

## Somatosensory Symptoms and Signs and Conditioned Pain Modulation in Chronic Post-Stroke Shoulder Pain

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**Abstract:** Persistent shoulder pain is a common complication after stroke. Its etiology and underlying mechanisms are not well understood and treatment is generally unsatisfactory. The objective of this study was to assess the role of central sensitization and disinhibition in chronic stroke patients with chronic PSSP (n = 19), pain-free stroke patients (n = 29), and healthy controls (n = 23). Positive and negative somatosensory symptoms and signs were assessed using clinical examination and electrical and mechanical quantitative sensory testing (QST). Conditioned pain modulation (CPM) was assessed by comparing QST thresholds before and after applying a cold pressor test. Sensory abnormalities were more frequently observed and more severe in patients with PSSP, including positive signs such as allodynia at the affected side and generalized hyperalgesia at the unaffected side. CPM was similar in stroke patients and healthy controls. This study showed that chronic PSSP was associated with several positive and negative somatosensory signs, implicating a role for central sensitization and possibly for disinhibition. Since the causal relationship remains unclear, and may be related to either neuroplasticity induced by ongoing nociception as well as to the neuropathic brain lesion, prospective studies are warranted.

**Perspective:** The assessment of somatosensory symptoms and signs and endogenous pain modulation demonstrated a role for central sensitization and possibly for disinhibition in chronic PSSP. Prevention and treatment of PSSP could benefit from a more detailed analysis of both peripheral and central pain mechanisms.

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**Key words:** Stroke, shoulder pain, somatosensory function, quantitative sensory testing, conditioned pain modulation, diffuse noxious inhibitory controls.

Pain is a common complication after stroke.<sup>20,33</sup> Post-stroke pain is a great burden for the patient and impedes rehabilitation.<sup>46,56</sup> One of the most reported

types is post-stroke shoulder pain (PSSP) which typically develops at the affected side after 2 to 3 months.<sup>13,15,20,41</sup> Although its etiology is largely unknown, several clinical conditions such as spasticity, glenohumeral subluxation, capsular inflammation, peripheral neuropathy, central post-stroke pain (CPSP), and autonomic dysfunction have been related to PSSP.<sup>48,51,63</sup> Furthermore, several studies have suggested that reduced motor function,<sup>14,15,17,31,33,39</sup> depression,<sup>14,15,33</sup> and reduced somatosensory function<sup>14,15,17,33,35,60</sup> may contribute to the development of PSSP. Clinical presentations of PSSP, CPSP, and post-stroke complex regional pain syndrome

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type 1 (shoulder-hand syndrome) may show considerable overlap complicating the diagnosis and prognosis of post-stroke pain.<sup>24,45</sup>

PSSP may resolve spontaneously in the course of rehabilitation, but is persistent (>12 months) in 65% of the patients.<sup>31</sup> The evidence for effective therapeutic interventions for PSSP is lacking or inconsistent and, in the case of successful treatment, it is often unclear what mechanisms have been responsible for the pain reduction.<sup>42</sup> Together, this suggests that the pain mechanisms underlying PSSP development and maintenance may be more complex than previously realized, and that the traditional view and approach of PSSP as purely ongoing nociceptive pain may need revision.<sup>45</sup>

The assessment of positive and negative somatosensory symptoms and signs in relation to the pain complaints is 1 of the first steps towards a better understanding of pain mechanisms.<sup>43,44</sup> Although the relationship between symptoms and signs and pain mechanisms is still under debate,<sup>18</sup> several symptoms and signs, such as sensory loss (eg spinothalamic tract lesions), allodynia, and generalized hyperalgesia, have been associated with experimentally induced central sensitization<sup>21,25,58</sup> and/or various forms of chronic nociceptive<sup>47</sup> or neuropathic<sup>6,10,57</sup> pain. In addition, endogenous pain modulation, involving supraspinal diffuse noxious inhibitory controls (DNIC),<sup>29</sup> has been shown to be impaired in various types of chronic pain, such as painful osteoarthritis,<sup>28</sup> whiplash,<sup>22</sup> and neuropathic pain.<sup>61</sup> So far, little is known about the role of central sensitization or disinhibition in the development and maintenance of PSSP.

The objective of this study was to assess the role of central sensitization and disinhibition in chronic stroke patients (>6 months post-stroke) with chronic (duration >3 months) PSSP (n = 19), pain-free stroke patients (n = 29), and healthy controls (n = 23). Positive and negative somatosensory symptoms and signs were assessed using clinical examination and electrical and mechanical quantitative sensory testing (QST). Conditioned pain modulation (CPM) was assessed by comparing QST thresholds before and after applying a cold pressor test. It was expected that both the frequency as well as the severity of somatosensory abnormalities would be higher in the patients with PSSP and that, in addition to previously reported associations with negative signs, PSSP would be associated with positive somatosensory symptoms and signs indicative of central sensitization and/or disinhibition such as allodynia, generalized hyperalgesia, and impaired endogenous inhibitory pain modulation.

## Methods

### Subjects

This study included stroke patients with persistent shoulder pain (PSSP, n = 19), pain-free stroke patients (PF, n = 29), and healthy controls (HC, n = 23). Stroke patients were recruited in 2 regional rehabilitation centers in the Netherlands (Roessingh Rehabilitation Center in Enschede and Sint Maartenskliniek in Nijmegen).

The outpatient databases were searched for stroke patients who had been hospitalized in the 2 years prior to the start of inclusion (Fall 2007). Patients fulfilling the inclusion and exclusion criteria were approached by mail. In addition, patients visiting the outpatient clinics with shoulder pain complaints were asked by their treating physician if they could be approached by 1 of the researchers (M.R.) by mail. Healthy subjects (age 40–60) were recruited through advertisements in local community centers and newspapers.

All stroke patients were 18 years or older and sustained a unilateral brain infarction with an onset at least 6 months prior to participation. For stroke patients to be included in the PSSP group, shoulder pain had to be unilateral, be confined to the affected side, have an onset after stroke, and be persistent (daily pain, duration longer than 3 subsequent months). Patients were included in the PF group if they had no long-lasting (>1 week in the last 3 months) pain complaints. Exclusion criteria were: Pregnancy, trauma, infection, signs of any possible concomitant neurological condition (eg, multiple sclerosis, HIV/AIDS, peripheral neuropathy), not being able to reliably determine sensory thresholds during a training session prior to the experiment, and other pain complaints than simple shoulder pain (eg, CPSP,<sup>24</sup> wide-spread pain, or shoulder-hand syndrome). Healthy control subjects had to be free of any neurological or psychiatric disorder, diabetes mellitus, psychotropic medication, or long-lasting (>1 week in the last 3 months) pain complaints. When subjects considered for the PF or HC groups reported minor pain complaints at the time of the experiment, the experiment was postponed until subjects were pain-free for at least 2 weeks. The study was approved by the human ethics committee of the Roessingh Rehabilitation Center in Enschede, the Netherlands. All subjects received written and oral information about the study protocol and all participants gave informed written consent prior to their participation.

### Demographic Data and Medical Examination

General demographic characteristics such as age, gender and (for the patients) lesion side, stroke onset, and medication use were registered. Shoulder pain was evaluated both at rest and during movement with an 11-point Numeric Rating Scale (NRS, 0 = no pain, 10 = maximum conceivable pain). The emotional state was assessed using the ZUNG self-rating depression scale (score: 20–80) which has been validated for both healthy subjects and stroke patients.<sup>50</sup> Cognitive state was assessed using the Mini Mental State Exam (MMSE, score: 0–30, cognitive impairment was defined as a MMSE score <24).<sup>49</sup> Physical examination included the assessment of trophic changes in the arms and hands (severe color or perspiration changes or asymmetry, edema, assessed by visual inspection and subject reports), glenohumeral subluxation (assessed by palpation, scored in steps of 5 mm), pain-free range of motion for passive shoulder elevation (0–180 degrees) and external rotation (0–90 degrees),

severity of paresis of the upper extremity (assessed with the Motricity Index; 0 = completely paretic, 100 = no paresis)<sup>9</sup> and spasticity of elbow flexor and shoulder internal rotator muscles (Modified Ashworth Scale, score: 0–5, spasticity was defined as MAS > 1).<sup>4</sup> For passive pain-free ranges of motion (shoulder elevation and external rotation) a ratio between sides was calculated for further analysis (PSSP and PF: affected/unaffected, HC; nondominant/dominant).

### **Routine Clinical Examination**

Subjects were tested for sensation to touch, cold, and sharpness at both upper arms (C5 dermatome) using, respectively, a cotton wool swab, a metal tuning fork at room temperature and a 6.65 (force: 300 grams) Semmes Weinstein filament (North Coast Medical Inc, Oxfordshire, UK).<sup>55</sup> Tests were always first performed at the unaffected (in PSSP and PF patients) or dominant (in HC) side. Proprioception was tested at the thumbs of both hands (joint position sense). Subjects had to indicate whether sensation was equal, diminished, or increased compared to the opposite side (affected versus unaffected side in stroke patients, nondominant versus dominant side in healthy controls). In healthy controls, all tests were perceived as being painless. If any of the evoked sensations was painful in patients, this was considered as allodynia (tactile, cold, sharpness).<sup>32</sup> All tests were performed by the same experimenter (M.R.)

### **Quantitative sensory testing (QST)**

For all tests, the method of limits was used and the start side of stimulation (affected or unaffected) was randomized between subjects. Modality specific assessment was performed using mechanical QST.<sup>18</sup> The tactile detection threshold (TDT) was determined using 5 Semmes Weinstein filaments (sizes: 2.83, 3.61, 4.31, 4.56, 6.65; Touch-Test Hand Kit, North Coast Medical Inc, Oxfordshire, UK). The filaments were applied on the upper arm over the higher and lower part of the middle deltoid muscle (C5 dermatome). The TDT was defined as the smallest filament that could be perceived at both locations. The pressure pain threshold (PPT) was determined using an experimenter-operated pressure algometer (Somedic, Horby, Sweden). A stimulation surface of 1 cm<sup>2</sup> and a slope of 50 kPa/s were used. The maximum pressure that could be delivered was 2,000 kPa. Subjects were instructed to keep their arm in 0 degrees shoulder abduction and 90 degrees elbow flexion to avoid displacement of the muscle. The PPT was determined at both upper arms at 3 locations over the middle deltoid muscle (higher, middle, and lower part of the muscle, C5 dermatome). In response to the increasing pressure delivered at the arm by the experimenter, subjects were instructed to verbally indicate when they first perceived the pressure as painful. The 3 PPTs were averaged for further analysis. All mechanical thresholds were determined by the same experimenter (M.R.).

In addition, somatosensory changes were assessed using electrical QST. With electrical QST, the primary afferent is activated directly, without involvement of

the peripheral receptor. Differences in electrical and natural QST thresholds can be used to assess the presence of peripheral receptor-mediated (de)sensitization. In the case of PSSP, this is relevant since sensitization may take place at both the peripheral as well as the central level. The electrical sensation threshold (EST), electrical pain threshold (EPT), and electrical pain tolerance threshold (EPTT) were determined using a custom build ambulant stimulator (Ambustim, University of Twente, Enschede, the Netherlands). This stimulator operated via a Bluetooth connection with a personal computer. The stimulator settings were controlled via custom built software (labVIEW, National Instruments, Austin, TX). The stimulator was set to generate electrical pulses with an increasing amplitude (pulse width: .2 ms, frequency: 100 Hz, ramp: .4 mA/s, maximum stimulus amplitude: 16 mA). The stimulator was attached to the upper arm via 2 Ag/AgCl electrodes (stimulation surface: 95 mm<sup>2</sup>, AMBU, Ballerup, Denmark) that were placed just above the deltoid tuberosity of the humerus. Subjects could manually activate the stimulator by pressing a switch. To determine the EST, subjects were instructed to release the switch when the electrical pulses were perceived for the first time. To determine the EPT, subjects were instructed to release the switch when the electrical pulses were perceived as both stinging and annoying. To determine the EPTT, subjects were instructed to release the switch when the electrical pulses were perceived as burning and very annoying. Subjects were trained to determine these thresholds reliably prior to participating in the experiment. All thresholds were determined 4 times on each side. The first threshold was considered a test measurement. The remaining 3 thresholds were averaged for further analysis.

### **Conditioned Pain Modulation**

After QST, subjects underwent a cold pressor test at the hand of the unaffected (in PSSP and PF patients) or dominant (in HC) side. Subjects had to place their hand in a polystyrene box filled with ice water (0–5°C). The hand was immersed up to the wrist with the fingers spread. Subjects were instructed to keep their hand in the water as long as possible but with a maximum of 3 minutes. Immersion time was recorded. After removing the hand from the water, subjects rated the pain in their hand using a NRS (0 = no pain, 10 = maximum conceivable pain). Directly afterwards, the EPT and PPT were determined twice at the affected (in PSSP and PF patients) or nondominant (in HC) upper arm. The thresholds were determined after immersion since not all patients were able to use the patient-operated switch with their affected hand. Threshold determination was similar as before. The 2 thresholds were averaged for further analysis.

### **Data Processing**

For demographic data and medical examination, for each group (PSSP, PF, HC), average and standard deviations or frequencies were determined. For routine clinical examination, frequencies of abnormal, diminished,

and increased sensation and allodynia were calculated for each stimulus. QST thresholds were log-transformed prior to statistical analysis. In unilateral pain syndromes, QST side-to-side differences have shown to be more sensitive for the detection of individual sensory abnormalities.<sup>44</sup> Therefore, in addition to the raw data, a within-subject ratio was calculated for all QST thresholds (ratio in PSSP and PF patients was obtained by dividing affected/unaffected, in the HC group by dividing nondominant/dominant). Moreover, threshold abnormalities were determined by normalizing individual QST ratios of patients to the HC data set using a z-transformation to assess the frequency of individually increased or decreased somatosensory function.<sup>44</sup> Hypoesthesia (TDT, EST) and hypoalgesia (EPT, EPTT, PPT) were defined as a z-score higher than 2. Hyperesthesia (TDT, EST) and hyperalgesia (EPT, EPTT, PPT) were defined as a z-score lower than -2. Cold pressor effects were assessed using both the pain thresholds determined before and after cold pressor testing as well as by calculating a prepost ratio (post/pre). All ratios were log-transformed prior to statistical analysis.<sup>44</sup>

### Statistical Analysis

Statistical software package SPSS v.16.0 for Windows was used (SPSS Inc, Chicago, IL). In order to identify the somatosensory changes related to PSSP, continuous data was statistically tested using 1-way analyses of variance (ANOVA) with factor Group (PSSP, PF, HC). The Least Significant Difference was used for post hoc multiple comparisons. Ordinal data was tested using Chi-square tests. In addition, QST thresholds before and after cold pressor testing were analyzed using a repeated measures ANOVA with within-subjects factor Cold pressor (pre, post) and between-subjects factor Group

(PSSP, PF, HC). Differences between groups were attributed to PSSP when a significant difference between PSSP and PF and/or a significant difference between PSSP and HC was observed.

Possible confounding effects of age, gender, dystrophic changes, and depression scores were ruled out using additional multivariate analyses, with either QST thresholds (affected, unaffected, ratios) or Cold pressor parameters (post/pre ratios, immersion time, pain intensity) as dependent factors, Group as a between-subjects factor and either Age, Gender, Dystrophic changes, or ZUNG score as a covariate. In brief, these analyses showed that gender was significantly related to QST parameters, however, only to the electrical pain tolerance and pressure pain thresholds, not to any other parameter. In addition, adding sex as a covariate had no influence on the observed differences between groups for these or any of the other parameters. Therefore, data correction was considered unnecessary.

For all tests, statistical significance was assigned at the  $P < .05$  level using 2-tailed analysis.

## Results

### Demographic Data and Medical Examination

A summary of the demographics and medical examinations is presented for each group in Table 1. Analgesics (cox-inhibitors or nonsteroidal anti-inflammatory drugs) were used on a regular basis by 7 PSSP patients. In addition, some patients used antidepressants (9 PSSP, 4 PF) and/or anti-epileptics (3 PSSP, 2 PF) either for pain, depression, and/or epilepsy.

Analysis of demographics and medical examinations revealed several differences between groups (see Table 1).

**Table 1. Demographic Data and Medical Characteristics**

	PSSP (n = 19)	PF (n = 29)	HC (n = 23)	P (VERSUS PF)	P (VERSUS HC)
Age (years)	57 ± 7	61 ± 10	56 ± 7	ns	ns
Male	10 (53%)	21 (72%)	10 (43%)	ns	ns
Right-hemispheric lesion	16 (84%)	12 (59%)		ns	
Time to stroke onset (months)	22 ± 14	25 ± 8		ns	
Cognitive deficits	2 (11%)	1 (3%)	0 (0%)	ns	ns
Depression score (ZUNG)	45.4 ± 6.0	35.9 ± 6.0	31.0 ± 4.8	<.001	<.001
Trophic changes hand/arm	8 (42%)	3 (14%)	0 (0%)	ns	.001
Severity of paresis (Motricity Index)	46 ± 38	59 ± 43	100 ± 0	ns	<.001
ROM shoulder abduction (ratio)	.41 ± .19	.74 ± .27	1.00 ± 0	<.001	<.001
ROM shoulder external rotation (ratio)	.41 ± .34	.76 ± .19	1.03 ± 9	<.001	<.001
Spasticity elbow flexors	15 (79%)	20 (69%)	0 (0%)	ns	<.001
Spasticity shoulder internal rotators	13 (68%)	17 (58%)	0 (0%)	ns	<.001
Glenohumeral subluxation	10 (53%)	11 (38%)	0 (0%)	ns	<.001
Severity (mm)	3.9 ± 4.6	3.8 ± 4.9	0 ± 0	ns	<.001
Shoulder pain intensity (NRS)					
Rest	3.5 ± 2.8				
Movement	5.7 ± 3.0				
Shoulder pain duration (months)	19 ± 13				

Abbreviations: PSSP, stroke patients with post-stroke shoulder pain; PF, pain-free stroke patients; HC, healthy controls; n, number of subjects; P, P value for statistical testing; SD, standard deviation; %, percentage of patients; A, affected side (patients); ND, nondominant side (HC); ROM, pain-free passive range of motion (patients: ratio score affected/unaffected side, HC: ratio score nondominant/dominant side).

NOTE. Data are presented as mean ± SD or as number of subjects (%). P values were obtained via Chi-square analysis (ordinal data) and analysis of variances (continuous data) with post hoc testing (corrected using the Least Significant Difference). P values <.05 were considered significant.

PSSP was associated with a higher frequency of trophic changes in the arm and hand, higher ZUNG scores, and reduced ranges of passive pain-free shoulder elevation and external rotation. PSSP was not associated with the severity of paresis, spasticity or glenohumeral subluxation.

**Routine Clinical Examination**

Table 2 presents the frequency of subjects with abnormal sensation and allodynia for each group. PSSP was associated with diminished touch sensation, abnormal cold sensation (both diminished and increased), cold allodynia, diminished sharpness sensation, and sharpness allodynia.

**Quantitative Sensory Testing**

The results of QST are presented in Table 3. At the unaffected side, PSSP was associated with higher TDTs as compared to HC. In addition, EPTs and EPTTs were reduced in all stroke patients as compared to HC, irrespective of the presence of pain. At the affected side, PSSP was associated with higher TDTs and ESTs as compared to both PF patients and HC.

Mean threshold ratios for each group are presented in Fig 1. PSSP was associated with higher TDT, EST, and EPT ratios as compared to both PF patients and HC.

Percentages of patients with abnormal z-scores (based on normalization of QST threshold ratios) are presented for PSSP and PF in Table 4. Hypoesthesia (TDT, EST) and

**Table 2. Clinical Examination: Abnormal Sensation and Allodynia**

	PSSP (n = 19)	PF (n = 29)	HC (n = 23)	P (vs PF)	P (vs HC)
<b>Touch</b>					
Abnormal	13 (68%)	12 (41%)	2 (9%)	ns	.000
Diminished	13 (68%)	9 (31%)	2 (9%)	.021	.000
Increased	0 (0%)	3 (10%)	0 (0%)	ns	ns
Allodynia	1 (5%)	0 (0%)	0 (0%)	ns	ns
<b>Cold</b>					
Abnormal	15 (79%)	13 (45%)	2 (8%)	.034	.000
Diminished	9 (47%)	11 (38%)	1 (4%)	ns	.000
Increased	6 (32%)	2 (7%)	1 (4%)	.025	.018
Allodynia	3 (16%)	0 (0%)	0 (0%)	.027	.048
<b>Proprioception</b>					
Abnormal	13 (68%)	12 (41%)	0 (0%)	ns	.000
Diminished	13 (68%)	12 (41%)	0 (0%)	ns	.000
Increased	0 (0%)	0 (0%)	0 (0%)	na	na
Allodynia	0 (0%)	0 (0%)	0 (0%)	na	na
<b>Sharpness</b>					
Abnormal	14 (74%)	14 (48%)	5 (22%)	ns	.001
Diminished	10 (53%)	7 (24%)	3 (13%)	ns	.002
Increased	4 (21%)	7 (24%)	2 (9%)	ns	ns
Allodynia	5 (26%)	0 (0%)	0 (0%)	.004	.009

Abbreviations: PSSP, stroke patients with post-stroke shoulder pain; PF, pain-free stroke patients; HC, healthy controls; n, number of subjects; P, P value for statistical testing; ns, not significant; na, not applicable. NOTE. Data are presented as number of subjects (%). P values were obtained via Chi-square analysis. P values <.05 were considered significant.

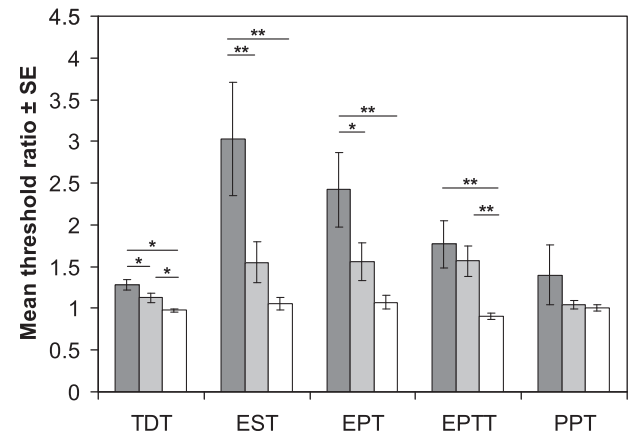
**Table 3. Quantitative Sensory Testing**

	PSSP (n = 19)	PF (n = 29)	HC (n = 23)	P (vs PF)	P (vs HC)
<b>UA (D)</b>					
TDT (size)	3.69 ± .44	3.52 ± .46	3.30 ± .45	ns	.007
EST (mA)	1.01 ± .40	1.14 ± .46	.93 ± .33	ns	ns
EPT (mA)	2.73 ± 1.94	2.94 ± 2.05	3.81 ± 1.95	ns	.026
EPTT (mA)	5.18 ± 3.07	5.57 ± 3.80	7.40 ± 2.48	ns	.007
PPT (kPa)	379 ± 178	434 ± 207	467 ± 176	ns	ns
<b>A (ND)</b>					
TDT (size)	4.71 ± 1.08	3.89 ± .73	3.20 ± .45	.001	.000
EST (mA)	3.00 ± 3.67	1.48 ± .80	.93 ± .30	.018	.000
EPT (mA)	5.49 ± 3.87	4.03 ± 3.00	3.85 ± 1.70	ns	ns
EPTT (mA)	7.66 ± 4.23	7.92 ± 5.48	6.65 ± 2.30	ns	ns
PPT (kPa)	454 ± 401	451 ± 230	462 ± 163	ns	ns

Abbreviations: SD, standard deviation; PSSP, stroke patients with post-stroke shoulder pain; PF, pain-free stroke patients; HC, healthy controls; n, number of subjects; P, P value for statistical testing; UA, unaffected side (patients); D, dominant side (HC); A, affected side (patients); ND, nondominant side (HC); TDT, tactile detection threshold; EST, electrical sensation threshold; EPT, electrical pain threshold; EPTT, electrical pain tolerance threshold; PPT, pressure pain threshold; ns, not significant.

NOTE. Data are presented as mean ± SD. Differences between groups were tested using 1-way analyses of variance. Post hoc multiple comparisons (PSSP versus PF and PSSP versus HC) were corrected using the least significant difference. P values <.05 were considered significant.

hypoalgesia (EPT) were more often observed in PSSP as compared to PF. Although no group mean differences were observed for the PPT, z-score analysis revealed both hypoalgesia and hyperalgesia for pressure pain stimuli in the patient groups. Hypoalgesia and hyperalgesia were more often observed in the PSSP group, but this was not statistically significant.



**Figure 1.** Threshold ratios for each group (mean ± standard error). Ratios are affected/unaffected side (patients) and non-dominant/dominant side (HC). Dark grey bars, stroke patients with shoulder pain (PSSP n = 19); light grey bars, pain-free stroke patients (PF, n = 29); white bars, healthy controls (HC, n = 23). Abbreviations: TDT, tactile detection threshold; EST, electrical sensation threshold; EPT, electrical pain threshold; EPTT, electrical pain tolerance threshold; PPT, pressure pain threshold. Differences between groups were tested using 1-way analyses of variance. Post hoc multiple comparisons were corrected using the Least Significant Difference. \*P < .05, \*\*P < .01.

**Table 4. Abnormal z-scores of Threshold Ratios**

	PSSP (n = 19)	PF (n = 29)	P
TDT			
Hypoesthesia	14 (74%)	20 (34%)	.015
Hyperesthesia	0 (0%)	0 (0%)	ns
EST			
Hypoesthesia	10 (53%)	5 (17%)	.014
Hyperesthesia	0 (0%)	0 (0%)	ns
EPT			
Hypoalgesia	9 (47%)	4 (14%)	.015
Hyperalgesia	0 (0%)	0 (0%)	ns
EPTT			
Hypoalgesia	11 (58%)	17 (59%)	ns
Hyperalgesia	0 (0%)	0 (0%)	ns
PPT			
Hypoalgesia	4 (21%)	3 (10%)	ns
Hyperalgesia	3 (16%)	1 (4%)	ns

Abbreviations: PSSP, stroke patients with post-stroke shoulder pain; PF, pain-free stroke patients; n, number of subjects; P, P value for statistical testing; TDT, tactile detection threshold; EST, electrical sensation threshold; EPT, electrical pain threshold; EPTT, electrical pain tolerance threshold; PPT, pressure pain threshold; ns, not significant.

NOTE. Data are presented as number of subjects (%). Z-scores were obtained via the z-transformation of individual threshold ratios (affected/unaffected) to the healthy control data. Abnormality was defined as  $-2 > Z > 2$ . P values were obtained via chi-square analysis. P values  $<.05$  were considered significant.

**Cold Pressor Test**

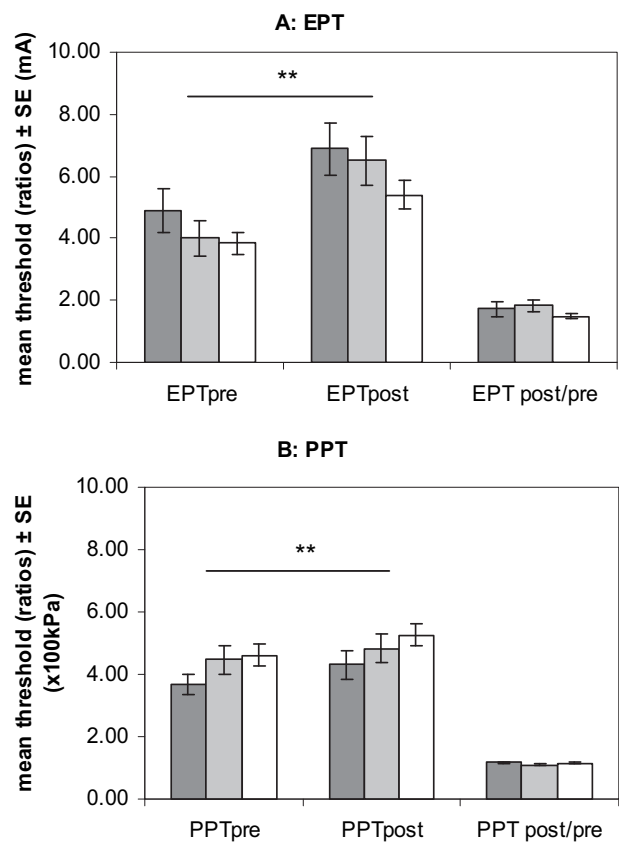
Mean thresholds before and after the cold pressor test and threshold ratios (post/pre) are depicted in Figs 2A (EPT) and 2B (PPT). In 1 PSSP and 1 PF patient, it was not possible to determine QST thresholds after the cold pressor test (PSSP, QST thresholds before cold pressor already at maximum stimulator output; PF, strong physical response to cold pressor hand immersion). In another PF patient, the PPT could not be determined due to a technical problem. In total, the effect of the cold pressor test could be determined in 18 PSSP, 28 PF, and 23 HC subjects with regard to the EPT and in 18 PSSP, 27 PF, and 23 HC subjects with regard to the PPT. Repeated measures analysis revealed significant higher EPTs ( $P < .001$ ) and PPTs ( $P < .001$ ) after the cold pressor test. This effect was not different comparing groups ( $P < .05$ ). In addition, also when comparing threshold ratios (post/pre), no significant differences were found comparing groups ( $P < .05$ ).

Mean duration  $\pm$  standard deviation of hand immersion was  $76 \pm 62$  seconds for PSSP,  $113 \pm 70$  seconds for PF, and  $153 \pm 45$  seconds for HC. Hand immersion time (cold pain tolerance) was significantly reduced in patients with PSSP as compared to both PF patients ( $P = .04$ ) and controls ( $P = .02$ ).

Mean cold pressor pain intensity (NRS)  $\pm$  standard deviation was  $6.5 \pm 1.7$  for PSSP,  $6.4 \pm 2.3$  for PF, and  $6.3 \pm 1.5$  for HC and was not statistically different between groups.

**Discussion**

This study investigated the role of central sensitization and disinhibition in chronic PSSP by assessing positive and negative somatosensory symptoms and signs and



**Figure 2.** Electrical pain thresholds (A) and pressure pain thresholds (B) before (pre) and after (post) cold pressor testing. Dark grey bars, stroke patients with shoulder pain (PSSP, n = 18); light grey bars, pain-free stroke patients (PF, EPT, n = 28; PPT, n = 27); white bars, healthy controls (HC, n = 23). Abbreviations: UA/D, unaffected (patients) or dominant (healthy controls); EPT, electrical pain threshold; PPT, pressure pain threshold. Differences in threshold ratios were tested using a repeated measures (thresholds pre and post, within subjects factor: Cold pressor, between subjects factor: Group) and 1-way analysis of variance (threshold ratios post/pre). **\*\*P < .01.**

CPM in patients with chronic PSSP, comparing them to pain-free stroke patients and healthy controls. It was shown that chronic PSSP was associated with a higher frequency of and more severe somatosensory loss. In addition, PSSP was associated with several positive somatosensory signs, such as allodynia and hyperalgesia. Interestingly, abnormalities were observed at both the affected as well as the unaffected side. CPM was similar in stroke patients and healthy controls.

**Somatosensory Loss**

Detailed somatosensory analysis in PSSP has seldom been performed and previous studies have mainly used clinical examination. Moreover, only a few studies have explicitly reported on the direction (increased/decreased) of somatosensory abnormalities or on positive signs such as allodynia and hyperalgesia. As in previous studies, this study showed that PSSP was associated with reduced tactile<sup>14,15,17,31</sup> and cold<sup>14,15</sup> sensation and with reduced proprioception<sup>35</sup> at the affected side as compared to control groups. Besides being more

frequent, somatosensory loss at the affected side for stimuli in the innocuous range was also more severe in patients with PSSP as observed with QST. Moreover, PSSP was associated with a small, but statistically significant, reduction of tactile sensation at the unaffected side compared with the HC, but not the PF, group.

A higher frequency of somatosensory loss as compared to controls has also been reported for central post-stroke pain<sup>1,30,54</sup> and for post-stroke complex regional pain syndrome.<sup>11,36</sup> Both the frequency<sup>1,16,30</sup> and severity<sup>7</sup> of somatosensory loss show considerable overlap with our findings in patients with chronic PSSP. Interestingly, an abnormal response (including both decreased and increased sensation) to thermal testing, a diagnostic criterion for central post-stroke pain,<sup>60</sup> was observed in 79% of PSSP patients.

Severe loss of sensory function may act as a risk factor for the development of PSSP since it puts the affected upper extremity at risk for repetitive microtrauma.<sup>41</sup> In addition, loss of sensory function, and specifically loss of spinothalamocortical tract function, has been implicated in mechanisms of central pain<sup>24</sup> and is considered a prerequisite for the development of central neuropathic pain. In a sub-analysis, in which the PSSP patients from the present study were classified on the basis of their score on the neuropathic pain diagnostic questionnaire,<sup>5</sup> it was shown that loss of spinothalamocortical tract function was more frequently present in the patients classified as having a possible neuropathic component to their pain (Roosink et al, *European Journal of Pain*, 2010, in press).

### Positive Somatosensory Signs

Only sharpness allodynia (referred to as punctate hyperalgesia by others also) has previously been implicated in PSSP.<sup>60</sup> Generally, allodynia to touch or cold is considered as a supportive factor for the diagnosis of CPCS.<sup>6,24,34</sup> In the present study, PSSP was clearly associated with positive signs. Allodynia (to touch, cold, and sharpness) was only observed in patients with PSSP and PSSP was associated with a higher frequency of increased sensation to cold stimuli and with a higher frequency of pressure pain hyperalgesia at the affected side. Interestingly, positive signs were also observed at the unaffected side. Electrical pain and pain tolerance thresholds and cold pain tolerance were generally reduced in patients with stroke, but this reduction was more pronounced in patients with PSSP.

Positive somatosensory signs in PSSP may be related to peripheral and/or to central sensitization or disinhibition. Since peripheral sensitization is expected to influence the processing of natural but not of electrical stimuli, the observed hyperalgesia to blunt pressure at the affected side of PSSP patients (but also in some PF patients) in the absence of hyperalgesia to nonreceptor-mediated electrical stimuli indeed suggests that peripheral nociception was increased.<sup>23</sup> This is supported by the observation that pain increased upon movement of the arm and that passive pain-free shoulder range of motion was reduced in patients with PSSP.

Theoretically, central sensitization or disinhibition may occur at both the spinal and supraspinal level and may be due to ongoing nociception (neuroplasticity) or to the brain lesion. From experimental studies it is known that cold allodynia,<sup>3,21</sup> punctate hyperalgesia,<sup>58</sup> and tactile (dynamic mechanical) allodynia<sup>26</sup> are (partly or completely) caused by central sensitization. Moreover, a reduction in pain thresholds in an unaffected region of patients with chronic pain is considered to be mediated by central sensitization and/or central disinhibition,<sup>8,40,47</sup> although a reduction in cold pain tolerance has also been related to disturbed cognitive and emotional aspects of clinical and experimental pain.<sup>19</sup>

Nonetheless, and whatever the initiating cause, central sensitization and possibly disinhibition seem to play a role in chronic PSSP maintenance, and may explain why treatment aimed at reducing peripheral nociception is generally unsatisfactory.

### Conditioned Pain Modulation

PSSP was not associated with impaired endogenous inhibition subserved by DNIC.<sup>29</sup> Using CPM paradigms,<sup>53,59</sup> DNIC have previously been shown to be impaired in several types of chronic pain, such as fibromyalgia,<sup>27</sup> osteoarthritis,<sup>28</sup> and whiplash,<sup>22</sup> and impaired DNIC may predict the development of chronic pain.<sup>22,62</sup> However, in pain-free stroke patients with thalamic or cortical lesions, but also in patients with central post-stroke pain, CPM has been shown to be equal to controls.<sup>12,52</sup> Therefore, based on these few studies, it seems that DNIC are functioning normally in patients with post-stroke pain, although endogenous pain modulation may be impaired at a higher supraspinal level.<sup>52</sup> Moreover, since CPM may have a differential effect on different test stimuli,<sup>28,61</sup> further study of the role of supraspinal disinhibition in post-stroke pain is warranted.

### Limitations

Being the first in its focus, this study has several limitations. First, it provides no insight into the causal role of any of the somatosensory symptoms or signs in the development of chronic PSSP. Previous studies have indicated that impaired somatosensory functions may act as risk factors for PSSP.<sup>2,15,33</sup> On the other hand, signs of peripheral and central sensitization may either precede or follow the development of PSSP. This should be further explored in longitudinal studies.

Age, gender, trophic changes, and depression scores could be ruled out as confounders in this study. However, some patients were using medications which, in theory, may have influenced somatosensory function. Analgesics, used only in the PSSP group, may have increased the pain thresholds of PSSP patients selectively. However, rather the opposite was observed, since pain thresholds at the unaffected side of both PSSP and PF patients were reduced and differences between PSSP and PF were also observed for innocuous stimuli.

A limitation regarding the assessment of CPM was that the duration of the conditioning stimulus was not equal across groups and that assessment was performed after,

rather than during, the conditioning stimulus. We standardized the cold pressor pain using self-reported pain intensities. It may be hypothesized that a fixed time-standardization or assessment during the cold pressor test would have given different outcomes. However, literature is inconsistent regarding the relation between the intensity of the conditioning stimulus and the magnitude of CPM.<sup>38</sup> Moreover, subjects may or may not adapt to tonic painful cold stimuli, involving a different timing of pain perception over the course of immersion.<sup>37</sup>

It would be interesting to assess CPM in patients with PSSP using a different conditioning stimulus, such as ischemia-induced pain, in which assessment during conditioning may be more easily performed and the intensity of the conditioning stimulus may be better controlled.

### Conclusion

The results from this study have clear implications for the clinical and the experimental approach to PSSP. This study showed that chronic PSSP was associated with several positive and negative somatosensory signs, implicating a role for central sensitization and possibly for disinhibition. Interestingly, chronic PSSP was not associated with biomechanical alterations commonly

associated with the development of PSSP, such as the severity of paresis, spasticity, and glenohumeral subluxation. Assessment of PSSP should, therefore, not only focus on the shoulder joint, but should also involve the somatosensory system. In this context, the use of pain research tools such as a thorough clinical examination, QST, or CPM is important since they may establish the presence of peripheral and/or central sensitization by quantifying sensory changes on both the affected and unaffected side of the stroke patients and by assessing supraspinal inhibitory functions. The use of these tools should be promoted in order to better understand the mechanisms underlying PSSP. Since the causal relationship between altered somatosensory functions and chronic PSSP remains unclear, and may be related to either neuroplasticity induced by ongoing nociception as well as to the neuropathic brain lesion, prospective studies are warranted.

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### References

- Andersen G, Vestergaard K, Ingeman-Nielsen M, Jensen TS: Incidence of central post-stroke pain. *Pain* 61:187-193, 1995
- Appelros P: Prevalence and predictors of pain and fatigue after stroke: A population-based study. *Int J Rehabil Res* 29:329-333, 2006
- Binder A, Binder A, Maag R, Peller M, Wasner G, Siebner HR, Baron R: Differential coding of cold allodynia - A fmri study. *Clin Neurophysiol* 118:e17, 2007
- Bohannon RW, Smith MB: Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 67:206-207, 1987
- Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114:29-36, 2005
- Bowsher D: Allodynia in relation to lesion site in central post-stroke pain. *Pain* 6:736-740, 2005
- Bowsher D, Leijon G, Thuomas KA: Central poststroke pain: Correlation of MRI with clinical pain characteristics and sensory abnormalities. *Neurology* 51:1352-1358, 1998
- Chu LF, Clark DJ, Angst MS: Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. *J Pain* 7:43-48, 2006
- Collin C, Wade D: Assessing motor impairment after stroke: A pilot reliability study. *J Neurol Neurosurg Psychiatry* 53:576-579, 1990
- Craig AD: Mechanisms of thalamic pain, in Henry JL, Panju A, Yashpal K (eds): *Central Neuropathic Pain: Focus on Poststroke Pain*, 1st ed. Seattle, WA, IASP Press, 2007, pp 81-99
- Daviet JC, Preux PM, Salle JY, Lebreton F, Munoz M, Dudognon P, Pelissier J, Perrigot M: Clinical factors in the prognosis of complex regional pain syndrome type I after stroke: A prospective study. *Am J Phys Med Rehabil* 81:34-39, 2002
- De Broucker T, Cesaro P, Willer JC, Le Bars D: Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. *Brain* 113:1223-1234, 1990
- Dromerick AW, Edwards DF, Kumar A: Hemiplegic shoulder pain syndrome: Frequency and characteristics during inpatient stroke rehabilitation. *Arch Phys Med Rehabil* 89:1589-1593, 2008
- Gamble GE, Barberan E, Bowsher D, Tyrrell PJ, Jones AK: Post stroke shoulder pain: More common than previously realized. *Eur J Pain* 4:313-315, 2000
- Gamble GE, Barberan E, Laasch HU, Bowsher D, Tyrrell PJ, Jones AK: Poststroke shoulder pain: A prospective study of the association and risk factors in 152 patients from a consecutive cohort of 205 patients presenting with stroke. *Eur J Pain* 6:467-474, 2002
- Greenspan JD, Ohara S, Sarlani E, Lenz FA: Allodynia in patients with post-stroke central pain (CSP) studied by statistical quantitative sensory testing within individuals. *Pain* 109:357-366, 2004
- Hadianfard H, Hadianfard MJ: Predictor factors of hemiplegic shoulder pain in a group of stroke patients. *Iran Red Crescent Me* 10:215-219, 2008
- Hansson P, Backonja M, Bouhassira D: Usefulness and limitations of quantitative sensory testing: Clinical and



- research application in neuropathic pain states. *Pain* 129: 256-259, 2007
19. Hirsh AT, George SZ, Bialosky JE, Robinson ME: Fear of Pain, Pain Catastrophizing, and Acute Pain Perception: Relative Prediction and Timing of Assessment. *J Pain* 9: 806-812, 2008
  20. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A: Prevalence and intensity of pain after stroke: A population based study focusing on patients' perspectives. *J Neurol Neurosurg Psychiatry* 77:590-595, 2006
  21. Jørum E, Warncke T, Stubhaug A: Cold allodynia and hyperalgesia in neuropathic pain: The effect of N-methyl-aspartate (NMDA) receptor antagonist ketamine - a double-blind, cross-over comparison with alfentanil and placebo. *Pain* 101:229-235, 2003
  22. 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* 9:561-569, 2005
  23. Kilo S, Schmelz M, Koltzenburg M, Handwerker HO: Different patterns of hyperalgesia induced by experimental inflammation in human skin. *Brain* 117:385-396, 1994
  24. Klit H, Finnerup NB, Jensen TS: Central post-stroke pain: Clinical characteristics, pathophysiology, and management. *Lancet Neurol* 8:857-868, 2009
  25. Koltzenburg M, Lundberg LER, Torebjörk HE: Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain* 51:207-219, 1992
  26. Koltzenburg M, Torebjörk HE, Wahren LK: Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. *Brain* 117:579-591, 1994
  27. Kosek E, Hansson P: Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain* 70:41-51, 1997
  28. Kosek E, Ordeberg G: Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain* 88:69-78, 2000
  29. Le Bars D, Dickenson AH, Besson JM: Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain* 6:283-304, 1979
  30. Leijon G, Boivie J, Johansson I: Central post-stroke pain-neurological symptoms and pain characteristics. *Pain* 36: 13-25, 1989
  31. Lindgren I, Jönsson AC, Norrving B, Lindgren A: Shoulder pain after stroke: A prospective population-based study. *Stroke* 38:343-348, 2007
  32. Loeser JD, Treede R-D: The Kyoto protocol of IASP Basic Pain Terminology. *Pain* 137:473-477, 2008
  33. Lundström E, Smits A, Terént A, Borg J: Risk factors for stroke-related pain 1 year after first-ever stroke. *Eur J Neurol* 16:188-193, 2009
  34. Misra UK, Kalita J, Kumar B: A study of clinical, magnetic resonance imaging, and somatosensory-evoked potential in central post-stroke pain. *J Pain* 9:1116-1122, 2008
  35. Niessen MH, Veeger DH, Meskers CG, Koppe PA, Konijnenbelt MH, Janssen TW: Relationship among shoulder proprioception, kinematics, and pain after stroke. *Arch Phys Med Rehabil* 90:1557-1564, 2009
  36. Pertoldi S, Di Benedetto P: Shoulder-hand syndrome after stroke. A complex regional pain syndrome. *Eura Medicophys* 41:283-292, 2005
  37. Polianskis R, Graven-Nielsen T, Arendt-Nielsen L: Modality-specific facilitation and adaptation to painful tonic stimulation in humans. *Eur J Pain* 6:475-484, 2002
  38. Pud D, Granovsky Y, Yarnitsky D: The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain* 144:16-19, 2009
  39. Rajaratnam BS, Venketasubramanian N, Kumar PV, Goh JC, Chan YH: Predictability of simple clinical tests to identify shoulder pain after stroke. *Arch Phys Med Rehabil* 88:1016-1021, 2007
  40. Ram KC, Eisenberg E, Haddad M, Pud D: Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - New perspective of opioid-induced hyperalgesia. *Pain* 139:431-438, 2008
  41. Ratnasabapathy Y, Broad J, Baskett J, Pledger M, Marshall J, Bonita R: Shoulder pain in people with a stroke: A population-based study. *Clin Rehabil* 17:304-311, 2003
  42. Renzenbrink GJ, Ijzerman MJ: Percutaneous neuromuscular electrical stimulation (P-NMES) for treating shoulder pain in chronic hemiplegia. Effects on shoulder pain and quality of life. *Clin Rehabil* 18:359-365, 2004
  43. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B: Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain* 123:231-243, 2006
  44. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, Treede RD: Quantitative sensory testing: A comprehensive protocol for clinical trials. *Eur J Pain* 10:77-88, 2006
  45. Roosink M, Geurts ACH, Ijzerman MJ: Defining post-stroke pain: Diagnostic challenges. *Lancet Neurol* 9:344, 2010
  46. Roy CW, Sands MR, Hill LD: Shoulder pain in acutely admitted hemiplegics. *Clin Rehabil* 8:334-340, 1994
  47. Schneider GM, Smith AD, Hooper A, Stratford P, Schneider KJ, Westaway MD, Frizzell B, Olson L: Minimizing the source of nociception and its concurrent effect on sensory hypersensitivity: An exploratory study in chronic whiplash patients. *BMC Musculoskeletal Disord* 11:29, 2010
  48. Teasell RW, Bhogal SK, Foley NC: Painful Hemiplegic Shoulder, in Teasell RW, Bhogal SK, Foley NC (eds): Evidence-based Review of Stroke Rehabilitation, 10th ed. London, Ontario, Canada, University of Western Ontario, 2007, pp 1-57
  49. Tombaugh TN, McIntyre NJ: The Mini-Mental State Examination: A comprehensive review. *J Am Geriatr Soc* 40: 922-935, 1992
  50. Turner-Stokes L, Hassan N: Depression after stroke: A review of the evidence base to inform the development of an integrated care pathway. Part 1: Diagnosis, frequency and impact. *Clin Rehabil* 16:231-247, 2002
  51. Turner-Stokes L, Jackson D: Shoulder pain after stroke: A review of the evidence base to inform the development of an integrated care pathway. *Clin Rehabil* 16:276-298, 2002
  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* 143:84-91, 2009

53. van Wijk G, Veldhuijzen DS: Perspective on Diffuse Noxious Inhibitory Controls as a Model of Endogenous Pain Modulation in Clinical Pain Syndromes. *J Pain* 11:408-419, 2010
54. Vestergaard K, Nielsen J, Andersen G, Ingeman-Nielsen M, Arendt-Nielsen L, Jensen TS: Sensory abnormalities in consecutive, unselected patients with central post-stroke pain. *Pain* 61:177-186, 1995
55. Walk D, Sehgal N, Moeller-Bertram T, Edwards RR, Wasan A, Wallace M, Irving G, Argoff C, Backonja MM: Quantitative sensory testing and mapping: A review of nonautomated quantitative methods for examination of the patient with neuropathic pain. *Clin J Pain* 25: 632-640, 2009
56. Wanklyn P, Forster A, Young J: Hemiplegic shoulder pain (HSP): Natural history and investigation of associated features. *Disabil Rehabil* 18:497-501, 1996
57. Wasner G, Lee BB, Engel S, McLachlan E: Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. *Brain* 131:2387-2400, 2008
58. Wasner G, Schattschneider J, Binder A, Baron R: Topical menthol—a human model for cold pain by activation and sensitization of C nociceptors. *Brain* 127:1159-1171, 2004
59. Watanabe S, Kakigi R, Hoshiyama M, Kitamura Y, Koyama S, Shimojo M: Effects of noxious cooling of the skin on pain perception in man. *J Neurol Sci* 135:68-73, 1996
60. Widar M, Samuelsson L, Karlsson-Tivenius S, Ahlstrom G: Long-term pain conditions after a stroke. *J Rehabil Med* 34: 165-170, 2002
61. Witting N, Svensson P, Jensen TS: Differential recruitment of endogenous pain inhibitory systems in neuropathic pain patients. *Pain* 103:75-81, 2003
62. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M: Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain* 138:22-28, 2008
63. Yu D: Shoulder pain in hemiplegia. *Phys Med Rehabil Clin N Am* 15:683-697, 2004