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1 **Central pain processing in patients with shoulder pain: a review of the literature**

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17

18 **ABSTRACT**

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

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

23 **RESULTS:** Eighteen full-text articles were included, methodological quality was scored and information was extracted.  
24 Studies were clustered on those studying patients with musculoskeletal (MSK) shoulder pain and those studying patients  
25 with hemiplegic shoulder pain (HSP). In particular, Quantitative Sensory Testing revealed hyperalgesia for pressure pain in

26 the MSK group, whereas these results were inconsistent in patients with HSP. Conditioned pain modulation was reduced  
27 in patients with MSK shoulder pain, but is functioning normally in the HSP-group.

28 CONCLUSION: This review has shown that a great progress has been made towards a better understanding of  
29 neurophysiologic pain mechanisms in patients with shoulder pain. Presence of generalized mechanical hyperalgesia,  
30 allodynia and impaired conditioned pain modulation in patients with MSK shoulder pain indicate the involvement of the  
31 central nervous system. Widespread somatosensory abnormalities observed in patients with HSP could suggest a central  
32 origin for their shoulder pain and predispose patients with HSP to develop CS, although results are inconsistent. Additional  
33 research is required adopting different assessment methods (especially dynamic methods) in order to establish the role of  
34 CS in patients with shoulder pain.

35 KEY WORDS: central sensitization, pain processing, shoulder, chronic pain, systematic review.

36

## 37 **INTRODUCTION**

38 Shoulder pain is the third most common musculoskeletal condition, with incidence rates up to 2.5% , <sup>1,2</sup>. Although more  
39 than half of all patients with shoulder pain recovers completely within one year after injury <sup>3-5</sup>, the remaining of this group  
40 reports persistent shoulder pain <sup>6</sup>. It is suggested in the literature that central sensitization (CS) might play a role in these  
41 persistent complaints in (some) patients with shoulder pain<sup>7</sup>.

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

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

52

53 Although a lot of research has already been done on the above mentioned chronic pain syndromes, the role of CS in  
54 shoulder pain patients has been poorly investigated. Shoulder pain is a prevalent health presentation with complex  
55 underlying factors. The exact pathology is not always clear; muscles and joints do not always seem to be the **main cause**  
56 **of the persistent problem** and biomedical approaches **are not always successful**. Shoulder pain can be related to a  
57 musculoskeletal problem, but is also a common disorder after a stroke <sup>16</sup>. Post-stroke shoulder pain is usually studied and  
58 treated as peripheral nociceptive or neuropathic pain, but evidence for the effectiveness of therapeutic interventions is  
59 lacking <sup>17</sup>. It can improve during rehabilitation <sup>18</sup>, but it may also be a durable or persistent problem <sup>19</sup>.  
60 Given the evidence of alterations in the central and peripheral nervous system in many other chronic pain populations  
61 <sup>8,9,20</sup>, CS might explain why some patients with shoulder pain, both musculoskeletal or post-stroke, do not respond to  
62 regular treatment procedures directed to the shoulder. Therefore, the primary aim of this review was to investigate  
63 whether there is evidence for abnormal central pain processing in patients with shoulder pain of musculoskeletal or  
64 neurologic origin.

65

## 66 **METHODS**

67 This systematic review is reported following the PRISMA- guidelines (Preferred Reporting Items for Systematic reviews and  
68 Meta-Analyses) <sup>21</sup>.

69

### 70 **Eligibility Criteria and Study Selection**

71 To be included in the present systematic review, articles had to evaluate signs of CS (I), as contributor to the pain (O), in  
72 patients with shoulder pain (P). The comparison (C) was not defined in order to obtain all articles regarding the presence  
73 of CS in patients with shoulder pain. All original study designs were included (S). Articles were eligible for this systematic  
74 review if they fulfilled the following inclusion criteria: 1) central pain processing was assessed, 2) in human adults (>18  
75 years) suffering from shoulder pain, and 3) the article reported original research in full text, and 4) published in English,  
76 French or Dutch. Studies were excluded if only primary hyperalgesia or peripheral sensitization was assessed, since these  
77 are not indicative for CS <sup>22</sup>.

78

## 79 **Information Sources and Search Strategy**

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

87

## 88 **Data items and collection**

89 Information was extracted from each included study about: 1) design and purpose of the study; 2) characteristics of study  
90 participants (including number of participants, mean age, sex and diagnosis) and inclusion and exclusion criteria; 3)  
91 methods of assessing the presence of CS; 4) outcome measures; and 5) main results.

92

## 93 **Risk of Bias in individual studies**

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

103

104 **Level of Evidence**

105 After pooling the results, the overall quality of evidence for each outcome was rated with the Grades of Recommendation,  
106 Assessment, Development, and Evaluation (GRADE) approach <sup>23</sup>.

107

108 **RESULTS**

109 **Study Selection and Study Characteristics**

110 The selection process of the articles is represented in Figure 1. After screening, 18 full-text articles were included in this  
111 systematic review. Of the 18 selected articles, 15 were observational studies (nine case-control <sup>7,17,24-30</sup>, three cohort <sup>31-33</sup>  
112 and three cross-sectional <sup>34-36</sup>) and three were RCT's. The characteristics of the included studies are presented in Table 2.

113

114 **Methodological Quality**

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

122

123 The level of evidence of the 3 RCTs <sup>37-39</sup> was determined starting as high-quality evidence according to the GRADE system.  
124 The methodological quality was low, according to the PEDro-classification. Two RCTs failed to get half of the maximum  
125 score <sup>38,39</sup> and were downgraded to a moderate level of evidence.

126

127 **Study Population**

128 Most studies included patients with chronic shoulder pain <sup>7,17,24-26,28,29,34,36-39</sup>; one study included patients in the acute  
129 phase <sup>31</sup>, while the rest of the studies did not specifically define the duration of shoulder pain <sup>27,30,32,35</sup>. The population of

130 patients in the different studies could be distinguished in 2 major groups: patients with musculoskeletal (MSK) shoulder  
131 pain and patients with a history of stroke suffering from hemiplegic shoulder pain (HSP).

132

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

140

141 Five articles studied CS in patients with HSP<sup>17,24,26,31,34</sup>. HSP was defined by Zeilig et al.<sup>24</sup> as “the presence of shoulder pain  
142 for at least 6 months, with no additional characteristics other than ruling out shoulder pathologies prior to the stroke”.  
143 Similarly, Roosink et al.<sup>31</sup> defined HSP as non-remitting shoulder pain confined to the shoulder and/or C5 dermatome of  
144 the contralesional side with an onset after an stroke episode, present during rest or during active or passive motion at  
145 both 3 and 6 months post-stroke. This study was part of a prospective cohort study<sup>40</sup> about the development of post-  
146 stroke shoulder pain in the first 6 months after stroke and included patients within 2 weeks after stroke. There were 2  
147 articles<sup>31,34</sup> that made a comparison between stroke patients with HSP and controls without HSP. The other three articles  
148<sup>17,24,26</sup> were case-controlled studies that compared post-stroke patients with and without HSP, and a healthy control  
149 group.

150

## 151 **Evidence for Central Sensitivity**

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

155

### **1. Static Methods**

## 156 **1.1 Quantitative Sensory Testing**

### 157 **1.1.1 Pain Threshold**

#### 158 **1.1.1.1. Musculoskeletal Shoulder Pain**

159 Pressure algometry was used as an outcome measure in eight <sup>7,28–30,35–38</sup> out of the 11 studies which were performed with  
160 patients suffering from unilateral MSK shoulder pain. Hidalgo-Lozano et al. <sup>37</sup> examined elite swimmers with and without  
161 shoulder pain and compared these groups with a control group of healthy elite athletes. Significantly reduced pressure  
162 pain thresholds (PPTs) were found in elite swimmers with shoulder pain as compared with healthy athletes over all  
163 muscles which were examined. In addition, elite swimmers without pain also presented significantly lower PPTs over the  
164 upper trapezius, m. subscapularis and m. tibialis anterior as compared with healthy athletes. Furthermore, no significant  
165 differences were found between elite swimmers with and without shoulder pain. From the three studies <sup>7,28,36</sup> performed  
166 in patients with unilateral shoulder impingement syndrome, two <sup>7,36</sup> found significantly lower PPTs at all locations (locally  
167 at the shoulder and remote at the knee), compared to a healthy control group. However, Albuquerque et al. <sup>28</sup> found no  
168 significant differences in PPT between the affected and non-affected side in people with shoulder impingement syndrome  
169 SIS; statistical differences were only found between both sides of the SIS group and dominant side of the control group in  
170 the m. supraspinatus PPT. Coronado et al. <sup>35</sup> reported significantly lower PPTs at the affected side compared to the non-  
171 affected side in patients with rotator cuff pathology, at both local and distal locations, which reflected augmented  
172 pressure pain sensitivity. In another study, these same authors <sup>29</sup> found lower PPTs measured locally at the affected side  
173 compared to the non-affected side. Furthermore, all local PPTs from the patients with unilateral MSK shoulder pain were  
174 lower in comparison to healthy controls. However, when considering the remote site, significantly lower PPTs were only  
175 found at the affected side of people with unilateral MSK shoulder pain in comparison to the control group.

176 Ge et al. <sup>38</sup> measured PPTs at TrPs of the painful m. infraspinatus at the affected side, at the same location but at the  
177 tender point in the contralateral m. infraspinatus and at a reference point in the m. tibialis anterior in patients with  
178 unilateral shoulder pain during normal expiration and elevated intrathoracic pressure (EITP). EITP is described by Ge et al.  
179 <sup>38</sup> as “a manoeuvre that increases sympathetic outflow of the skeletal muscle when holding the breath with the glottis  
180 closed”. PPTs were significantly lower at the m. infraspinatus of the affected shoulder than at the same point of the  
181 unaffected shoulder during both conditions. PPTs during normal respiration and EITP in the m. tibialis anterior were



182 similar. Gwilym et al. <sup>30</sup> used QST to measure thresholds for mechanical stimuli, by using punctate sharpness threshold  
183 and sharpness of a 256 mN punctate stimulus in patients awaiting arthroscopic subacromial decompression. They found a  
184 lower mean detection threshold at which the mechanically induced pain from the punctate stimulus was perceived as  
185 painful/ sharp in the affected shoulder of patients with chronic SIS compared to controls. In addition, more than half of  
186 the patients reported referred pain radiating down the arm. The presence of either hyperalgesia to punctate stimulus or  
187 referred pain before surgery was related to worse outcomes 3 months after arthroscopic subacromial depression.

188

### 189 **1.1.1.2 Hemiplegic Shoulder Pain**

190 Pressure algometry was used as an outcome measure in four <sup>17,26,31,34</sup> of the five studies performed with people with HSP.  
191 Soo Hoo et al. <sup>34</sup> compared patients with HSP with pain-free stroke patients. Patients with HSP had overall significantly  
192 lower local PPTs at all locations (e.g. affected and unaffected shoulder, m. tibialis anterior). Moreover, Roosink et al. <sup>17,31</sup>  
193 found significantly higher PPT ratios (affected/ unaffected side) **in the affected shoulder of** patients with HSP, already 3  
194 months after stroke <sup>17</sup>. **There** were no differences in PPT at the unaffected side between HSP and pain-free stroke patients  
195 <sup>17,31</sup>. In addition, ratios for electric pain threshold and tolerance became significantly different in patients with HSP as  
196 compared to both pain-free stroke patients and the healthy control group <sup>17,31</sup>. On the other hand, Lindgren et al. <sup>26</sup> found  
197 no significant differences between the group with HSP and without HSP for any of the QST assessments. In addition, the  
198 PPTs between the post-stroke groups and healthy controls and wide ranges in PPT thresholds were not significantly  
199 different. Thermal pain thresholds (TPTs) and thermal tolerance were measured by Coronado et al. <sup>29,35</sup> in patients with  
200 unilateral shoulder pain and rotator cuff pathology. No differences in thermal threshold or tolerance temperatures were  
201 found in these studies<sup>29,35</sup>.

### 202 **1.1.2 Hypoesthesia**

#### 203 **1.1.2.1 Hemiplegic Shoulder Pain**

204 In both post-stroke groups with and without shoulder pain significantly higher detection thresholds were found as  
205 compared to healthy controls for touch, thermal stimuli and graphesthesia in the affected shoulder and lower leg in the  
206 study of Zeilig et al. <sup>24</sup>. Furthermore, patients with HSP had higher heat detection thresholds than those without pain, but  
207 only at the affected side. In the HSP group, thermal detection thresholds were significantly higher at the affected side

208 compared to the unaffected side <sup>24</sup>. Roosink et al. <sup>17,31</sup> also found hypoesthesia for tactile <sup>17,31</sup> and electrical sensation  
209 thresholds <sup>17</sup> and hypoalgesia (higher electrical pain thresholds EPT <sup>17,31</sup>) were more often observed in patients with HSP (6  
210 months post stroke) as compared to the pain-free patients. HSP was associated with reduced touch sensation, abnormal  
211 cold sensation (both reduced and elevated), cold allodynia, reduced sharpness sensation, and sharpness allodynia [19].  
212 Lindgren et al. <sup>26</sup> reported higher thermal thresholds and a wider range of mechanical thresholds in both stroke groups  
213 with and without shoulder pain when compared to healthy controls.

214

## 215 **2. Dynamic Methods**

### 216 **2.1 Suprathreshold Heat Pain Response**

#### 217 **2.1.1 Musculoskeletal Shoulder Pain**

218 Suprathreshold Heat Pain Response (SHPR) results in the perception of elevated pain although the peripheral afferent  
219 input is constant or even diminished and is thus considered a perceptual manifestation of augmented central sensitivity <sup>32</sup>.  
220 Valencia et al. <sup>32</sup> included this dynamic method in order to acquire the pain modulatory capacity of the central nervous  
221 system. They found that the 5<sup>th</sup> pain rating after five consecutive heat pulses was significantly higher in patients having  
222 shoulder surgery as compared to healthy controls. The 5<sup>th</sup> pain rating decreased significantly from the pre-surgical time  
223 point to 3 months after surgery and was comparable to baseline values of the healthy controls. The same SHPR principle  
224 was used by Coronado et al. <sup>29</sup>, who found **an increased** SHPR of small to moderate magnitude between the affected and  
225 non-affected side of patients with unilateral shoulder pain in comparison to pain-free controls.

226

### 227 **2.2 Conditioned Pain Modulation**

#### 228 **2.2.1 Musculoskeletal Shoulder Pain**

229 Valencia et al. <sup>32</sup> used SHPR as the test-stimulus and the cold pressor test as the conditioning stimulus. Although, there  
230 was a significant main effect of CPM, meaning that the conditioning stimulus significantly inhibited the test stimulus in  
231 both groups, the patients having shoulder surgery had a lower percentage increase of change for CPM at baseline  
232 compared to the healthy controls. The percent change of CPM and the absolute difference on CPM did not change  
233 significantly three months later in both groups. Another study by Valencia et al. <sup>27</sup> revealed that **fluctuation** in pain

234 intensity **of the patient** had no significant effect on between session stability of CPM. In addition, the CPM trial led to  
235 significantly greater inhibition **at the pre surgical time point** as compared to the trial after surgery.

236

## 237 **2.2.2 Hemiplegic Shoulder Pain**

238 Patients with HSP showed significantly lower hand immersion time (cold pain tolerance) as compared to pain-free stroke  
239 patients in both studies of Roosink et al. <sup>17,31</sup>. They found significantly higher EPTs and PPTs after the cold pressor test  
240 (CPT) **in these patients, but** no significant differences were found between groups when comparing threshold ratios for  
241 EPT and PPT (pre-cold pressor/post-cold pressor) <sup>17,31</sup>.

242

## 243 **2.3 Exercise-induced Endogenous Analgesia**

### 244 **2.3.1 Musculoskeletal Shoulder Pain**

245 After a unilateral static endurance test at the most painful shoulder, Persson et al. <sup>39</sup> found that the PPT levels over the  
246 affected shoulder muscles (i.e. trapezius and deltoid muscle) significantly increased immediately and 10 and 20 minutes  
247 after the test in women with chronic shoulder pain. On the unexposed side, the PPTs were significantly increased in the  
248 shoulder region only at 20 minutes after the test. Inconsistent changes were found of PPTs measured over the m.  
249 quadriceps on both sides.

250 Lannersten and Kosek <sup>25</sup> showed that patients with chronic unilateral myofascial shoulder pain had significantly lower  
251 PPTs at baseline compared to healthy controls at the m. infraspinatus bilaterally, but not at the m. quadriceps. During  
252 contraction of the painful (for the shoulder myalgia patients) m. infraspinatus, PPTs increased at all sites compared to  
253 baseline at the middle and end of contraction in healthy controls, but not in patients with shoulder myalgia. During  
254 contraction of the quadriceps, PPTs increased at all sites compared to baseline at the end of contraction in healthy  
255 controls and patients with shoulder **myalgia**.

256

## 257 **2.4 Dynamic tactile allodynia and hyperpathia**

### 258 **2.4.1 Hemiplegic Shoulder Pain**

259 Dynamic tactile allodynia was described as pain provoked by a non-noxious stimulus <sup>41</sup>. Hyperpathia was described as the  
260 development of a sudden, strong painful sensation that continued after the stimulation was switched off <sup>41</sup>. Higher rates  
261 of pathologically evoked pain (hyperpathia and dynamic tactile allodynia) were found in the affected shoulder and lower  
262 leg of the HSP-group compared to the HSP-group without shoulder pain <sup>24</sup>.

263

## 264 **DISCUSSION**

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

268

### 269 **1. Musculoskeletal Shoulder Pain**

#### 270 **1.1 Static Methods**

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

275

276 In the study of Hidalgo-Lozano et al. <sup>37</sup> PPTs were lower in both elite swimmers with and without shoulder pain, which was  
277 unexpected for the latter. This finding may indicate that pain sensitivity of neck and shoulder girdle tissues to mechanical  
278 stimuli in elite swimmers with and without shoulder pain could be associated with the swimming-specific demands or as a  
279 result of exercising on a regular/ high intensity basis as seen in many other athletes. There is currently no consensus about  
280 the magnitude of the difference in PPT levels necessary to consider real changes between patients with shoulder pain and  
281 healthy controls <sup>42</sup>. The lower PPT levels in patients with SIS and elite swimmers with and without shoulder pain in both  
282 painful and distant pain-free areas suggest the presence of both peripheral and central sensitization mechanisms <sup>7,37</sup>. Note  
283 that in both studies of Hidalgo-Lozano <sup>7,37</sup> the PPT levels were only investigated at the affected side (but also distal to the  
284 pain location). Paul et al. <sup>36</sup> also suggested evidence for central hypersensitivity in patients with SIS, although they did not

285 limit analgesic usage, evaluators were not blinded to case and control subjects (which could have introduced bias) and  
286 sex, age and ethnicity of the sample were not standardized. In another study occurrence of CS was investigated in a  
287 subgroup of patients with unilateral shoulder pain<sup>30</sup>. In particular, the presence of referred pain, or hyperalgesia, was  
288 associated with worse outcomes after subacromial decompression. Therefore, this study showed heterogeneity within  
289 patients presenting with SIS and suggested that pre-operatively presence of CS negatively affects outcome three months  
290 after subacromial decompression<sup>30</sup>.

291

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

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

305

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

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

317

## 318 **1.2 Dynamic Methods**

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

329 Two studies used a static endurance test<sup>25,39</sup> to evaluate the influence of exercise-induced endogenous analgesia in  
330 patients with shoulder pain. Their findings were rather contradictory. Persson et al.<sup>39</sup> found a proper activation of central  
331 antinociceptive mechanisms in chronic shoulder pain patients after static contraction of the painful shoulder.  
332 Nevertheless, although PPT values increased, patients' sensation of pain was increased. Contrarily, Lannersten and Kosek  
333<sup>25</sup> only found proper activation of endogenous analgesia in shoulder myalgia patients when non-painful body parts (but  
334 not the painful shoulder) were exercised. In fibromyalgia patients (**commonly centrally sensitized in a subset of patients**),  
335 all contractions induced generalized hyperalgesia independently of where they were performed<sup>25</sup>. These patients have an

336 overall inability to activate pain inhibitory mechanisms, which supports previous findings <sup>46</sup>. A limitation of this study is  
337 that the examiner could not be blinded to the group assigned to each subject.

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

## 347 **2. Hemiplegic Shoulder Pain**

### 348 **2.1 Static Methods**

349 There is a level of evidence 2 for somatosensory differences, such as reduced PPTS <sup>34</sup> and allodynia <sup>17,24</sup>, in patients with  
350 HSP, suggesting a role for central hypersensitivity <sup>17,24,34</sup>. In addition, a neuropathic pain component has been shown in  
351 this population <sup>17,24,31</sup>.

352  
353 The study by Soo Hoo et al. <sup>34</sup> was the only study that found lower PPTs at local and remote pain-free sites in patients with  
354 HSP as compared to pain-free control, suggesting CS. If these findings were restricted to the affected shoulder, it would  
355 not be possible to distinguish between peripheral or central hypersensitivity and sensory abnormalities caused by a  
356 spinothalamocortical lesion. However, the finding that pain was experienced at lower pressure levels at remote pain-free  
357 sites supports the notion that central processes may influence the overall perception of pain in patients with chronic HSP  
358 <sup>34</sup>.

359 Recent studies have provided preliminary evidence that patients with HSP have somatosensory abnormalities <sup>17,40,47</sup>.  
360 Roosink et al. <sup>17,31</sup> reported the presence of widespread somatosensory abnormalities, such as allodynia and hyperalgesia,  
361 already in the first 6 months after stroke. This might suggest the presence of a neuropathic pain component contributing

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

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

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

382

## 383 **2.2 Dynamic Methods**

384 There is a level of evidence 2 for the dynamic methods to evaluate HSP. No difference in CPM was observed in patients  
385 with HSP when compared to pain-free controls<sup>17,31</sup>. Impaired endogenous pain modulation may predict the development  
386 of CS<sup>49,50</sup> and persistent pain<sup>31</sup> and was reduced or absent in several types of chronic pain patients<sup>51,52</sup>. **The results of both**  
387 **studies of Roosink et al.**<sup>17,31</sup> suggest that HSP is not associated with impaired endogenous inhibition. This may indicate



388 that CPM is functioning normally in patients with post-stroke pain, although it is plausible that endogenous inhibitory pain  
389 pathways may be defective at a higher supraspinal level<sup>52</sup>. This interpretation of the results is limited by the small sample  
390 size and the differences between groups in terms of timing and intensity of the conditioning stimulus. CPM should  
391 therefore be repeated in a larger study.

392

### 393 **CONCLUSION**

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

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

405

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