ORIGINAL ARTICLE

Multimodal and Widespread Somatosensory Abnormalities in Persistent Shoulder Pain in the First 6 Months After Stroke: An Exploratory Study

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ABSTRACT. 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;93:1968-74.

Objective: To explore the role of multimodal and widespread somatosensory abnormalities in the development of persistent poststroke shoulder pain (pPSSP) in the first 6 months after stroke.

Design: Prospective inception cohort study.

Setting: Stroke units of 2 teaching hospitals.

Participants: The data of a strict selection of patients (N=31) with a clinical diagnosis of stroke were analyzed.

Interventions: Not applicable.

Main Outcome Measures: The development of pPSSP within the first 6 months after stroke. Bilateral sensation and pain thresholds at 3 (t1) and 6 (t2) months, and conditioned pain modulation (CPM) at 3 months after stroke. Clinical examination within 2 weeks after stroke (t0), at t1, and at t2.

Results: pPSSP (n=9) was associated with increased sensation and pain threshold ratios at the affected side (t1, t2), and with reduced cold pain tolerance at the unaffected side (t1). CPM was not different from patients without pPSSP (n=22). Notably, in patients with pPSSP reporting increased sensation on clinical examination, multiple body sites across multiple stimulus modalities were involved, and increased sensation persisted from t1 to t2.

Conclusions: pPSSP in the first 6 months after stroke was associated with somatosensory loss to both innocuous and noxious stimuli (affected side). In addition, pPSSP was associated with sensitization to cold pain (unaffected side) and with widespread sensitization to multimodal innocuous stimuli (affected side). The results support the notion that central somatosensory sensitization could play an important role in the development of pPSSP, the maintenance of pPSSP, or both.

Key Words: Central nervous system sensitization; Rehabilitation; Sensory thresholds; Shoulder pain; Stroke.

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POSTSTROKE SHOULDER PAIN (PSSP) is traditionally considered and clinically managed as peripheral nociceptive pain. However, recent studies suggest that the development of PSSP may be related to abnormal central somatosensory processing and central nervous system sensitization both in the acute[1-5] and chronic[6-9] phases after stroke.[10] Theoretically, somatosensory abnormalities in patients with PSSP may be explained by central lesions affecting somatosensory pathways as well as by ongoing nociceptive input from the shoulder.[11,12] In addition, other factors, either predisposing or related to the stroke or to ongoing pain, may indirectly contribute to abnormal somatosensory processing in patients with PSSP, such as depression[6,13,14] and altered cognitions.[15,16]

In the chronic phase after stroke, multimodal somatosensory abnormalities, including sensory loss and sensitization, have been reported for both the affected and unaffected sides in patients with persistent PSSP (pPSSP), suggesting involvement of both peripheral and central pain mechanisms.[6,7] Moreover, these patients often reported neuropathic-like pain complaints which, combined with an abnormal spino-thalamo-cortical function, could be indicative of neuropathic pain.[8,17]

Recently, pPSSP was found to be associated with clinical signs indicative of sensitization already in the first 6 months after stroke. Notably, sensitization seemed to be part of a vicious cycle of pain, limited range of shoulder motion, and reinjury, which could play a key role in the development and maintenance of pPSSP.[4] However, since this study focused merely on the presence, rather than on the severity and extensiveness of somatosensory abnormalities, the assessment was limited to a clinical examination at the affected side.

List of Abbreviations

CPM	conditioned pain modulation
DN4	neuropathic pain diagnostic questionnaire
EPT	electrical pain threshold
EPTT	electrical pain tolerance threshold
EST	electrical sensation threshold
NoPSSP	pain-free stroke patients
pPSSP	persistent poststroke shoulder pain
PPT	pressure pain threshold
PSSP	poststroke shoulder pain
QST	quantitative sensory testing
TDT	tactile detection threshold
VDT	vibration detection threshold

In the present exploratory study, we used electrical and mechanical quantitative sensory testing (QST) and conditioned pain modulation (CPM) to assess bilateral somatosensory abnormalities and endogenous pain modulation in a strict selection of patients at 3 and 6 months after stroke. In addition, a clinical examination was performed within 2 weeks and at 3 and 6 months after stroke, of which the results for the hand, arm, and face were analyzed separately.

METHODS

Participants

This study was part of a prospective cohort study on the development of pPSSP in the first 6 months after stroke. A detailed account of the strict inclusion procedure, including a listing of all exclusion criteria, has been published previously.[4] All consecutive stroke patients (age ≥18y) admitted to the neurologic and stroke units of 2 teaching hospitals in the Netherlands with a clinical diagnosis of stroke (n=357) were screened for participation between May and December 2009. A total of 281 patients were excluded, and 76 patients were approached for participation. The final study population consisted of 31 stroke patients. All participants sustained a first-ever cortical or subcortical unilateral stroke (infarction or hemorrhage) resulting in somatosensory and/or motor symptoms or signs. None of the participants presented with severe depressive or cognitive complaints, diabetic neuropathies, central poststroke pain, or shoulder-hand syndrome.[4] pPSSP was defined as nonremitting shoulder pain confined to the shoulder and/or C5 dermatome of the contralesional side with an onset after stroke, present during rest or during active or passive motion at both 3 and 6 months poststroke (n=9). Patients who recovered from PSSP after t1 (n=2) were excluded from the analysis. Patients who did not develop pain during the study period or who had PSSP only at baseline and not at 3 and 6 months after stroke (n=3) were included in the control group (pain-free stroke patients [NoPSSP], n=22). The study was approved by the local medical ethical committee. Patients received oral and written information about the study protocol and signed informed consent before participation.

Study Protocol

Patients were examined within 2 weeks (t0), and at 3 (t1) and 6 months (t2) after stroke. A clinical and pain examination was performed at each time point. QST was performed at t1 and t2. CPM was only performed at t1, in a subgroup of pPSSP (n=4) and NoPSSP (n=10) patients. All data were collected by the same researcher (M.R.).

Demographic and Clinical Data at t0

Demographic and clinical data have been reported elsewhere.[4] Here, the age, sex, type of stroke (ischemic, hemorrhagic), lesion side, days since stroke onset, prestroke pain, and upper extremity motor function (Motricity Index, 0, complete paresis; 100, no paresis)[18] at t0 are reported.

Pain Complaints in Patients With pPSSP

Pain complaints and the presence of spontaneous or evoked paresthesias and dysesthesias were recorded at t0, t1, and t2 using a pain diagram. Paresthesia was defined as an abnormal sensation, whereas dysesthesia was defined as an unpleasant abnormal sensation according to general accepted pain terminology.[19] Pain characteristics included PSSP intensity during rest and during movement (0, no pain; 10, maximum conceivable pain), and PSSP distribution, frequency, and pattern. Neuro-pathic PSSP complaints were assessed using the neuropathic pain diagnostic questionnaire (DN4), which consists of 10 items including pain descriptors and somatosensory signs. A positive score on at least 4 items is suggestive of pain of predominantly neuropathic origin.[17,20]

Clinical Examination

The details of the clinical examination can be found elsewhere.[4] In brief, sensation to touch, cold, and sharpness was tested at the face, upper arms, hands, and lower legs. Proprioception was tested at the thumbs of both hands. Tests were always performed first at the unaffected side. Subjects had to indicate whether sensation at the affected side was equal, diminished, or increased compared with the unaffected side. All tests were perceived as being painless at the unaffected side. Painful evoked sensations at the affected side were scored as allodynia,[21] whereas unpleasant and abnormal (but painless) evoked sensations were scored as dysesthesia.[19] If the evoked sensation was reported as being merely abnormal, this was recorded as paresthesia.[19] The sensations recorded at the arm, hand, and face were analyzed separately.

Quantitative Sensory Testing

All QST thresholds, except the vibration detection threshold (VDT), were determined on the affected (contralesional) and unaffected (ipsilesional) sides as described previously.[6] The VDT was determined at the styloid process of the ulnar bone using a 128-Hz Rydel Seiffer tuning fork.[a] The tuning fork was maximally activated and, while the vibration decayed, subjects were asked to respond as soon as they no longer perceived the vibration. The VDT was defined as the highest score at which the vibration could still be perceived (0, maximal vibration; 8, minimal vibration). The VDT was recorded once at each side. All other tests were performed over the middle deltoid muscle. The tactile detection threshold (TDT) was determined at 2 locations using Semmes-Weinstein filaments,[b] and was defined as the smallest filament that could be perceived at both locations. The pressure pain threshold (PPT) was determined using a pressure algometer[c] with a stimulation surface of 1cm^2, a slope of 50kPa/s, and a cutoff point of 1000kPa, and was defined as the pressure intensity at which patients first perceived the pressure as painful. The PPT was determined at 3 locations and averaged for further analysis.

The electrical sensation threshold (EST), electrical pain threshold (EPT), and electrical pain tolerance threshold (EPTT) were determined using a custom-built stimulator (pulse width, 0.2ms; frequency, 100Hz; ramp, 0.4mA/s; maximum stimulus amplitude, 16mA) that was attached to the upper arm via 2 silver/silver chloride electrodes. Patients could manually activate the stimulator. The EST was defined as the stimulus intensity at which the electrical pulses were perceived for the first time; the EPT as the stimulus intensity at which the electrical pulses were perceived as both stinging and annoying; and the EPTT as the stimulus intensity at which the electrical pulses were perceived as burning and very annoying. Thresholds were determined 4 times at each side, of which the last 3 were averaged for analysis. Patients were trained to determine these thresholds reliably before the actual measurements. In addition to the raw QST data, a within-subject ratio was calculated for all QST thresholds (affected/unaffected side).[22]

Conditioned Pain Modulation

CPM assesses the effect of a heterogeneously applied noxious conditioning stimulus on pain thresholds or scores. CPM commonly leads to increased pain thresholds, reduced pain

scores, or both. This effect is thought to be mediated primarily by the activation of supraspinal descending inhibition acting at the level of the spinal cord.[23-26] The CPM procedure of this study was similar to that described previously.[6] After the QST procedure, patients placed their unaffected hand in a polystyrene box filled with ice water (0–0.5°C). Patients were instructed to keep their hand in the water as long as tolerable (maximum 3min). Immersion time was recorded as a measure of cold pain tolerance. After removing the hand from the water, patients rated the pain in their hand (0, no pain; 10, maximum conceivable pain). Directly afterwards, the EPT and PPT were determined twice at the affected side in a similar manner as before. The 2 thresholds were averaged for further analysis. CPM was then assessed by calculating a pre-post ratio of the QST thresholds measured before and after the cold pressor test (thresholds post/pre).

Statistical Analysis

Statistical software package SPSS 16.0 for Windows[d] was used. For each group, average and SDs, median (range), or frequencies were determined. QST data and ratios did not have a normal distribution. To allow for testing under normality assumptions, all QST thresholds and ratios were log-transformed before statistical analysis, similar to previous studies.[6,27] Differences between groups for raw QST thresholds (unaffected side only), QST threshold ratios, and CPM data were statistically tested using 1-way analyses of variance. Differences in frequencies of abnormal clinical somatosensory signs (increased/diminished sensation, allodynia/dysesthesia, paresthesia) were statistically tested only when the difference between groups was deemed clinically relevant—that is, greater than 30% (χ^2 tests). For all tests, statistical significance was assigned at the $P<.05$ level using 2-tailed analysis.

RESULTS

Demographic and Clinical Data

All patients had an ischemic stroke (table 1). Prestroke pain was equally common in both patient groups.

Pain Complaints in Patients With pPSSP

Pain was increased during movement in all patients at all time points and occurred mostly in attacks (table 2). Based on the DN4, only 1 patient with pPSSP could be classified as having neuropathic pain (t0 and t1). Frequencies of self-reported dysesthesia and paresthesia were generally low and were not different between groups (data not presented).

Clinical Examination

At t0, diminished proprioception (hand) was more common in patients who later developed pPSSP (table 3). At t1, dimin-

Table 1: Demographic and Clinical Data at t0

Characteristics	pPSSP (n=9)	NoPSSP (n=22)
Age (y)	72±10	65±13
Men	6 (67)	8 (36)
Ischemic stroke	9 (100)	22 (100)
Right hemispheric stroke	6 (67)	14 (64)
Baseline (days after stroke)	8±3	7±3
Prestroke pain	3 (33)	8 (36)
Motor function	47 (0–100)	76 (9–100)

NOTE. Values are mean ± SD, n (%), or median (range).

Table 2: Pain Complaints in Patients With pPSSP

Pain Characteristics	t0 (n=4)	t1 (n=9)	t2 (n=9)
Pain intensity			
Rest	1.5 (0–5)	0 (0–4)	0 (0–3)
Move	5 (3–10)	8 (7–10)	6 (3–10)
Pain worsened by movement	4	9	9
Pain frequency			
Sometimes	1	3	1
>2d/wk	0	0	2
Daily	2	6	6
Constant	1	0	0
Pain pattern			
Attacks	3	7	7
Intermittent	1	2	2
Neuropathic pain (DN4 ≥4)	1	1	0
Analgesic medication	4	2	3

NOTE. Values are median (range) or n. Analgesic medications were paracetamol or nonsteroidal anti-inflammatory drugs.

ished touch sensation (arm and face) and diminished proprioception (hand) were significantly more common in patients with pPSSP. At t2, increased sensation to cold (arm) and decreased sensation to sharpness (face) were more common in patients with pPSSP. In addition, increased sensation to touch and cold (all locations) was only observed in patients with pPSSP. All patients with pPSSP with increased sensation to cold or sharpness at the affected side at t2 also reported increased sensation to cold or sharpness at t1. Frequencies of evoked allodynia/dysesthesia and paresthesia at the affected side were generally low and were not different between groups (data not presented).

Quantitative Sensory Testing

At the unaffected side, thresholds were not significantly different between groups (table 4). Except for the VDT, mean QST thresholds ratios (affected/unaffected side) were generally higher in patients with pPSSP (fig 1). This was significant for the EPT and PPT ratios at t1, and for the TDT, EPT, EPTT, and PPT ratios at t2.

Conditioned Pain Modulation

Cold pain tolerance was significantly lower in patients with pPSSP as compared with pain-free patients (median [range]: 42s [22–62] vs 117s [30–180], $P=.043$). No significant differences were observed between groups for the EPT ratio (1.00 [.59–3.07] vs 1.45 [1.04–2.55], $P=.314$), the PPT ratio (.95 [.80–1.12] vs 1.08 [.73–1.42], $P=.508$), or the cold pressor pain intensity (6 [5–8] vs 7 [2–8]).

DISCUSSION

This study explored multimodal and widespread somatosensory abnormalities in patients with pPSSP in the first 6 months after stroke. pPSSP was associated with increased sensation and pain threshold ratios at the affected side (t1, t2), and with reduced cold pain tolerance at the unaffected side (t1). CPM was not different from patients without pPSSP. Notably, in patients with pPSSP reporting increased sensation on clinical examination, multiple body sites across multiple stimulus modalities were involved, and increased sensation persisted from t1 to t2.

Combined Somatosensory Loss and Sensitization

Although previous studies have reported an association between PSSP and clinical signs of innocuous somatosensory loss

Table 3: Clinical Examination of Affected Versus Unaffected Side

Sensation to Stimuli at Different Locations	t0		t1		t2	
	pPSSP (n=9)	NoPSSP (n=21)	pPSSP (n=9)	NoPSSP (n=22)	pPSSP (n=9)	NoPSSP (n=22)
Arm						
Touch						
−	4 (44)	3 (14)	5 (56)*	2 (9)	3 (33)	2 (9)
+	0 (0)	1 (5)	0 (0)	0 (0)	1 (11)	0 (0)
Cold						
−	2 (22)	4 (19)	2 (22)	1 (5)	2 (22)	5 (23)
+	1 (11)	2 (10)	3 (33)	2 (9)	3 (33)*	0 (0)
Sharpness						
−	4 (44)	7 (33)	2 (22)	5 (23)	2 (22)	3 (14)
+	2 (22)	2 (10)	2 (22)	0 (0)	2 (22)	2 (9)
Hand						
Touch						
−	4 (44)	7 (33)	4 (44)	4 (18)	4 (44)	5 (23)
+	1 (11)	2 (10)	0 (0)	0 (0)	2 (22)	0 (0)
Cold						
−	4 (44)	7 (33)	4 (44)	5 (23)	4 (44)	6 (27)
+	2 (22)	2 (10)	3 (33)	2 (9)	2 (22)	0 (0)
Sharpness						
−	5 (56)	6 (29)	2 (22)	4 (18)	3 (33)	3 (14)
+	1 (11)	4 (19)	3 (33)	2 (9)	3 (33)	4 (18)
Proprioception						
−	6 (67)*	5 (24)	4 (44)*	2 (9)	3 (33)	2 (9)
Face						
Touch						
−	2 (22)	2 (10)	4 (44)*	2 (9)	4 (44)	4 (18)
+	0 (0)	1 (5)	0 (0)	0 (0)	1 (11)	0 (0)
Cold						
−	3 (33)	4 (19)	2 (22)	3 (14)	1 (11)	1 (5)
+	1 (11)	2 (10)	3 (33)	1 (5)	1 (11)	0 (0)
Sharpness						
−	5 (56)	6 (29)	2 (22)	0 (0)	3 (33)*	0 (0)
+	1 (11)	2 (10)	3 (33)	3 (14)	2 (22)	0 (0)

NOTE. Values are n (%).
Abbreviations: −, diminished; +, increased.
*Risk difference >30% and $P<.05$ (χ^2 tests).

at the affected side,[1-5,9,28,29] somatosensory sensitization and noxious sensory functions have not been commonly assessed. Only recently, pPSSP has been associated with widespread bilateral somatosensory loss and sensitization to several multimodal innocuous and noxious stimuli in the chronic phase after stroke,[6-8] and with (clinically) increased sensation to innocuous stimuli at the affected side in the first 6 months after stroke.[4] By using QST and CPM and by analyzing clinical assessments of the hand, arm, and face separately, the present study extended these findings and showed that pPSSP could be associated with widespread and multimodal somatosensory abnormalities already in the first 6 months after stroke. As was reported for the chronic phase after stroke, these abnormalities included both somatosensory loss and sensitization, and were observed in response to both innocuous and noxious stimuli. In addition, longitudinal assessment of these abnormalities showed that sensitization persisted over time from 3 to 6 months after stroke. Together, these findings provide further evidence for the importance of somatosensory abnormalities in the pathophysiology of pPSSP.

Traditionally, the relationship between pPSSP and somatosensory loss has been explained by the "trauma hypothesis," in which somatosensory loss in combination with impaired vol-

untary motor control and/or hemi-inattention is thought to increase the risk of (repetitive) microtrauma of soft tissues around the shoulder joint, leading to subsequent pain.[30] Indeed, PSSP complaints in the early phase after stroke are mostly indicative of nociceptive pain, and only a minority of patients with PSSP can be diagnosed as having central neuropathic pain.[4] However, if somatosensory loss caused by the brain lesion is multimodal and widespread, as was found in this study, this is likely to affect the central processing of (subsequent) noxious input resulting from trauma or injury. As has been suggested for other types of persistent pain,[31,32] this could indirectly predispose patients to develop central sensitization, (persistent) pain, or both.[11] Indeed, this study showed multimodal and widespread somatosensory sensitization in patients with pPSSP, suggesting that sensitization occurred at the central rather than peripheral level. In addition, a predisposition to develop central sensitization after stroke would be consistent with frequent accounts of worsened prestroke[33] and mixed pain,[8,34] and with observations of somatosensory sensitization in pain-free stroke patients.[6]

Table 4: QST: Raw Thresholds

	t1		t2	
Thresholds	pPSSP (n=9)	NoPSSP (n=22)	pPSSP (n=9)	NoPSSP (n=22)
Unaffected side				
VDT	8 (7–8)	7 (6–8)	8 (7–8)	8 (6–8)
TDT	3.61 (2.83–4.31)	3.61 (2.82–4.31)*	3.61 (2.83–4.31)	3.61 (2.82–4.31)
EST	1.18 (0.59–2.16)	1.10 (0.43–2.16)	1.02 (0.65–2.08)	1.06 (0.58–2.14)
EPT	2.52 (1.45–3.53)	2.16 (1.10–10.09)	2.97 (1.33–7.07)	1.89 (0.95–12.54)
EPTT	3.31 (1.29–6.57)	3.62 (1.75–13.61)	5.13 (1.28–11.27)	3.01 (1.36–15.47)
PPT	332 (172–597)	335 (156–939)	305 (115–669)	275 (165–1000)
Affected side				
VDT	7 (1–8)	7 (1–8)	8 (1–8)	8 (1–8)
TDT	4.31 (2.83–6.65)	3.61 (2.83–4.31)*	4.31 (3.61–6.65)	3.61 (2.83–4.56)
EST	1.84 (0.69–7.57)	1.05 (0.57–3.24)	1.56 (0.64–16.00)	1.09 (0.60–2.89)
EPT	2.74 (1.57–11.33)	2.32 (0.80–7.70)	2.52 (2.11–16.00)†	1.85 (0.69–13.15)
EPTT	4.56 (2.78–8.27)	3.54 (1.13–11.59)	5.24 (3.30–16.00)	2.68 (0.69–16.00)
PPT	353 (224–587)	276 (158–1000)	350 (213–621)	237 (100–1000)

NOTE. Values are median (range). For VDT: 0, no sensation; 8, normal sensation.
*n=21.
†n=8.

Endogenous Pain Modulation

Impaired endogenous pain modulation may play an important role in the development of central sensitization and persistent pain. In several types of chronic pain, such as fibromyalgia,[35] osteoarthritis,[36] and whiplash,[31] CPM was found to be reduced or absent. In addition, CPM may predict the development of chronic pain.[31,32] In the present study, no significant differences were found between groups. This seems consistent with 2 previous studies[6,37] on CPM in patients with poststroke pain in the chronic phase after stroke that reported normal CPM, although the results have not yet been replicated. Moreover, the interpretation of the present results is complicated by the small sample size and by the possible influence of differences between groups in the timing and intensity of the conditioning stimulus.[38] The relationship between pPSSP and CPM should therefore be reassessed in a larger study.

Study Limitations

This was an explorative study assessing multiple modalities and body sites in a relatively small study sample in the first 6 months after stroke, and only continuous data and data showing a risk difference of at least 30% were statistically tested. By using a strict selection of patients we aimed to minimize the influence of many potential confounders, including premorbid pain complaints, other neurologic or musculoskeletal diseases, cognitive deficits, and bilateral stroke symptoms. Ideally, the present results should be replicated in a larger sample with a longer study duration.

The pain research tools that were used in this study have some limitations. First, the subjective nature of QST, and subsequent demands on cooperation of the patient and the testing environment, hampered valid assessment at t0.[39] Still, objective assessments (eg, electroencephalography) also contain many disadvantages (lab-bound and time-consuming). Future studies may increase their methodological strength by assessing QST at an earlier time point (eg, at 1mo), as long as the conditions for valid QST assessment can be met. Second, the electrical stimulation that was used in the present study bypasses the peripheral receptors and, compared with natural stimuli, provides a more direct assessment of the nervous system. However, electrical stimulation is not modality specific, and the recorded thresholds represent an unknown assembly of both nociceptive and innocuous fiber types. Therefore, other QST protocols,[27] including more extensive mechanical and thermal testing, may provide additional information on the
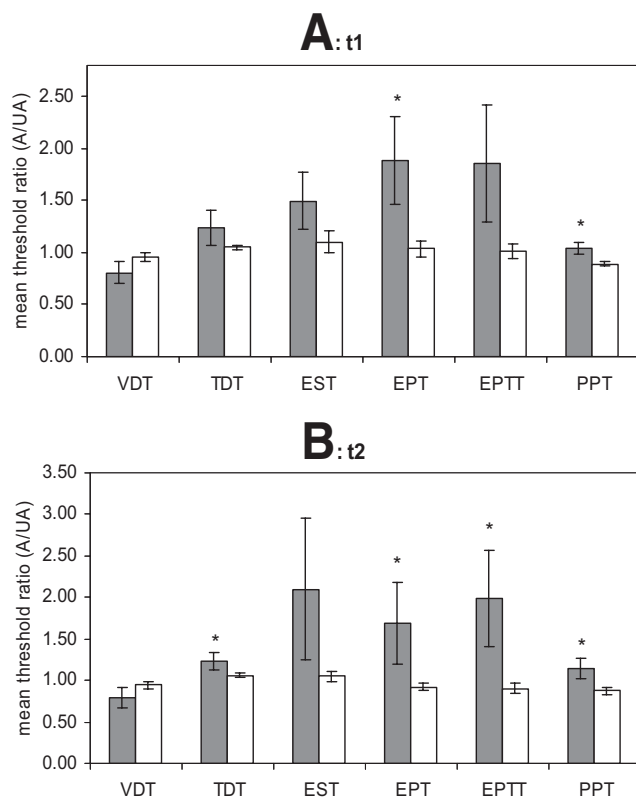

Fig 1. QST: threshold ratios at t1 (A) and t2 (B). Results are presented as mean ± SE. Gray bars represent the pPSSP group (n=9) and white bars the NoPSSP group (n=22). Abbreviation: A/UA, affected/unaffected. *P<.05.

specific receptors and fibers involved in the bilateral somatosensory abnormalities found in patients with PSSP.

CONCLUSIONS

This study showed that pPSSP was associated with widespread and multimodal somatosensory abnormalities already in the first 6 months after stroke. These included both somatosensory loss and sensitization, to both innocuous and noxious stimuli, at both the affected and unaffected body sides. Importantly, somatosensory sensitization persisted over time. The results support the notion that central somatosensory sensitization could play an important role in the development of pPSSP, the maintenance of pPSSP, or both, and warrant more attention for the assessment, monitoring, and normalization of abnormal central somatosensory processing after stroke.[40]

Several interventions may be beneficial for restoring somatosensory functions and for reducing somatosensory sensitization, including electrical stimulation,[41,42] mirror therapy, mental imagery,[43,44] or pharmacologic interventions (eg, antidepressants and anticonvulsants).[33]

Future studies should focus on a better understanding of the pathophysiologic role of somatosensory abnormalities in the development of poststroke pain, for example, by comparing somatosensory abnormalities between patients who develop persistent pain after stroke, patients who develop pain but recover within 3 months, and patients who do not develop pain at all. Given the above-mentioned considerations, this would require large multicenter studies based on collaborative efforts of clinicians and researchers in rehabilitation, pain, and neurology.

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