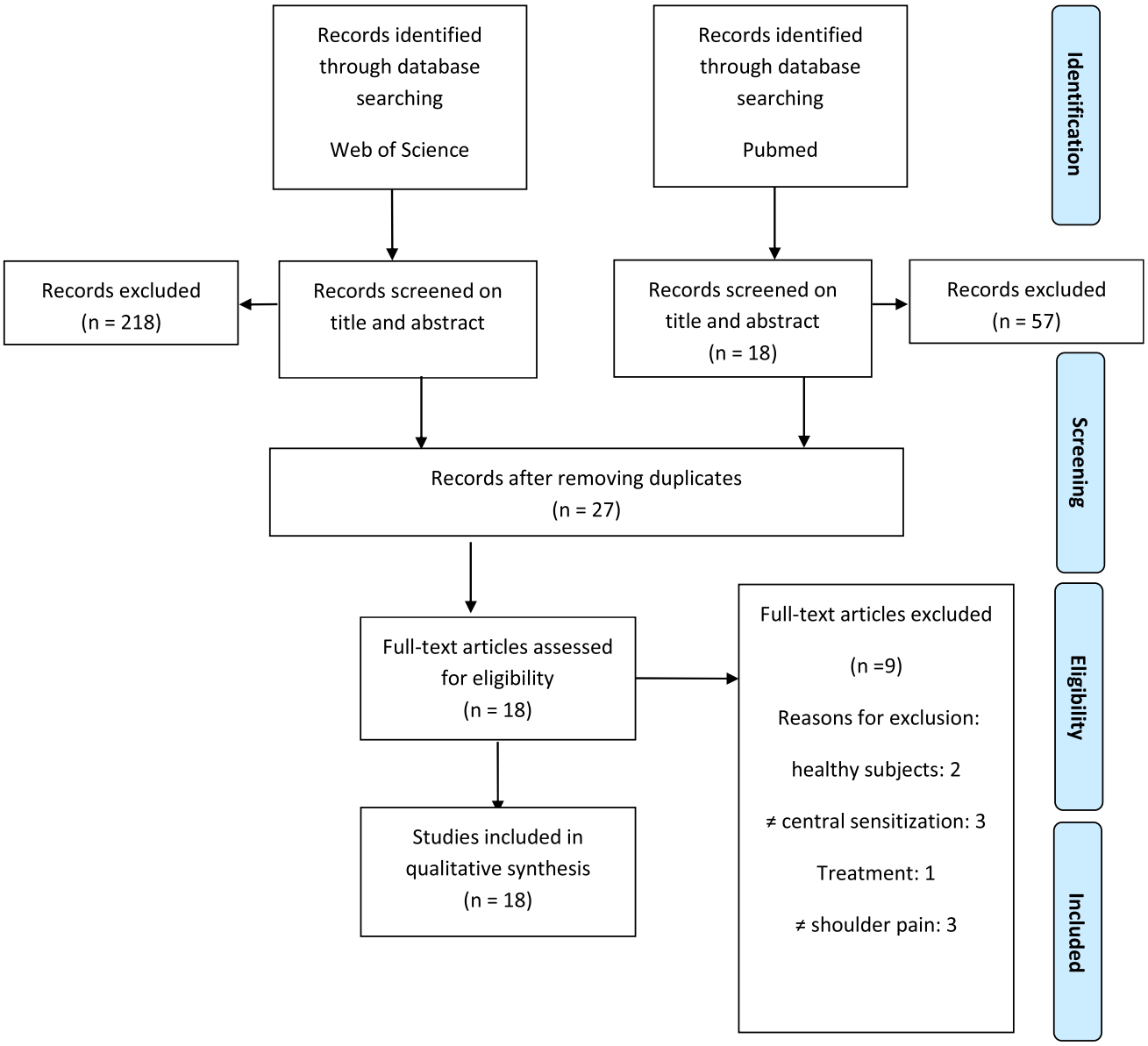

Figure 1. Flowchart of study selection.

Studies that included patients with MSK shoulder pain, both unilateral[7,27–30,32,35–39] or bilateral,[25] could be separated in different subgroups. Four of these articles were conducted in patients with shoulder impingement syndrome.[7,28,30,36] There were 4 studies that assessed patients awaiting for surgical treatment of rotator cuff pathology.[27,32,35] Hidalgo-Lozano[37] included elite swimmers with unilateral shoulder pain. Three studies only included female patients.[25,38,39] Ge et al.[38] investigated female Caucasian patients with chronic unilateral shoulder pain, while Persson et al.[39] examined hospital cleaners with unilateral shoulder pain. Patients with uni- or bilateral shoulder myalgia related to the infraspinatus muscle were evaluated in the study by Lannersten and Kosek.[25]

Five articles studied CS in patients with HSP.[17,24,26,31,34] HSP was defined by Zeilig et al.[24] as "the presence of shoulder pain for at least 6 months, with no additional characteristics other than ruling out shoulder pathologies prior to the stroke." Similarly, Roosink et al.[31] defined HSP as nonremitting shoulder pain confined to the shoulder and/or C5 dermatome of the contralesional side with an onset after a stroke episode, present during rest or during active or passive

Table 2. Characteristics of Included Studies

Authors	Patients (P)	Controls (C)	Outcome Measures	Results
Albuquerque et al. (2013)[28]	Unilateral shoulder impingement *N* = 27 35.6 ± 12.1 (30.8 to 40.4)y 13♂14♀	Healthy controls *N* = 20 37.0 ± 11.2(31.8 to 42.2)y ♂ 9♀11	PPT—Articular pillar of C5-C6 zygapophyseal joint, Delt, IS, LS, SSp, SA, TA, UT—A/UA, D/ND	P ↔ C ↓ PPT SSp (A/UA ↔ D)
Coronado et al. (2011)[35]	Unilateral RC pathology involved side *N* = 59 50.4 ± 14.9 (18 to 85)y 35♂ 24♀	Uninvolved side	PPT—AP, BR, IS, M, SSp TPT and tolerance—thermal stimuli at A/UA volar forearms, +0.5°C/s TS—10 heat pulses at Th—A/UA, baseline 35°C + 10°C/s to max 49°C and—10°C/s back to 35°C, interpulse 2.5 to 3.0 s	P ↔ C ↓ PPT in all muscles no difference in thermal pain sensitivity clinical pain intensity ~ PPT A shoulder
Coronado et al. (2014)[29]	Unilateral shoulder pain *N* = 58 32.3 ± 11.6y 41♂ 17♀	Pain-free controls *N* = 56 28.7 ± 8.4y 40♂ 16♀	PPT—AP, M TPT and tolerance—thermal stimuli at A/UA volar forearms SHPR—5 heat pulses at thenar at 30°C/s, interstimulus interval 2.5 s, peak temperature 50°C	P ↔ C ↓ PPT acromion A vs. UA ↓ PPT acromion UA/A vs. control ↓ PPT masseter A vs. control ↑ SHPR UA/A vs. control
Ge et al. (2006)[38]	Chronic unilateral myofascial SP *N* = 21 45.58 ± 3.16 (24 to 60)y 19♀	/	PPT during normal respiration and EITP—IS—A/UA, TA—right side at trigger and tender point	Trigger ↔ tender point ↓ PPT in A and UA IS
Gwilyn et al. (2011)[30]	Patients awaiting arthroscopic subacromial decompression *N* = 17 55 (42 to 60)y 7♂ 10♀	Healthy controls *N* = 17 53 (38 to 59)y 7♂ 10♀	QST—Punctuate sharpness threshold and sharpness of 256 Nm stimulus (VAS)—A/UA, C	P ↔ C ↓threshold painful/sharp punctate stimuli P (A) ↔ C ↓ Mechanical pain threshold A ↔ UA ↑ sharpness rating
Hidalgo-Lozano et al. (2010)[7]	Unilateral shoulder impingement *N* = 12 25 ± 9 (20 to 38)y 7♂ 5♀	Healthy controls *N* = 10 26 ± 8 (20 to 38)y 5♂ 5♀	PPT—LS—A/D, SSp—A/D, IS—A/D, PMa—A/D, BB—A/D, TA—A/D; A = D = right	P (A) ↔ C (D) ↓ PPT in all muscles ↑ PPT index in BB, TA compared to LS, SSp, IS, PMa P spontaneous pain intensity ~ PPT LS, SSp, BB
Hidalgo-Lozano (2012)[37]	1. Elite swimmers SP *N* = 17 21 ± 3 (18 to 28)y 9♂ 8♀ 2. Elite swimmers no SP *N* = 18 20 ± 3 (18 to 26)y 9♂ 9♀	Healthy elite athletes *N* = 15 23 ± 4 (16 to 28)y 7♂ 8♀	PPT—LS—D, SCM—D, UT—D, IS—D, Sc—D, SSc—D, TA—D	P_1 ↔ C ↓ PPT in all muscles P_2 ↔ C ↓ PPT in UT, SSc, TA P_1 ↔ P_2 no differences in PPT
Lannersten and Kosek (2010)[25]	1. Uni- or bilateral Shoulder myalgia *N* = 20 40 (28 to 57)y 20♀ 2. Fibromyalgia *N* = 20 38 (24 to 47)y 20♀	Healthy controls *N* = 21 37 (19 to 49)y 21♀	PPT—at baseline, during contraction IS and Q (start, middle and end), IS, Q	P_1 ↔ C ↓ PPT at middle IS, both sides P_2 ↔ P_1, C ↓ PPT at all sides At middle and end of contraction IS C ↔ P_1, P_2 ↑ PPT at all sites At end of contraction Q P_1, C ↔ P_2 ↑ PPT at all sides ↔ ↓ PPT at all sides
Lindgren et al. (2014)[26]	1. Poststroke with HSP *N* = 24 65 (45 to 81)y 19♂ 5♀ 2. Poststroke no HSP	Healthy controls *N* = 11 64 (55 to 74)y 7♂4♀	THT—WDT, CDT, HPT, CPT baseline 32°C ± 1°C/s (min. 10°C, max. 50°C) PPT—upper, middle and lower part of middle Delt—	P_1 = P_2 P_1 ↔ C ↑ CDT, WDT in upper arm and leg ↑ HPT in affected arm

Table 2. (Continued)

Authors	Patients (P)	Controls (C)	Outcome Measures	Results
	N = 25 65 (44 to 77)y 16♂ 9♀		UA/D, A/ND PPPT—3 points at upper, middle and lower Delt, anteriorly and posteriorly—UA/D, A/ND	P_2 ↔ C ↑ CDT, WDT in affected arm and reference point A ↔ UA ↑ CDT, HPT in P_1 ↑ PPT, PPPT in P_2
Paul et al. (2012)[36]	Subacromial impingement syndrome *N* = 31 51.7 ± 10.0y 15♂ 16♀	Healthy controls *N* = 31 39.5 ± 10.9y 10♂ 21♀	PPT—middle Delt—A/D, UA/ND, TA—UA/ND	P ↔ C ↓ PPT in all muscles
Persson et al. (2003)[39]	Hospital cleaners with unilateral chronic SP *N* = 19 (2 dropouts) 47 (24 to 62)y 19♀	Unaffected side	PPT—T—A/UA, Delt—A/UA, Q—A/UA, immediately, 10 and 20 m after endurance test	P ↑ PPT T and Delt immediately, 10 and 20 m after endurance test C ↑ PPT T and Delt 20 m after endurance test
Roosink et al. (2011)[17]	1. Poststroke with HSP *N* = 19 57 ± 7y 10♂ 9♀ 2. Poststroke no HSP *N* = 29 61 ± 10y 21♂ 8♀	Healthy controls 56 ± 7y 10♂ 13♀	TDT—bilateral: 5 filaments on Delt PPT—bilateral: 3 locations over middle Delt EST, EPT, EPTT—bilateral: ↑ amplitude on upper arm CPM—test stimulus: QST, conditioning stimulus: immerging UA/ND hand in cold water bath	P_1 ↔ C ↑ TDT at UA ↓ EPT, EPTT at UA P_1 ↔ C, P_2 ↑ TDT, EST at A ↑ TDT, EST, EPT ratios (A/UA, D/ND) P_1 ↔ P_2 ↑ hypoesthesia (TDT, EST) and hypoalgesia (EPT) $P_{1,2}$ ↔ C ↑ EPT, PPT after CPT
Roosink et al. (2012)[31]	Poststroke with HSP *N* = 9 72 ± 10y 6♂ 3♀	Poststroke no HSP *N* = 22 65 ± 13y 8♂ 14♀	t1 = 3 month TDT—2 filaments bilateral PPT—3 locations EST, EPT, EPTT—↑ amplitude on upper arm VDT—at styloid process with tuning fork CPM—test stimulus: QST, conditioning stimulus: CPT, UA/ND hand in cold water bath, 2x EPT + PPT A/ND t2 = 6 month QST CPM	P ↔ C ↓ CPT t1: ↑ PPT, EPT ratios (A/UA) in A shoulder t2: ↑ PPT, EPT, EPTT, PPT ratios (A/UA) in A shoulder
Soo Hoo et al. (2012)[34]	Poststroke with HSP *N* = 20 57.5 (54.0 to 68.5)y 5♂ 15♀	Poststroke no HSP *N* = 20 52.0 (45.3 to 60.0)y 12♂ 8♀	PPT—middle Delt—A/ND, NA/D, TA—NA/ND	P ↔ C ↓ PPT in A/D Delt ↓ PPT in UA/ND Delt and TA ↓ PPT in contralesional Delt ↓ PPT in ipsilesional Delt and TA
Valencia et al. (2012)[32]	P having shoulder surgery *N* = 58 32.34 ± 11.55y 41♂ 17♀	Healthy controls *N* = 56 28.71 ± 8.44y 40♂ 16♀	SHPR—5 heat pulses at thenar A/D and UA/ND baseline 41°C, +30°C/s, to max 46/48/50°C and 30°C/s back to 41°C; interpulse 2.5 CPM—test stimulus: SHPR UA/ND, conditioning stimulus: immerging A/D hand in cold water bath	P ↔ C ↑ 5th pain rating at 50°C ↓ %increase = inhibitory effect CPM P ↓ 5th pain rating at 50°C postsurgery
Valencia et al. (2013)[27]	Shoulder disorder *N* = 134 43.83 ± 17.80y 87♂ 47♀	Healthy controls *N* = 190 23.03 ± 6.04y 74♂ 116♀	CPM—test stimulus: SHPR 5 heat pulses at thenar UA/ND, < 1 s, 0.33 Hz, target 46/48/50°C, conditioning stimulus: immerging A/D hand in cold water bath	Trial 1 ↔ Trial 2 ↑ CPM inhibition

Table 2. (Continued)

Authors	Patients (P)	Controls (C)	Outcome Measures	Results
Zeilig et al. (2013)[24]	1. Poststroke with HSP *N* = 16 60.9 ± 7.9y 11♂ 5♀ 2. Poststroke no HSP *N* = 14 59.1 ± 12.1y 6♂ 8♀	Healthy controls *N* = 15 53 ± 15y 7♂ 8♀	ThT—WDT, CDT, HPT at Delt—A/UA, lat upper part of lower leg—A, baseline 32°C ± 2°C/s TT—monofilaments in ↑ order G—identification of number or geometric shape on skin	P (A) ↔ C ↑ WDT, CDT, HPT, TT, G in A MD and lower leg P_1 ↔ P_2 ↑ HPT in A Delt and lower leg P_1 HPT in A Delt ~ intensity of chronic HSP in A Delt HPT in lower leg ~ HPT in A Delt P_1 (A) ↔ P_1 (UA) ↑ HPT, CDT, TT

C, controls; P, patients; A, affected side; UA, unaffected side; D, dominant side; ND, nondominant side; M, minutes; Mo, months; S, seconds; Max, maximum; Y, years; HSP, hemiplegic shoulder pain; RC, rotator cuff; SP, shoulder pain; CDT, cold detection threshold; CPM, conditioned pain modulation; CPT, cold pain threshold; EITP, elevated intrathoracic pressure; EPT, electrical pain threshold; EPTT, electrical pain tolerance threshold; EST, electrical sensation threshold; G, graphesthesia; HPT, heat pain threshold; PPPT, pin-prick pain threshold; PPT, pressure pain threshold; QST, Quantitative Sensory Testing; SHPR, Suprathreshold Pain Response; TDT, tactile detection threshold; ThT, thermal threshold; TPT, thermal pain threshold; TS, temporal summation; TT, touch threshold; WDT, warm detection threshold; VDT, vibration detection threshold; AP, acromion process; BB, biceps brachii; BR, brachioradialis; Delt, deltoid; IS, infraspinatus; LS, levator scapulae; M, masseter; PMa, pectoralis major; Q, quadriceps; SA, serratus anterior; Sc, scalene; SCM, sternocleidomastoid; SSc, subscapularis; SSp, supraspinatus; T, trapezius; TA, tibialis anterior; UT, upper trapezius.

motion at both 3 and 6 months poststroke. This study was part of a prospective cohort study[40] about the development of poststroke shoulder pain in the first 6 months after stroke and included patients within 2 weeks after stroke. There were 2 articles[31,34] that made a comparison between stroke patients with HSP and controls without HSP. The other 3 articles[17,24,26] were case-controlled studies that compared poststroke patients with and without HSP and a healthy control group.

Evidence for Central Sensitivity

In the following section, the results of this review are structured according to the different aspects of central pain processing that have been identified. Methods for identifying CS are divided into static and dynamic methods for both groups of subjects (MSK and HSP).

Static Methods. *Quantitative Sensory Testing* – **Pain Threshold.** *Musculoskeletal shoulder pain* – Pressure algometry was used as an outcome measure in 8[7,28–30,35–38] of the 11 studies which were performed with patients suffering from unilateral MSK shoulder pain. Hidalgo-Lozano[37] examined elite swimmers with and without shoulder pain and compared these groups with a control group of healthy elite athletes. Significantly reduced pressure pain thresholds (PPTs) were found in elite swimmers with shoulder pain as compared with healthy athletes over all muscles which were examined. In addition, elite swimmers without pain also presented significantly lower PPTs over the upper trapezius, m. subscapularis, and m. tibialis anterior as compared with healthy athletes. Furthermore, no significant differences were found between elite swimmers with and without shoulder pain. From the 3 studies[7,28,36] performed in patients with unilateral shoulder impingement syndrome, 2[7,36] found significantly lower PPTs at all locations (locally at the shoulder and remote at the knee), compared to a healthy control group. However, Albuquerque et al.[28] found no significant differences in PPT between the affected and nonaffected side in people with shoulder impingement syndrome (SIS); statistical differences were only found between both sides of the SIS group and dominant side of the control group in the m. supraspinatus PPT. Coronado et al.[35] reported significantly lower PPTs at the affected side compared to the nonaffected side in patients with rotator cuff pathology, at both local and distal locations, which reflected augmented pressure pain sensitivity. In another study, these same authors[29] found lower PPTs measured locally at the affected side compared to the nonaffected side. Furthermore, all local PPTs from the patients with unilateral MSK shoulder pain were lower in comparison with healthy controls. However, when considering the remote site, significantly lower PPTs were only found at the affected side of people with unilateral MSK shoulder pain in comparison with the control group.

Ge et al.[38] measured PPTs at TrPs (trigger points) of the painful m. infraspinatus at the affected side, at the same location, but at the tender point in the contralateral m. infraspinatus and at a reference point in the m.

Table 3. Evaluation Scores on Methodological Quality for Each of the Studies Selected Following Pedro and CBO Scales

	1	2	3	4	5	6	7	8	9	10	11	Total	Level of Evidence
Randomized controlled trials (RCTs) (Pedro)													
Hidalgo-Lozano[37]	+	+	–	+	/	+	/	/	/	+	+	6/11	A2
Ge et al.[38]	+	–	–	–	/	–	/	/	/	+	+	3/11	B
Persson et al.[39]	+	–	–	/	/	/	/	/	/	+	+	3/11	B

	1	(2)	3	4	(5)	6	Total	Level of Evidence
Cross-sectional studies (CBO)								
Soo Hoo et al.[34]	+		+	+		+	4/4	B
Coronado et al.[35]	+		+	+		+	4/4	B
Paul et al.[36]	+	+	+	+	-	+	5/6	B

	1	2	3	4	5	6	Total	Level of Evidence
Case–control studies (CBO)								
Roosink et al.[17]	+	+	+	+	+	+	6/6	B
Zeilig et al.[24]	+	+	+	+	+	+	6/6	B
Alburquerque-Sendin et al.[28]	+	+	+	+	+	/	5/6	B
Hidalgo-Lozano et al.[7]	+	+	+	+	+	/	5/6	B
Lannersten and Kosek[25]	+	+	+	+	+	/	5/6	B
Coronado et al.[29]	+	+	+	+	/	–	4/6	B
Lindgren et al.[26]	+	+	+	+	/	–	4/6	B
Valencia et al.[27]	+	+	+	+	/	–	4/6	B
Gwilym et al.[30]	+	+	/	+	/	–	3/6	B

	1	2	3	4	5	6	7	8	Total	Level of Evidence
Cohort study (CBO)										
Valencia et al.[33]	+	+	+	+	+	+	–	+	7/8	B
Roosink et al.[31]	+	/	+	+	+	–	+	+	6/8	B
Valencia et al.[32]	+	+	+	+	+	–	–	+	6/8	B

tibialis anterior in patients with unilateral shoulder pain during normal expiration and elevated intrathoracic pressure (EITP). EITP is described by Ge et al.[38] as "a manoeuvre that increases sympathetic outflow of the skeletal muscle when holding the breath with the glottis closed." PPTs were significantly lower at the m. infraspinatus of the affected shoulder than at the same point of the unaffected shoulder during both conditions. PPTs during normal respiration and EITP in the m. tibialis anterior were similar. Gwilym et al.[30] used QST (quantitative sensory testing) to measure thresholds for mechanical stimuli, using punctate sharpness threshold and sharpness of a 256-mN punctate stimulus in patients awaiting arthroscopic subacromial decompression. They found a lower mean detection threshold at which the mechanically induced pain from the punctate stimulus was perceived as painful/sharp in the affected shoulder of patients with chronic SIS compared to controls. In addition, more than half of the patients reported referred pain radiating down the arm. The presence of either hyperalgesia to punctate stimulus or referred pain before surgery was related to worse outcomes 3 months after arthroscopic subacromial depression.

Hemiplegic shoulder pain – Pressure algometry was used as an outcome measure in 4[17,26,31,34] of the 5 studies performed with people with HSP. Soo Hoo et al.[34] compared patients with HSP with pain-free stroke patients. Patients with HSP had overall significantly lower local PPTs at all locations (eg, affected and unaffected shoulder, m. tibialis anterior). Moreover, Roosink et al.[17,31] found significantly higher PPT ratios (affected/unaffected side) in the affected shoulder of patients with HSP, already 3 months after stroke.[17] There were no differences in PPT at the unaffected side between HSP and pain-free stroke patients.[17,31] In addition, ratios for electric pain threshold and tolerance became significantly different in patients with HSP as compared to both pain-free stroke patients and the healthy control group.[17,31] On the other hand, Lindgren et al.[26] found no significant differences between the group with HSP and without HSP for any of the QST assessments. Furthermore, the PPTs between the post-stroke groups and healthy controls and wide ranges in PPT thresholds were not significantly different. Thermal pain thresholds (TPTs) and thermal tolerance were measured by Coronado et al.[29,35] in patients with unilateral shoulder pain and rotator cuff pathology.

No differences in thermal threshold or tolerance temperatures were found in these studies.[29,35]

Hypoesthesia. *Hemiplegic shoulder pain* – In both poststroke groups, with and without shoulder pain, significantly higher detection thresholds were found as compared to healthy controls for touch, thermal stimuli, and graphesthesia in the affected shoulder and lower leg in the study of Zeilig et al.[24] Furthermore, patients with HSP had higher heat detection thresholds than those without pain, but only at the affected side. In the HSP group, thermal detection thresholds were significantly higher at the affected side compared to the unaffected side.[24] Roosink et al.[17,31] also found hypoesthesia for tactile[17,31] and electrical sensation thresholds,[17] and hypoalgesia (higher electrical pain thresholds; EPT[17,31]) were more often observed in patients with HSP (6 months poststroke) as compared to the pain-free patients. HSP was associated with reduced touch sensation, abnormal cold sensation (both reduced and elevated), cold allodynia, reduced sharpness sensation, and sharpness allodynia.[19] Lindgren et al.[26] reported higher thermal thresholds and a wider range of mechanical thresholds in both stroke groups with and without shoulder pain when compared to healthy controls.

Dynamic Methods. *Suprathreshold Heat Pain Response. Musculoskeletal shoulder pain* – Suprathreshold heat pain response (SHPR) results in the perception of elevated pain although the peripheral afferent input is constant or even diminished and is thus considered a perceptual manifestation of augmented central sensitivity.[32] Valencia et al.[32] included this dynamic method to acquire the pain modulatory capacity of the central nervous system. They found that the fifth pain rating after 5 consecutive heat pulses was significantly higher in patients having shoulder surgery as compared to healthy controls. The fifth pain rating decreased significantly from the presurgical time point to 3 months after surgery and was comparable to baseline values of the healthy controls. The same SHPR principle was used by Coronado et al.,[29] who found an increased SHPR of small-to-moderate magnitude between the affected and nonaffected side of patients with unilateral shoulder pain in comparison with pain-free controls.

Conditioned Pain Modulation. Musculoskeletal shoulder pain – Valencia et al.[32] used SHPR as the test stimulus and the cold pressor test as the conditioning stimulus. Although, there was a significant main effect of CPM, meaning that the conditioning stimulus significantly inhibited the test stimulus in both groups, the patients having shoulder surgery had a lower percentage increase of change for CPM at baseline compared to the healthy controls. The percent change of CPM and the absolute difference on CPM did not change significantly 3 months later in both groups. Another study by Valencia et al.[27] revealed that fluctuation in pain intensity of the patient had no significant effect on between-session stability of CPM. In addition, the CPM trial led to significantly greater inhibition at the presurgical time point as compared to the trial after surgery.

Hemiplegic shoulder pain – Patients with HSP showed significantly lower hand immersion time (cold pain tolerance) as compared to pain-free stroke patients in both studies of Roosink et al.[17,31] They found significantly higher EPTs and PPTs after the cold pressor test (CPT) in these patients, but no significant differences were found between groups when comparing threshold ratios for EPT and PPT (precold pressor/postcold pressor).[17,31]

Exercise-induced Endogenous Analgesia. Musculoskeletal shoulder pain – After a unilateral static endurance test at the most painful shoulder, Persson et al.[39] found that the PPT levels over the affected shoulder muscles (ie, trapezius and deltoid muscle) significantly increased immediately as well as 10 and 20 min after the test in women with chronic shoulder pain. On the unexposed side, the PPTs were significantly increased in the shoulder region only 20 min after the test. Inconsistent changes were found of PPTs measured over the m. quadriceps on both sides.

Lannersten and Kosek[25] showed that patients with chronic unilateral myofascial shoulder pain had significantly lower PPTs at baseline compared to healthy controls at the m. infraspinatus bilaterally, but not at the m. quadriceps. During contraction of the painful (for the shoulder myalgia patients) m. infraspinatus, PPTs increased at all sites compared to baseline at the middle and end of contraction in healthy controls, but not in patients with shoulder myalgia. During contraction of the quadriceps, PPTs increased at all sites compared to baseline at the end of contraction in healthy controls and patients with shoulder myalgia.

Dynamic Tactile Allodynia and Hyperpathia – Hemiplegic shoulder pain – Dynamic tactile allodynia was described as pain provoked by a non-noxious stimulus.[41] Hyperpathia was described as the development of

a sudden, strong painful sensation that continued after the stimulation was switched off.[41] Higher rates of pathologically evoked pain (hyperpathia and dynamic tactile allodynia) were found in the affected shoulder and lower leg of the HSP group compared to the HSP group without shoulder pain.[24]

DISCUSSION

The goal of this systematic review was to analyze the scientific literature addressing the role of central pain processing mechanisms in patients with musculoskeletal shoulder pain and those with a history of stroke leading to hemiplegic shoulder pain.

Musculoskeletal Shoulder Pain

Static Methods. There is a level of evidence 2 for the presence of CS in people with MSK shoulder pain. In particular, PPTs were significantly decreased not only at local but also at distal muscles (Table 2) in patients with shoulder pain when compared to pain-free controls.[7,36,37] Widespread mechanical hyperalgesia (lower PPT measured at a distant site) is a recognized indicator of central hyperexcitability and indicate the involvement of the central nervous system.[22]

In the study of Hidalgo-Lozano,[37] PPTs were lower in both elite swimmers with and without shoulder pain, which was unexpected for the latter. This finding may indicate that pain sensitivity of neck and shoulder girdle tissues to mechanical stimuli in elite swimmers with and without shoulder pain could be associated with the swimming-specific demands or as a result of exercising regularly at a high intensity as seen in many other athletes. There is currently no consensus about the magnitude of the difference in PPT levels necessary to consider real changes between patients with shoulder pain and healthy controls.[42] The lower PPT levels in patients with SIS and elite swimmers with and without shoulder pain in both painful and distant pain-free areas suggest the presence of both peripheral and central sensitization mechanisms.[7,37] Note that in both studies of Hidalgo-Lozano,[7,37] the PPT levels were only investigated at the affected side (but also distal to the pain location). Paul et al.[36] also suggested evidence for central hypersensitivity in patients with SIS, although they did not limit analgesic usage, evaluators were not blinded to case and control subjects (which could have introduced bias) and sex, age, and ethnicity of the sample were not standardized. In another study, occurrence of CS was investigated in a subgroup of patients with unilateral shoulder pain.[30] In particular, the presence of referred pain, or hyperalgesia, was associated with worse outcomes after subacromial decompression. Therefore, this study showed heterogeneity within patients presenting with SIS and suggested that preoperatively presence of CS negatively affects outcome 3 months after subacromial decompression.[30]

In contrast to the results for thermal stimuli, pressure stimuli revealed increased pain sensitivity of patients with unilateral shoulder pain, as found in the study by Coronado et al.[35] This study was limited by the absence of a healthy control group which impedes explicit conclusions about central and peripheral pain processing.[35] Pressure and thermal stimuli measure various modalities of pain processing, with pressure stimuli requiring sensitivity of deep tissue afferents and thermal stimuli requiring C-fiber hyperexcitability.[35] Nijs et al.[43] recommended the use of various modalities for pain sensitivity at local and distal locations if the goal was to determine CS in patients with musculoskeletal pain. Using only 1 stimulus may lead to inaccurate conclusions regarding the underlying pain processing mechanisms of patients. Inconsistent findings between the pressure and thermal sensitivity in the study of Coronado et al.[35] highlights the necessity of using various stimuli, as it gives a more complete overview of pain processing mechanisms in clinical conditions. Further studies should therefore include various stimuli when investigating the pain profile of patients with musculoskeletal conditions.

In addition to the aforementioned studies, no difference in mechanical sensitivity in SIS patients was found; therefore, no presence of CS was found in these patients.[28] Coronado et al.[29] found a difference between sides in pressure sensitivity in patients with unilateral shoulder pain which supports increased peripheral sensitisation and thus reinforcing this finding.

Ge et al.[38] showed that increasing the sympathetic outflow to the muscle decreased PPTs at the painful and nonpainful shoulder, but not at the m. tibialis anterior. Pathological circumstances can cause changes in the peripheral neurons, which may result in interactions between sympathetic and afferent neurons,[44] indicating facilitatory contribution of sympathetic hyperactivity to mechanical sensitization. Sympathetic activity may increase the release of norepinephrine which has been shown to interact with nociceptors, but other substances cannot be excluded.[45] Therefore, the presence

of sympathetic activity can facilitate local pain reaction, such as mechanical hyperalgesia and allodynia, which has been demonstrated in patients with myofascial pain syndromes. These mechanisms are probably peripherally mediated due to the fact that only local PPTs were decreased after the sympathetic outflow increased. The results of this study suggest a sympathetic contribution to the underlying mechanisms creating referred pain. However, these mechanisms are still unknown and need to be investigated in further studies. Further work is also required to establish the interactions between sensory and sympathetic systems in the central nervous system.

Dynamic Methods. There is a level of evidence 2 for the dynamic methods[25,32,39] to evaluate MSK shoulder pain. The results of SHPR in the study of Valencia et al.[32] in the clinical cohort provide direct evidence for altered pain sensitivity before having shoulder surgery. Interestingly, SHPR decreased 3 months after surgery that reasonably may indicate potential reversibility of altered central pain processing mechanisms after eliminating the nociceptive source with operation. In addition, pain intensity decreased significantly 3 months after surgery, but the absolute differences on CPM did not differ between pre- and postsurgical stages.[32] This implies that despite that the local problem can be resolved after surgery and patients' reporting of pain diminish, impaired endogenous inhibition can still be present, indicating that central hypersensitivity may have not been resolved. Future research should investigate which are the indications of having altered central pain processing mechanisms before shoulder surgery and which is its function in the development of chronic postoperative pain.

Two studies used a static endurance test[25,39] to evaluate the influence of exercise-induced endogenous analgesia in patients with shoulder pain. Their findings were rather contradictory. Persson et al.[39] found a proper activation of central antinociceptive mechanisms in chronic shoulder pain patients after static contraction of the painful shoulder. Nevertheless, although PPT values increased, patients' sensation of pain was increased. Contrarily, Lannersten and Kosek[25] only found proper activation of endogenous analgesia in shoulder myalgia patients when nonpainful body parts (but not the painful shoulder) were exercised. In fibromyalgia patients (commonly centrally sensitized in a subset of patients), all contractions induced generalized hyperalgesia independently of where they were performed.[25] These patients have an overall inability to activate pain inhibitory mechanisms, which supports previous findings.[46] A limitation of this study is that the examiner could not be blinded to the group assigned to each subject.

Besides bilateral pressure hypersensitivity, Coronado et al.[29] also demonstrated thermal hypersensitivity at local and distal locations compared to healthy controls, which indicates that CS is present. However, the same study also demonstrated side-to-side differences in pressure pain sensitivity, supporting peripheral sensitization. Therefore, heterogeneous findings were obtained according to sensitization processes in patients with unilateral shoulder pain, meaning that neither peripheral nor CS processes were dominant. This may imply that patients with shoulder pain having a similar clinical presentation may not have equal pain processing mechanisms underlying their symptoms. This mixed presentation of sensitization patterns is potentially meaningful for clinical practice and underlines the importance of awareness, because this could explain why some patients fail to recover after standard treatment directed at peripheral targets.

Hemiplegic Shoulder Pain

Static Methods. There is a level of evidence 2 for somatosensory differences, such as reduced PPTS[34] and allodynia,[17,24] in patients with HSP, suggesting a role for central hypersensitivity.[17,24,34] In addition, a neuropathic pain component has been shown in this population.[17,24,31]

The study by Soo Hoo et al.[34] was the only study that found lower PPTs at local and remote pain-free sites in patients with HSP as compared to pain-free control, suggesting CS. If these findings were restricted to the affected shoulder, it would not be possible to distinguish between peripheral or central hypersensitivity and sensory abnormalities caused by a spinothalamocortical lesion. However, the finding that pain was experienced at lower pressure levels at remote pain-free sites supports the notion that central processes may influence the overall perception of pain in patients with chronic HSP.[34]

Recent studies have provided preliminary evidence that patients with HSP have somatosensory abnormalities.[17,40,47] Roosink et al.[17,31] reported the presence of widespread somatosensory abnormalities, such as allodynia and hyperalgesia, already in the first 6 months after stroke. This might suggest the presence of a

neuropathic pain component contributing to HSP. In addition, early occurrence of somatosensory sensitization in the acute phase after stroke might favor the development or maintenance of HSP. However, it was not discernable whether findings are related to central hypersensitivity, because examination sites were limited to the shoulder. Furthermore, results are limited by a small sample size and the fact that evaluators were not blinded to group allocation might have introduced bias. Future studies should include larger samples to provide further information about the role of CS in HSP, as important differences may exist between subgroups of people within this population. In contrast to Soo Hoo et al.,[34] Roosink et al.[17] used intra-individual, side-to-side comparisons when measuring PPTs. Although this method is more sensitive to detect sensory abnormalities, intra-individual, side-to-side comparisons may not be convenient for unraveling widespread hyperalgesia, typical of CS.[48]

Zeilig et al.[24] also found differentiated sensory characteristics of the affected shoulder (higher thermal thresholds and high amounts of pathologically evoked pain) in the affected lower leg. These somatosensory abnormalities in a pain-free remote site may suggest a central origin for HSP. In contrast to the aforementioned studies,[17,24] no significant differences in the QST assessments were found in the study of Lindgren et al.[26] and thus could not demonstrate the presence of a neuropathic or central component influencing the perception of pain as well as the presence of a widespread neuropathic component. These discrepancies may be explained by different stroke locations, characteristics, and intensity of shoulder pain, as well as the usage of medicine between studies. The latter may have resulted in a diminished pain perception with psychophysical testing.

Overall results indicate that somatosensory impairments might play a role in patients with HSP. However, convincing evidence cannot be determined as these impairments are commonly observed in patients both with and without HSP. The causal role of somatosensory symptoms in the development of HSP should be further explored in longitudinal studies.

Dynamic Methods. There is a level of evidence 2 for the dynamic methods to evaluate HSP. No difference in CPM was observed in patients with HSP when compared to pain-free controls.[17,31] Impaired endogenous pain modulation may predict the development of CS[49,50] and persistent pain[31] and was reduced or absent in several types of chronic pain patients.[51,52] The results of both studies of Roosink et al.[17,31] suggest that HSP is not associated with impaired endogenous inhibition. This may indicate that CPM is functioning normally in patients with poststroke pain, although it is plausible that endogenous inhibitory pain pathways may be defective at a higher supraspinal level.[52] This interpretation of the results is limited by the small sample size and the differences between groups in terms of timing and intensity of the conditioning stimulus. CPM should therefore be repeated in a larger study.

In conclusion, this review has shown that great progress has been made toward a better understanding of neurophysiologic pain mechanisms of patients with shoulder pain. Presence of generalized mechanical hyperalgesia and allodynia in patients with MSK shoulder pain may indicate the involvement of the central nervous system in a subgroup of this population. In addition, enhanced temporal summation and impaired endogenous inhibition in people with MSK shoulder pain are also indicative of CS, although results are not univocal in this regard (eg, antinociceptive response to exercise).

Widespread somatosensory abnormalities observed in patients with HSP suggest a central origin for shoulder pain in this population. Early occurrence of somatosensory abnormalities may predispose patients with HSP to develop CS. This review revealed that CPM is functioning normally in patients with poststroke pain, although impaired, endogenous pain inhibitory pathways at higher supraspinal levels cannot be ruled out. Additional research is now required adopting different assessment methods to confirm the preliminary role of CS in subjects with shoulder pain.

REFERENCES

1. Luime J, Koes B, Hendriksen I, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scand J Rheumatol*. 2004;33:73–81.

2. Luime J, Koes B, Miedem H, Verhaar J, Burdorf A. High incidence and recurrence of shoulder and neck pain in nursing home employees was demonstrated during a 2-year follow-up. *J Clin Epidemiol*. 2005;58:407–413.

3. Croft P, Pope D, Silman A. The clinical course of shoulder pain: prospective cohort study in primary care. Primary Care Rheumatology Society Shoulder Study Group. *BMJ*. 1996;313:601–602.

4. van der Windt D, Koes B, Boeke A, Deville W, De Jong B, Bouter L. Shoulder disorders in general practice: prognostic indicators of outcome. *Br J Gen Pract*. 1996;46:519–523.

5. Kuijpers T, van der Windt D, Boeke A, et al. Clinical prediction rules for the prognosis of shoulder pain in general practice. *Pain*. 2006;120:276–285.

6. Kuijpers T, van Tulder M, van der Heijden G, Bouter L, van der Windt D. Costs of shoulder pain in primary care consulters: a prospective cohort study in The Netherlands. *BMC Musculoskelet Disord*. 2006;7:83.

7. Hidalgo-Lozano A, Fernández-De-Las-Peñas C, Alonso-Blanco C, Ge HY, Arendt-Nielsen L, Arroyo-Morales M. Muscle trigger points and pressure pain hyperalgesia in the shoulder muscles in patients with unilateral shoulder impingement: a blinded, controlled study. *Exp Brain Res*. 2010;202:915–925.

8. Latremoliere A, Woolf C. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10:895–926. http://www.ncbi.nlm.nih.gov/pubmed/?term=1.%09Latremoliere+A%2C+Woolf+CJ%3A+Central+sensitization%3A+A+generator+of+pain+hypersensitivity+by+central+neural+plasticity.+J+Pain+2009%3B10%3A895Y926.

9. Curatolo M, Arendt-Nielsen L, Petersen-Felix S. Central hypersensitivity in chronic pain: mechanisms and clinical implications. *Phys Med Rehabil Clin N Am*. 2006;17:287–302.

10. Scott D, Jull G, Sterling M. Widespread sensory hypersensitivity is a feature of chronic whiplash-associated disorder but not chronic idiopathic neck pain. *Clin J Pain*. 2005;21:175–181. http://www.ncbi.nlm.nih.gov/pubmed/15722811.

11. Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum*. 2003;48:1420–1429.

12. Fernández-de-las-Peñas C, de la Llave-Rincón AI, Fernández-Carnero J, Cuadrado ML, Arendt-Nielsen L, Pareja JA. Bilateral widespread mechanical pain sensitivity in carpal tunnel syndrome: evidence of central processing in unilateral neuropathy. *Brain*. 2009;132(Pt 6):1472–1479.

13. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain*. 2010;149:573–581.

14. Bendtsen L, Jensen R, Olesen J. Decreased pain detection and tolerance thresholds in chronic tension-type headache. *Arch Neurol*. 1996;53:373–376. http://www.ncbi.nlm.nih.gov/pubmed/8929161.

15. Svensson P, List T, Hector G. Analysis of stimulus-evoked pain in patients with myofascial temporomandibular pain disorders. *Pain*. 2001;92:399–409. http://www.ncbi.nlm.nih.gov/pubmed/11376913.

16. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke: a multicenter study. *Stroke*. 2000;31:1223–1229. http://www.ncbi.nlm.nih.gov/pubmed/10835436.

17. Roosink M, Renzenbrink GJ, Buitenweg JR, Van Dongen RTM, Geurts ACH, Ijzerman MJ. Somatosensory symptoms and signs and conditioned pain modulation in chronic post-stroke shoulder pain. *J Pain*. 2011;12:476–485.

18. Lindgren I, Jönsson A-C, Norrving B, Lindgren A. Shoulder pain after stroke: a prospective population-based study. *Stroke*. 2007;38:343–348.

19. Lindgren I, Lexell J, Jönsson A-C, Brogårdh C. Left-sided hemiparesis, pain frequency, and decreased passive shoulder range of abduction are predictors of long-lasting poststroke shoulder pain. *PM R*. 2012;4:561–568.

20. Petersen-Felix S, Curatolo M. Neuroplasticity-an important factor in acute and chronic pain. *Swiss Med Wkly*. 2002;132:273–278.

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2009;6:336–341.

22. Koelbaek Johansen M, Graven-Nielsen T, Schou Olesen A, Arendt-Nielsen L. Generalised muscular hyperalgesia in chronic whiplash syndrome. *Pain*. 1999;83:229–234. http://www.ncbi.nlm.nih.gov/pubmed/10534594.

23. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.

24. Zeilig G, Rivel M, Weingarden H, Gaidoukov E, Defrin R. Hemiplegic shoulder pain: evidence of a neuropathic origin. *Pain*. 2013;154:263–271.

25. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain*. 2010;151:77–86.

26. Lindgren I, Ekstrand E, Lexell J, Westergren H, Brogårdh C. Somatosensory impairments are common after stroke but have only a small impact on post-stroke shoulder pain. *J Rehabil Med*. 2014;46:307–313.

27. Valencia C, Kindler LL, Fillingim RB, George SZ. Stability of conditioned pain modulation in two musculoskeletal pain models: investigating the influence of shoulder pain intensity and gender. *BMC Musculoskelet Disord*. 2013;14:182.

28. Alburquerque-Sendín F, Camargo PR, Vieira A, Salvini TF. Bilateral myofascial trigger points and pressure pain thresholds in the shoulder muscles in patients with unilateral shoulder impingement syndrome: a blinded, controlled study. *Clin J Pain*. 2013;29:478–486.

29. Coronado RA, Simon CB, Valencia C, George SZ. Experimental pain responses support peripheral and central sensitization in patients with unilateral shoulder pain. *Clin J Pain*. 2014;30:143–151.

30. Gwilym SE, Oag HCL, Tracey I, Carr AJ. Evidence that central sensitisation is present in patients with shoulder impingement syndrome and influences the outcome after surgery. *J Bone Joint Surg Br*. 2011;93:498–502.

31. Roosink M, Van Dongen RT, Buitenweg JR, Renzenbrink GJ, Geurts AC, Ijzerman MJ. Multimodal and widespread somatosensory abnormalities in persistent shoulder pain in the first 6 months after stroke: an exploratory study. *Arch Phys Med Rehabil*. 2012;93:1968–1974.

32. Valencia C, Kindler LL, Fillingim RB, George SZ. Investigation of central pain processing in shoulder pain:

converging results from 2 musculoskeletal pain models. *J Pain*. 2012;13:81–89.

33. Valencia C, Fillingim RB, George SZ. Suprathreshold heat pain response is associated with clinical pain intensity for patients with shoulder pain. *J Pain*. 2011;12:133–140.

34. Soo Hoo J, Paul T, Chae J, Wilson R. Central hypersensitivity in chronic hemiplegic shoulder pain. *Changes*. 2012;29:997–1003.

35. Coronado RA, Kindler LL, Valencia C, George SZ. Thermal and pressure pain sensitivity in patients with unilateral shoulder pain: comparison of involved and uninvolved sides. *J Orthop Sports Phys Ther*. 2011;41:165–173.

36. Paul TM, Hoo JS, Chae J, et al. Central hypersensitivity in patients with subacromial impingement syndrome. *Arch Phys Med Rehabil*. 2012;93:2206–2209.

37. Hidalgo-Lozano A. Elite swimmers with unilateral shoulder pain demonstrate altered pattern of cervical muscles activation during a functional upper limb task. *J Orthop Sports Phys Ther*. 2012;42:552–558.

38. Ge HY, Fernández-de-las-Peñas C, Arendt-Nielsen L. Sympathetic facilitation of hyperalgesia evoked from myofascial tender and trigger points in patients with unilateral shoulder pain. *Clin Neurophysiol*. 2006;117:1545–1550.

39. Persson AL, Hansson GÅ, Kalliomäki J, Sjölund BH. Increases in local pressure pain thresholds after muscle exertion in women with chronic shoulder pain. *Arch Phys Med Rehabil*. 2003;84:1515–1522.

40. Roosink M, Renzenbrink GJ, Buitenweg JR, Van Dongen RT, Geurts AC, Ijzerman MJ. Persistent shoulder pain in the first 6 months after stroke: Results of a prospective cohort study. *Arch Phys Med Rehabil*. 2011;92:1139–1145.

41. Merskey H, Bogduk N. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle, WA: IASP Press; 1994.

42. Sterling M. Testing for sensory hypersensitivity or central hyperexcitability associated with cervical spine pain. *J Manipulative Physiol Ther*. 2008;31:534–539.

43. Nijs J, Van Houdenhove B, Oostendorp RAB. Recognition of central sensitization in patients with musculoskeletal pain: application of pain neurophysiology in manual therapy practice. *Man Ther*. 2010;15:135–141.

44. Jänig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. *Prog Brain Res*. 1996;113:161–184. http://www.ncbi.nlm.nih.gov/pubmed/9009734 (accessed December 15, 2015).

45. Burnstock G. Structural and chemical reorganization of the autonomic neuroeffector system. In: Bolis C, Lincinio J, Govoni S, eds. *Handbook of the Autonomic Nervous System in Health and Disease*. New York, NY: Marcel Dekker; 2002.

46. Kadetoff D, Kosek E. The effects of static muscle contraction on blood pressure, heart rate and pressure pain thresholds in fibromyalgia patients. *Eur J Pain*. 2007;11:39–47.

47. Roosink M, Buitenweg JR, Renzenbrink GJ, Geurts ACH, Ijzerman MJ. Altered cortical somatosensory processing in chronic stroke: a relationship with post-stroke shoulder pain. *NeuroRehabilitation*. 2011;28:331–344.

48. Rolke R, Magerl W, Campbell K, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain*. 2006;10:77–88.

49. Kasch H, Qerama E, Bach FW, Jensen TS. Reduced cold pressor pain tolerance in non-recovered whiplash patients: a 1-year prospective study. *Eur J Pain*. 2005;9:561–569.

50. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138:22–28.

51. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with pain-ful osteoarthritis before, but not following, surgical pain relief. *Pain*. 2000;88:69–78.

52. Tuveson B, Leffler A-S, Hansson P. Influence of heterotopic noxious conditioning stimulation on spontaneous pain and dynamic mechanical allodynia in central post-stroke pain patients. *Pain*. 2009;143:84–91.