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Altered cortical somatosensory processing in chronic stroke: A relationship with post-stroke shoulder pain

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Abstract. Post-stroke shoulder pain (PSSP), traditionally regarded as purely nociceptive pain, is often persistent and the mechanisms underlying the pain complaints are not well understood. This explorative study is the first to address the possible changes in cortical somatosensory processing in patients with PSSP. Cortical potentials were recorded following intracutaneous electrostimulaton in stroke patients with chronic PSSP ($n = 6$), pain-free stroke patients (PF, $n = 14$) and healthy controls (HC, $n = 20$) using EEG. Amplitudes and latencies of both sensory discriminative (N90) as well as cognitive evaluative (N150, P200, the N150-P200 peak-to-peak difference and P300) evoked potential components were evaluated. Stroke was associated with reduced N150 and P300 amplitudes and increased N90, N150 and P300 latencies at both sides. Compared to PF and HC, the P200 and N150-P200 latencies were increased in PSSP patients after stimulation at both sides, even when comparing subgroups with similar lesion size and location. Stroke was associated with reduced sensory-discriminative as well as with reduced cognitive-evaluative cortical somatosensory processing. This reduction was more pronounced in patients with PSSP and may be related to the central effects of persistent nociceptive pain.

Keywords: Stroke, shoulder pain, somatosensory function, evoked potentials

1. Introduction

Pain is a common complication after stroke. In recent studies, post-stroke shoulder pain (PSSP) has been reported in about 40% of patients [1,21,22,35,38,47,51]. PSSP is typically regarded as nociceptive pain [57]. Nociception occurs after tissue damage and can be defined as the neural processes of encoding and processing noxious stimuli [37]. In contrast, central post-stroke pain (CPSP) is diagnosed when the pain is a direct consequence of a brain lesion affecting the central somatosensory system [37]. CPSP is observed in 8% of stroke patients [34].

In PSSP, treatment aimed at reducing peripheral nociception through relief of biomechanical stress or capsular inflammation (e.g. by strapping or corticosteroid injection) is often unsatisfactory and many patients report persistent pain [35,57]. In addition, patients with chronic PSSP may present with several signs of

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central sensitization (allodynia, generalized hyperalgesia) [50]. Indeed, the clinical presentations of patients with PSSP and CPSP show considerable overlap [34, 49], suggesting that central (pain) processing may be altered in patients with PSSP.

Theoretically, altered central (pain) processing in PSSP may be directly due to the brain lesion and/or indirectly due to central changes associated with ongoing nociception from the periphery. For example, brain lesions within the spinothalamocortical tract may lead to increased supra-spinal excitability and have been related to the development of CPSP [34]. Indirectly, ongoing pain from the periphery may lead to sensitization of spinal and supra-spinal structures [13]. In addition, ongoing pain may induce functional [20] as well as structural [40] cortical reorganization of somatosensory and motor systems, as has been observed in patients with chronic neuropathic or musculoskeletal pain. Moreover, the central processing of somatosensory stimuli has been shown to be impaired in patients with chronic pain [56] in whom pain is suggested to cause a chronic interruption of attentional engagement [19].

The central processing of somatosensory stimuli can be objectively assessed using cortical evoked potentials (EPs). EPs can be measured at the scalp in response to various peripheral stimuli (i.e. laser, electrical stimulation). In pain-free stroke patients, abnormalities in early EPs after median (N20, P25) or tibial (N35, P40) nerve stimulation have been related to impaired processing of input from the dorsomedial lemniscal pathway, resulting in reduced touch sensation and proprioception [33,63], whereas abnormalities in laser evoked potentials have been related to impaired processing of input from the spino-thalamo-cortical tract [7], resulting in reduced thermal and pinprick sensations [27, 64]. Late EP components, for example in response to electrocutaneous stimulation (N150, P200, P300), have been related to cognitive-evaluative processes involved in the processing of somatosensory stimuli [41, 65,67]. In stroke research, assessment of late electrical EP components has received little attention and results are inconsistent [15,66]. So far, there is no report of any type of EP assessment in patients with PSSP. In patients with central pain, the presence of pain has been related to reduced amplitudes and/or longer EP latencies suggesting that somatosensory deficits are a prerequisite for the development of neuropathic pain [10, 25,29]. In contrast, central pain [26,52] and experimentally induced central sensitization [39] have also been associated with increased EP amplitudes. So far, the precise relation between (clinical) pain complaints and alterations in EPs is (therefore) not well understood.

The goal of this explorative study was to investigate whether PSSP was associated with alterations in the cortical processing of somatosensory stimuli. Cortical potentials were evoked in stroke patients with chronic PSSP, pain-free stroke patients (PF) and healthy controls (HC) using intracutaneous electrical stimulation at the middle finger of both hands at two stimulation intensities and were recorded using EEG. Amplitudes and latencies of middle-late and late EP components (N90, N150, P200, the N150-P200 peak-to-peak difference and P300) were evaluated. In addition, sensory examination was performed using clinical examination and quantitative sensory testing (QST).

2. Methods

2.1. Subjects

Cortical somatosensory processing was assessed in stroke patients with persistent shoulder pain (PSSP, $n = 10$), pain-free stroke patients (PF, $n = 17$) and healthy controls (HC, $n = 21$). Patients were recruited in a rehabilitation center in the Netherlands (Roessingh Rehabilitation Center in Enschede) as part of a larger cross-sectional study. The outpatient databases were searched for stroke patients that had been hospitalized in the two 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 one of the researchers (M.R.) by mail. Healthy subjects (age 40–60 years) were recruited through advertisements in local community centers and newspapers.

All patients (age $>$ 18 years) sustained a unilateral brain infarction (clinical diagnosis). All patients had a stroke onset of at least six months prior to participation. Patients with persistent shoulder pain (daily pain lasting longer than three subsequent months) with an onset post-stroke were allocated to the PSSP group. Pain-free patients with no long-lasting pain complaints ($>$ one week in the last three months) were allocated to the PF group. Exclusion criteria were: pregnancy, trauma, infection, signs of any possible concomitant neurological condition (e.g. epilepsy, multiple sclerosis, peripheral neuropathy), the presence of other pain complaints (e.g. wide-spread pain, complex regional pain syndrome or shoulder-hand syndrome) or not being able to reliably determine sensory thresholds during a training session

prior to the experiment. Healthy control subjects had to be free of any neurological or psychiatric disorder, diabetes mellitus, psychotropic medication or long-lasting pain complaints. The study was approved by the local human ethics committee. All subjects received written and oral information about the study protocol and all participants gave informed written consent prior to their participation.

2.2. Demographics and medical examination

General demographic characteristics such as age, sex and (for the patients) stroke latency, lesion side, lesion size, lesion location and medication use were registered. Lesion size (small, medium, large, very large) and lesion location (cortical, subcortical, both cortical and subcortical, involvement of insula, anterior cingulate cortex and/or thalamus) were assessed by a radiologist from computed tomography or magnetic resonance scans (when available). Cognitive state was assessed using the Mini Mental State Exam (MMSE, score: 0–30) and severe cognitive impairment was defined as an MMSE score < 24 [58]. 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 [60]. Arm function was assessed using the Motricity Index ($0 =$ complete paresis, $100 =$ normal function) [14]. The presence of glenohumeral subluxation was assessed by palpation (in steps of 5 mm). Shoulder pain intensity was evaluated both at rest and during movement with an 11-point Numeric Rating Scale (NRS, $0 =$ no pain, $10 =$ maximum conceivable pain). Pain duration was registered. In addition, neuropathic-like shoulder pain complaints were assessed using the neuropathic pain diagnostic questionnaire (DN4, score: 0–10) [6]. The DN4 consist of ten items comprising pain descriptors and somatosensory signs. Scoring at least four items positively is suggestive of pain of predominantly neuropathic origin. Patients were classified as having neuropathic-like shoulder pain when scoring at least 4 on the DN4 [6].

2.3. Sensory examination

Sensory examination consisted of clinical examination and mechanical and electrical QST and took place in a separate experimental session, preceding the evoked potential recordings. Clinical examination included subjective sensation (normal, increased, diminished, allodynia) to touch, cold and pinprick at the upper arm and proprioception of the thumb. All QST thresholds were determined at the upper arm (C5 dermatome) using the method of limits and the start side of stimulation was randomized between subjects [12]. Tactile detection thresholds were determined using Semmes Weinstein filaments (sizes: 2.83, 3.61, 4.31, 4.56, 6.65). Pressure pain thresholds were determined using a somedic pressure algometer (stimulation surface: 1 cm2, slope: 50 kPa, maximum output: 2000 kPa). For the electrical QST thresholds an ambulant electrical stimulator was used (pulse width: 0.2 ms, frequency: 100 Hz, ramp: 0.4 mA/s, Ag/AgCl electrodes (AMBU Denmark) with stimulation surface: 95 cm2). Subjects could manually activate the stimulator by pressing a switch. To determine the electrical sensation threshold (EST), subjects were instructed to release the switch when the electrical pulses were perceived for the first time. To determine the electrical pain threshold (EPT), subjects were instructed to release the switch when the electrical pulses were perceived as both stinging and annoying. To determine the electrical pain tolerance threshold (EPTT) subjects were instructed to release the switch when the electrical pulses were perceived as burning and very annoying. Patients were trained to determine electrical QST thresholds reliably prior to participating in the experiment. For analysis, absolute thresholds were used for the unaffected side and relative (affected/unaffected) thresholds for the affected side. Ratios were log-transformed prior to statistical analysis [48].

2.4. Evoked potentials

2.4.1. Electrical stimulation

Cortical potentials were evoked at the tip of the middle finger of both hands by intracutaneous electrical stimulation according to the method described by Bromm and Meier [8]. With this method, combined activation of Aβ and Aδ cutaneous afferents is achieved. Two electrodes with a 1 mm diameter tip of gold in insulating material were used. The electrode was placed in a small opening that was drilled in the upper layer of the skin using a dental gimlet (diameter: 1 mm). The sensation threshold (Is) had to be below 1 mA. If not, preparation was regarded insufficient and tried again. A rectangular surface electrode (4×9 cm Klinerva Blue Electrode) was placed at the distal part of the upper forearm as an anode. A battery-driven computer-controlled current stimulator was used to generate the stimuli. The stimulus was a bipolar rectangular current pulse with a stimulus duration of 0.2 ms. The Is and

pain threshold (Ip) were determined for each hand, using the ascending method of limits by increasing the stimulus amplitude from zero with steps of 0.1 mA. The Is was defined as the stimulation amplitude at which the stimulus was perceived for the first time. The Ip was defined as the stimulation amplitude at which the stimulus was first perceived as painful. Is and Ip were each determined three times and averaged. The final fixed stimulation amplitude (Ie) was calculated by averaging Is and Ip [61]. The intensity of the stimulus was varied using pulse modulation. Single pulses and pulse trains of five pulses were used. The inter-pulse interval used for the pulse trains was 5 ms. To make sure that stimulation with the pulse trains was tolerable, the trains were applied with increasing amplitude starting from Is before starting the actual protocol. If necessary, Ie was adjusted so that pulse trains were described as a tolerable but clear pricking painful sensation.

2.4.2. EEG recordings

Electrical brain activity was continuously recorded using a 64-channel EEG Refa-72 system (ANT, the Netherlands). A 64-channel Waveguard EEG cap with Ag/AgCl electrodes was used according to the international 10-5 system. All scalp electrode impedances were below 5 kΩ. The ground electrode was placed at the forehead or just below the right eye (depending on what provided the best raw signal). Two Ag/AgCl electrodes were placed just above and under the left eye to record the electrooculogram (EOG). Data was recorded using ASA software (ANT software BV, the Netherlands) with a sample frequency of 1024 Hz. The signals were filtered offline at band-pass 0.3–120 Hz. Data from -100 to -10 ms pre-stimulus was used for baseline correction. The time window of analysis was -100 ms pre-stimulus to 400 ms post-stimulus. Data recorded at Cz was referred to linked earlobes (A1A2) and data recorded at C3 and C4 was referred to Fz. All off-line data analysis was performed in Matlab®.

2.4.3. Procedure

The stimulus protocol consisted of 3 blocks. During each block, stimuli were delivered alternately to the affected and unaffected (PSSP and PF) or non-dominant and dominant (HC) side. Each hand was stimulated 20 times using 10 single pulse stimuli and 10 pulse train stimuli. The start side of stimulation was randomized between subjects. The order of stimulus intensity (1 or 5 pulses) was semi-randomized. The inter-stimulus-interval between two successive stimuli varied randomly between 5 and 7 seconds. In order to maintain attention, subjects were asked to verbally rate the perceived strength of each stimulus on an 11-point numeric rating scale (0 = no sensation, 10 = maximum conceivable pain). The first stimulus corresponded to a pulse train stimulus. Subjects were instructed to rate this first stimulus as a six on the numeric rating scale. Each block was followed by a short break. For each subject the average Ie (across the 3 blocks) was calculated for further analysis. NRS scores were not further analyzed.

2.4.4. EP analysis

First, trials with an EOG artifact exceeding $\pm$ 70 μV in a time window of -10 to -100 ms pre-stimulus and 60 to 400 ms post-stimulus were rejected. Non-rejected data was accepted after visual inspection for missed EOG or muscular artifacts. Over all blocks, at least 10 (out of 30) EP trials had to be available for analysis (for each hand and stimulus intensity) otherwise subjects were excluded. For each subject, the remaining trials were averaged separately for each of the used stimulus intensities (single pulse, pulse train) and for each hand (both hands: Cz-A1A2, right hand: C3-Fz, left hand: C4-Fz). In addition, EPs were averaged for each group (PSSP, PF, HC). Due to high variation across subjects, the amplitudes and latencies of late EP components were determined manually by visual inspection of the individual averaged EPs. The N90 EP component (around 90 ms post-stimulus) was detected in the contralateral EP (C3-Fz for right hand stimulation and C4-Fz for left hand stimulation). At the vertex (Cz-A1A2), the amplitudes and latencies of the N150 peak (negative peak around 150 ms), the P200 peak (positive peak around 200 ms) and P300 peak (positive peak around 300 ms) were determined. The peak-to-peak amplitude and latency for N150 and P200 (N150-P200) was calculated as well. For each group (PSSP, PF, HC), averages, standard deviations and standard errors were calculated for Ie (for each hand) and for the amplitude and latencies of the late EP components (N90, N150, P200, N150-P200 and P300 for each hand and stimulus intensity). Preliminary analysis showed that pulse train stimulation lead to higher EP amplitudes in all the EP components and in all groups alike. Furthermore, no latency differences were observed comparing single pulse to pulse train stimulation. Therefore, to increase statistical power, EPs after single pulse and pulse train stimulation were pooled.

Table 1
Demographic data and medical characteristics

	PSSP ($n = 6$)	PF ($n = 14$)	HC ($n = 20$)
Age	56 ± 9	*61 ± 9*	55 ± 7
Male/Female	4/2	8/6	8/12
Stroke latency (months)	19 ± 9	24 ± 9	
Right-hemispheric lesion	6 (100%)	9 (64%)	
Lesion confirmed (CT/MRI)	5 (83%)	9 (64%)	
Small/Moderate/Large/Very large	2/0/2/1	5/2/2/0	
Cortical/Subcortical/Both	4/1/0	5/2/2	
Insula/ACC/Thalamus	3/2/0	3/3/0	
Cognitive deficits (MMSE < 24)	0 (0%)	1 (7%)	0 (0%)
Depression score (20–80)	**49 ± 5**	34 ± 6	31 ± 5
Arm function (0–100)	*56 ± 44*	*70 ± 43*	100 ± 0
Glenohumeral subluxation	*4 (67%)*	*4 (29%)*	0 (0%)
Analgesics	PC (3), NSAID (1)		
Anti-depressants	TCA (3), SSRI (1)	TCA (1), SSRI (2)	

Data are presented as mean ± standard deviation or as number of patients (%). Abbreviations: PSSP: stroke patients with post-stroke shoulder pain, PF: pain-free stroke patients, HC: healthy controls, CT: computed tomography, MRI: magnetic resonance imaging, PC: paracetamol, ACC: anterior cingulate cortex, NSAID: non-steriodal anti-inflammatory drug, TCA: tricyclic antidepressant, SSRI: selective serotonin reuptake inhibitor. Patient data in italic is significantly different from HC ($p < 0.05$). PSSP data in bold is significantly different from PF ($p < 0.05$).

2.5. Statistical analysis

Statistical software package SPSS 16.0 for Windows was used (SPSS Inc., Chicago, IL, USA). For each group, frequencies or means ± standard deviations were calculated for the demographic data and for the results of medical and sensory examinations. Group differences for demographic, medical and sensory examinations were statistically tested using either Chi-square tests or Kruskal-Wallis (comparison of three groups) and Mann-Whitney U (pairwise comparisons) testing. Group differences for Ie and for amplitudes and latencies of the EP components (N90, N150, P200, N150-P200 and P300) were tested separately using a repeated measures analysis of variance with the between-subjects-factor 'Group' (PSSP, PF and HC) and the within-subjects-factor 'Side' (affected and unaffected for PSSP and PF, non-dominant and dominant for HC). Bonferroni correction was used for post-hoc multiple comparisons between groups. Significant interaction effects between 'Group' and 'Side' were evaluated using one-way analysis of variance for each side separately, using the factor 'Group' (PSSP, PF and HC). For all tests, statistical significance was assigned at the $p < 0.05$ level using two-tailed analysis.

To control for the potential confounding of lesion size and location, a sub-analysis was performed in which all patients without a confirmed lesion or with a very large lesion were excluded. The PF group was matched for lesion size and location to resemble the PSSP group. The sub-analysis was performed similarly as the overall analysis, however, statistical testing was only performed for amplitudes and latencies of the EP components.

3. Results

3.1. Demographic data and medical characteristics

Four PSSP and 3 PF patients and 1 HC subject were excluded from analysis because visible EP components were lacking or less than 10 (out of 30) EP trials (for each hand and stimulus intensity) were available. Thus, data from a total number of 6 PSSP and 14 PF patients and 20 healthy controls could be used for analysis. In patients with PSSP, pain duration was 20 ± 9 (mean ± SD) months and pain intensity was 3.7 ± 1.5 during rest and 6.0 ± 1.4 during movement. Two PSSP patients scored at least 4 on the DN4 and were classified as having neuropathic-like pain complaints. A summary of the demographics and medical examinations is presented for each group in Table 1. The groups were comparable for gender, lesion side, stroke latency and severe cognitive deficits. Although many patients in this study had right-hemispheric lesions, none of them showed clinical signs of severe hemi-inattention. In addition, the MMSE intersecting pentagons sub-task, assessing visuospatial neglect, was performed correctly by the majority of patients (only 1 PSSP patient and 3 PF patients failed on this sub-task). Age was significantly higher in the PF group. Larger brain lesions were

Table 2
Sensory examination

		PSSP ($n = 6$)	PF ($n = 14$)	HC ($n = 20$)
Clinical examination				
Touch	diminished	2 (33%)	3 (21%)	1 (5%)
	increased	0 (0%)	2 (14%)	0 (0%)
Cold	diminished	*3 (50%)*	*5 (36%)*	0 (0%)
	increased	1 (17%)	0 (0%)	1 (5%)
Proprioception	diminished	*3 (50%)*	*4 (29%)*	0 (0%)
	increased	0 (0%)	0 (0%)	0 (0%)
Pinprick	diminished	3 (50%)	4 (29%)	2 (10%)
	increased	2 (33%)	3 (21%)	3 (14%)
QST				
ratio A/UA, ND/D	TDT	**1.18 ± 0.20**	1.05 ± 0.18	0.97 ± 0.11
	EST	1.94 ± 1.26	1.02 ± 0.36	1.05 ± 0.39
	EPT	1.44 ± 0.96	1.45 ± 0.95	1.09 ± 0.40
	EPTT	1.17 ± 0.42	1.48 ± 0.98	0.92 ± 0.18
	PPT	1.04 ± 0.24	1.03 ± 0.27	1.03 ± 0.17
UA, D	TDT (size)	3.47 ± 0.56	3.49 ± 0.50	3.33 ± 0.45
	EST (mA)	1.18 ± 0.56	1.21 ± 0.55	0.91 ± 0.33
	EPT (mA)	4.25 ± 2.64	2.87 ± 1.89	3.57 ± 1.83
	EPTT (mA)	6.72 ± 3.60	5.72 ± 4.42	7.12 ± 2.12
	PPT (kPa)	363 ± 192	391 ± 137	443 ± 131

Data are presented as mean ± standard deviation or as number of patients. Abbreviations: PSSP: stroke patients with post-stroke shoulder pain, PF: pain-free stroke patients, HC: healthy controls, QST: quantitative sensory testing, A/UA: ratio affected/unaffected (patients), ND/D: ratio non-dominant/dominant (HC), TDT: tactile detection threshold, EST: electrical sensation threshold, EPT: electrical pain threshold, EPTT: electrical pain tolerance threshold, PPT: pressure pain threshold, UA: unaffected side (patients), D: dominant side (HC). Patient data in italic is significantly different from HC ($p < 0.05$). PSSP data in bold is significantly different from PF ($p < 0.05$).

more common in the PSSP group. PSSP was associated with significantly higher depression scores. Stroke was associated with reduced arm function, glenohumeral subluxation and dystrophic changes regardless of the presence of pain. Analgesics (paracetamol and non-steroidal anti-inflammatory drugs) were only used in the PSSP group. Several PSSP and PF patients used anti-depressants (either tricyclic antidepressants or selective serotonin reuptake inhibitors).

3.2. Sensory examination

The results of sensory examination are presented for each group in Table 2. At the affected side, diminished cold sensation and proprioception were more often observed in stroke patients (PSSP and PF) as compared to controls. Two PSSP patients reported pain in response to innocuous pinprick stimulation at the affected side. In addition, one of these patients also reported pain in response to the innocuous cold stimulus at the affected side. Tactile detection threshold ratios were significantly higher in patient with PSSP as opposed to HC. In addition, the mean electrical sensation threshold ratio was higher, however, this difference was not significant. At the unaffected side of PSSP patients, the mean electrical pain threshold was higher and the pressure pain threshold was lower, however, these differences were also not significant.

3.3. Evoked potentials

3.3.1. Stimulation amplitude

Mean stimulation amplitude (mA) ± standard deviation was 2.32 ± 0.80 (affected hand) and 1.88 ± 0.51 (unaffected hand) in PSSP patients, 1.91 ± 1.00 (affected hand) and 1.78 ± 0.84 (unaffected hand) in PF patients and 1.48 ± 0.37 (non-dominant hand) and 1.77 ± 0.59 (dominant hand) in HC subjects. Repeated measures analysis showed a significant interaction effect of 'Side' by 'Group'. Post-hoc testing showed that stimulation amplitude at the affected side was significantly higher in PSSP as opposed to HC ($p < 0.05$).

3.3.2. EP amplitudes

The grand average EPs calculated for each group are presented in Fig. 1 A-C (somatosensory cortex) and Fig. 1 D-F (vertex). Mean amplitudes ± standard errors of EP component are presented in Fig. 2 (A-E). Repeated measures analysis showed statistically significant differences between the groups ($F(10,148) =$

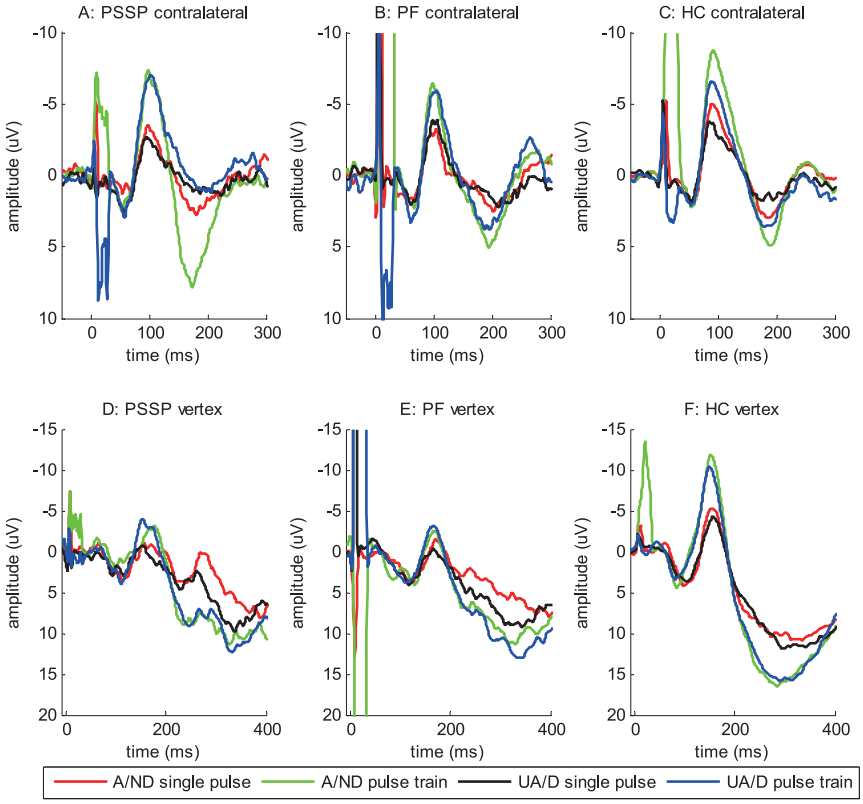

Fig. 1. A-C: Grand average EPs recorded at the somatosensory cortex ($C_{3/4}$-F_z), A: PSSP ($n = 6$), B: PF ($n = 14$) and C: HC ($n = 20$). D-F: Grand average EPs recorded at the vertex (C_z-A_1A_2), D: PSSP ($n = 6$), E: PF ($n = 14$) and F: HC ($n = 20$). A/ND: affected side (patients)/non-dominant side (healthy controls), UA/D: unaffected side (patients)/dominant side (healthy controls).)

3.34, $p = 0.001$). Post-hoc testing revealed that the N150 amplitude was significantly lower at both sides in stroke patients (both PSSP and PF) compared to controls ($p < 0.05$). Moreover, the P300 amplitude was lower at both sides in patients as compared to controls, but this difference was only significant for PF ($p < 0.05$).

3.3.3. EP latencies

Mean latencies ± standard errors of the EP components are presented in Fig. 3 (A-E). Repeated measures analysis showed statistically significant differences between sides (F(5,73) = 2.94, $p = 0.018$) and between groups (F(10,148) = 5.81, $p < 0.001$) and a statistically significant interaction effect of 'Side' by 'Group' (F(10,148) = 2.68, $p = 0.005$). Post-hoc testing showed that differences between sides were significant for the P300, differences between groups for all components and interaction effects for the N90 and the P300. One-way analysis of variance for each hand separately (N90 and P300 components) and post-hoc multiple comparisons (other components) showed that latencies of the N90, N150, P300 components were significantly higher at both sides in all stroke patients (PSSP and PF) compared to controls. In addition, only in PSSP patients, the N90 latencies at the affected side ($p < 0.05$), P200 latencies at both sides ($p < 0.05$) and N150-P200 peak-to-peak latencies at both sides ($p < 0.05$) were significantly higher compared to both PF and HC.

3.4. Sub-analysis

Lesion characteristics were not known for all patients in the overall analysis. Demographic and medical characteristics of lesion-matched stroke groups (PSSP: $n = 4$, PF: $n = 4$) are presented in Table 3. For evoked potentials, mean stimulation amplitude (mA) [min-max] was 2.05 [1.54–2.97] (affected hand) and 2.07 [1.67–2.60] (unaffected hand) in PSSP patients, 1.27 [0.94–1.9] (affected hand) and 1.14 [0.95–1.43] (unaffected hand) in PF patients. Sub-analyses for amplitude and latency of evoked potential components are presented in Figs 4 and 5 respectively. For amplitude, group

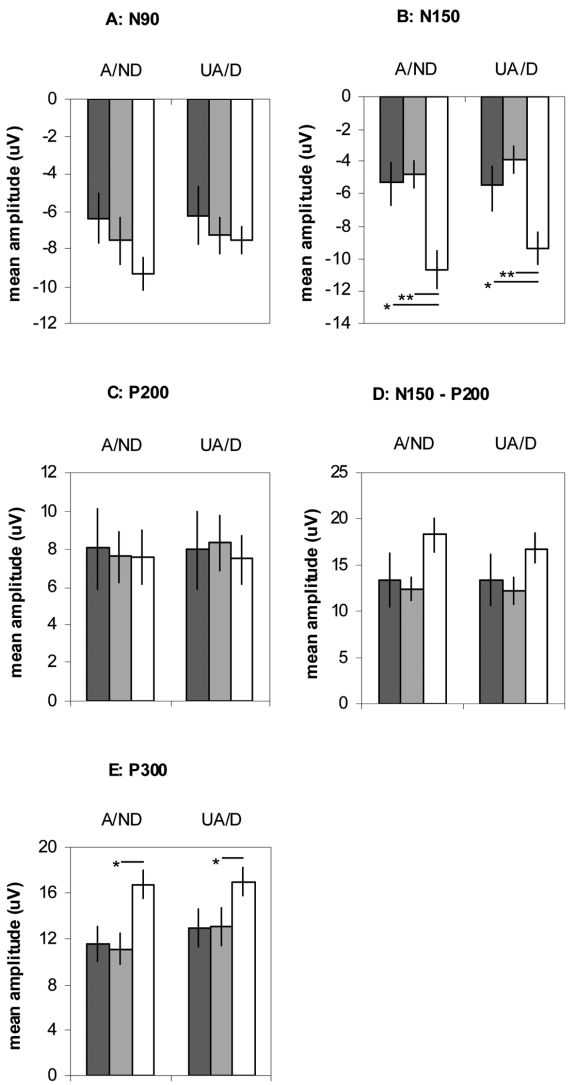

Fig. 2. A-E. Mean amplitude (μV) $\pm$ standard error of late evoked potential components. Dark grey bars: stroke patients with shoulder pain (PSSP, $n = 6$), grey bars: pain-free stroke patients (PF, $n = 14$), white bars: healthy controls (HC, $n = 20$). A/ND: affected side (patients)/non-dominant side (healthy controls), UA/D: unaffected side (patients)/dominant side (healthy controls). $^{*}p < 0.05$, $^{**}p < 0.001$.

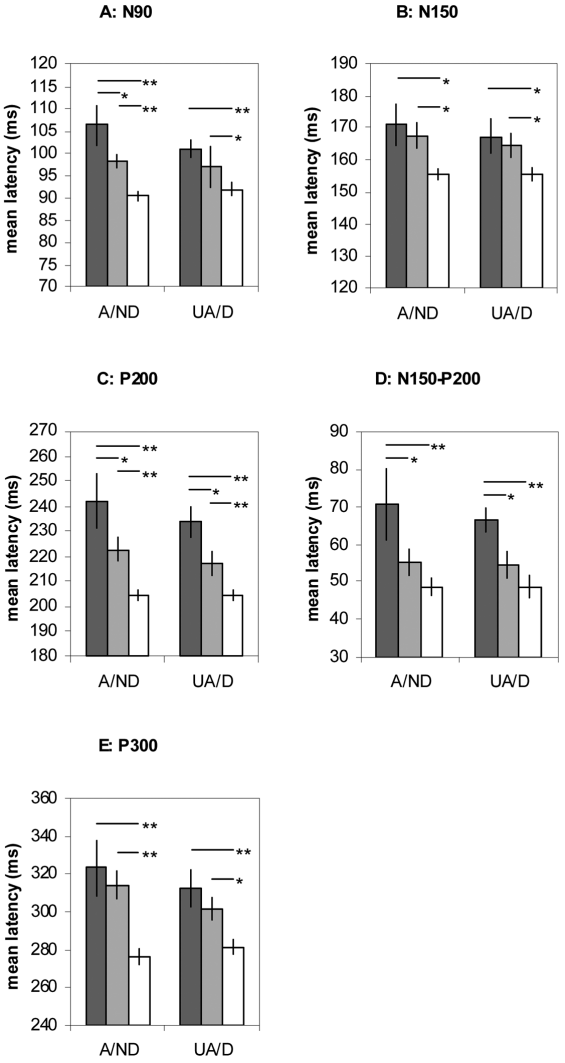

Fig. 3. A-E. Mean latency (ms) $\pm$ standard error of late evoked potential components. Dark grey bars: stroke patients with shoulder pain (PSSP, $n = 6$), grey bars: pain-free stroke patients (PF, $n = 14$), white bars: healthy controls (HC, $n = 20$). A/ND: affected side (patients)/non-dominant side (healthy controls), UA/D: unaffected side (patients)/dominant side (healthy controls). $^{*}p < 0.05$, $^{**}p < 0.001$.

differences were observed for the N150 ($p = 0.014$) and P300 ($p = 0.037$) components. Post-hoc testing revealed that N150 and P300 amplitudes were significantly lower at both sides in stroke patients compared to controls, however this was only significant for the PF group ($p < 0.05$). For latency, group differences were observed for all components ($p < 0.01$). In addition, side differences and interaction effects of 'Side' by 'Group' were observed for the P200 ($p < 0.05$) and P300 ($p < 0.05$). One-way analysis of variance for each hand separately (P200 and P300 components) and post-hoc multiple comparisons (other components) showed that latencies of the N90, N150 and P300 components were higher at both sides in all stroke patients (PSSP and PF) compared to controls. For the N90 this was significant for both groups (PSSP, $p < 0.01$; PF, $p < 0.05$), for the N150 this was significant for the PSSP group only ($p < 0.05$) and for the P300 this was significant for both the PSSP ($p < 0.01$) as well as the PF group (affected side, $p < 0.01$). No significant difference was observed between the PSSP and PF group

Table 3
Sub-analysis: Demographic data and medical characteristics

	PSSP ($n = 4$)	PF ($n = 4$)
Age	56 [39–65]	61 [48–69]
Male/Female	2/2	3/1
Stroke latency (months)	17 [6–26]	18 [12–24]
Right-hemispheric lesion	4	3
Small/Large	2/2	2/2
Cortical/Subcortical	3/1	3/1
Insula/ACC	2/2	1/2
Cognitive deficits	0	0
Depression score (20–80)	50 [45–57]	38 [32–46]
Arm function (0–100)	61 [0–91]	70 [14–100]
Glenohumeral subluxation	2	2
Trophic changes hand/arm	2	0
Abnormal sensation (T/C/P/S)	1/3/2/3	2/0/0/1
Analgesics	PC (1), NSAID (1)	
Anti-depressants	TCA (2), SSRI (1)	

Data are presented as mean [min-max] or as number of patients. Abbreviations: PSSP: stroke patients with post-stroke shoulder pain, PF: pain-free stroke patients, ACC: anterior cingulate cortex, T/C/P/S: Touch/Cold/Proprioception/Sharpness, PC: paracetamol, NSAID: non-steriodal anti-inflammatory drug, TCA: tricyclic antidepressant, SSRI: selective serotonin reuptake inhibitor.

for the N90 latency. However, in PSSP patients, the P200 latency and N150-P200 peak-to-peak latency was significantly higher compared to both PF (P200, $p < 0.05$) and HC groups (P200, $p < 0.01$; N150-P200, $p < 0.01$).

4. Discussion

This explorative study evaluated alterations in the cortical processing of somatosensory stimuli in stroke patients with unilateral brain lesions and chronic PSSP using electrocutaneous stimulation and EEG. Patients with PSSP were compared to both pain-free stroke patients and to healthy controls. In all stroke patients reduced EP amplitudes (N150, P300) and increased EP latencies (N90, N150, P300) were found in response to stimulation at both the affected and unaffected side. In addition, PSSP was associated with increased P200 and N150-P200 peak-to-peak latencies after stimulation at both sides.

4.1. Intracutaneous electostimulation and EPs

The method used in this experiment to perform intracutaneous electrostimulation activates both Aβ and Aδ primary afferents [8]. Stimulation was, thus, never nociceptive-specific, although subjects were stimulated with a low intensity (clear non-painful pricking sensation) and a high intensity (clear painful pricking sensation) stimulus. All EP components that were studied in this experiment were observed after stimulation with either the low or high intensity stimulus, with similar effects, so that data could be pooled. After a non-specific stimulus, based on the 'first come, first served' principle [23], the EP is thought to reflect the processing of the activity from the fastest conducting fibers only, in this case Aβ fibers. On the other hand, even when the stimulus is entirely noxious, the EP may not

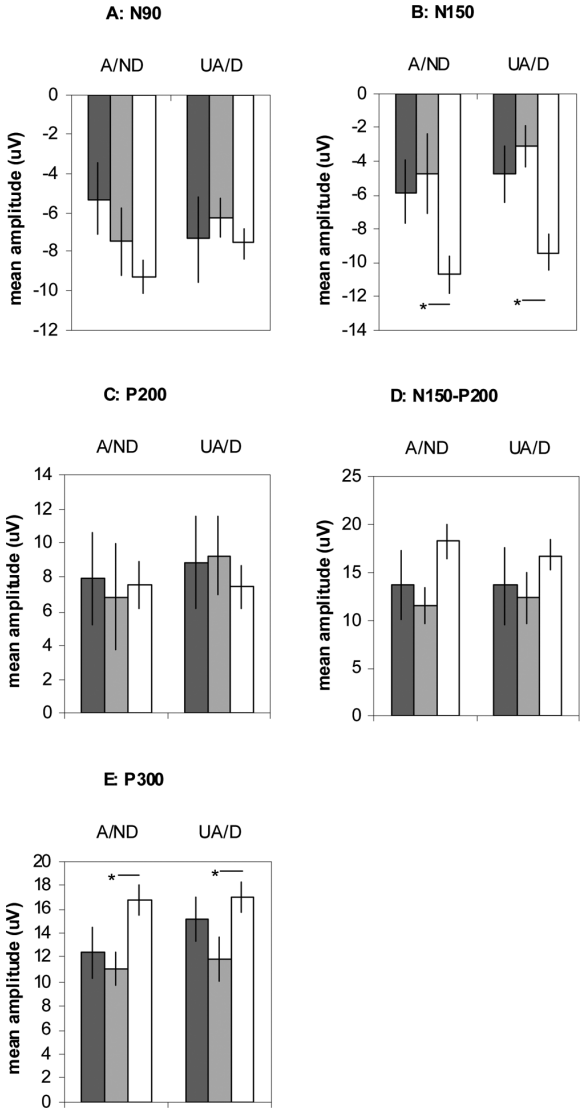

Fig. 4. A-E. Sub-analysis: Mean amplitude (μV) $\pm$ standard error of late evoked potential components. Dark grey bars: stroke patients with shoulder pain (PSSP, $n = 4$), grey bars: pain-free stroke patients (PF, $n = 4$), white bars: healthy controls (HC, $n = 20$). A/ND: affected side (patients)/non-dominant side (healthy controls), UA/D: unaffected side (patients)/dominant side (healthy controls). $^{*}p < 0.05$, $^{**}p < 0.001$.

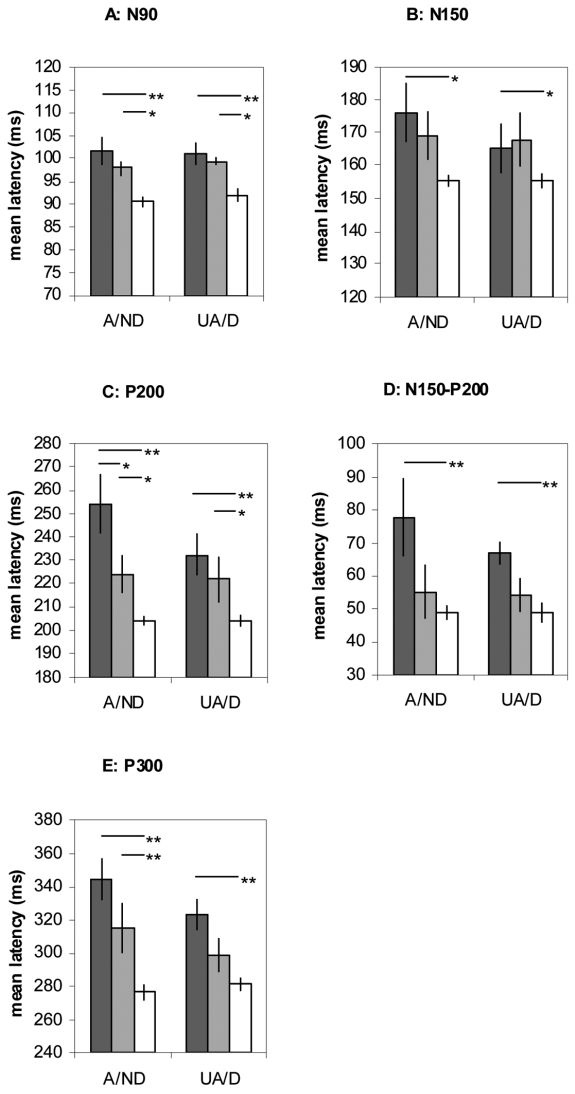

Fig. 5. A-E. Sub-analysis: Mean latency (ms) ± standard error of late evoked potential components. Dark grey bars: stroke patients with shoulder pain (PSSP, $n = 4$), grey bars: pain-free stroke patients (PF, $n = 4$), white bars: healthy controls (HC, $n = 20$). A/ND: affected side (patients)/non-dominant side (healthy controls), UA/D: unaffected side (patients)/dominant side (healthy controls). $^{*}p < 0.05$, $^{**}p < 0.001$.

be nociceptive-specific [44].

4.2. N90

The N90, one of the first components to be observed in the EP after intracutaneous electrical stimulation, originates from the somatosensory cortex and reflects sensory-discriminative processes involved in stimulus perception [9,30].

This study showed increased N90 latencies in stroke patients (PSSP and PF) as opposed to healthy controls. In pain-free patients, similar increases in latency (7–8 ms delays) have been observed for early EP components, reflecting impaired processing of input from the dorsomedial lemniscal pathway [33]. Remarkably, the N90 latency was increased after stimulation at both the affected and unaffected side, which may result from changes in sensory-discriminative processing at both the ipsilesional as well as contralesional hemisphere [17] and/or from a reduction in attentional arousal [24]. In patients with PSSP, a further increase in the N90 latency was observed after stimulation at the affected side as compared to the PF group, corresponding to the increased tactile detection thresholds, quantitative electrical sensation thresholds (EST) and stimulation amplitudes (Ie) observed at the affected side of patients with PSSP. Since the electrical stimulation to evoke EPs in this study activated both Aβ and Aδ fibers, the increase in N90 latency reflects a loss of both dorsomedial-lemnisco-cortical as well as spino-thalamo-cortical integrity, and objectively confirms the clinical findings. Since the difference in N90 latency between PSSP and PF patients was not observed after matching for lesion size and location, the presence of PSSP seems not dependent on the (functional) loss of brain structures that are responsible for the generation of the N90 peak.

Several studies of central neuropathic (post-stroke) pain reporting on median and tibial electrical EPs [29, 42] or laser evoked potentials [10,25] reported reduced EP amplitudes and/or longer latencies in these patients. However, in these studies, patients with pain were only compared to healthy controls, so it cannot be concluded that the reported differences were specific for pain.

In contrast to Parkinson patients with central pain [52] and fibromyalgia patients [26], no signs of central hyperexcitability were observed for any of the EP components after stroke. However, in the patients with PSSP that could be included in this study, the incidence of clinical signs of central hyperexcitability (allodynia, generalized hyperalgesia) was generally low. In addition, ongoing central hyperexcitability after stroke may be masked by loss of somatosensory function and/or loss of attentional capabilities [59].

4.3. N150, P200, N150-P200

The N150-P200 complex originates from the insula, secondary somatosensory and cingulate cortices [7,31, 32] and its peak-to-peak amplitude has been related to

subjective ratings of stimulus intensity and pain [9,11]. Both the N150 and the P200 are, therefore, thought to reflect cognitive-evaluative processes involved in stimulus perception. In the present study, only the N150 but not the P200 or the N150-P200 peak-to-peak amplitude was significantly reduced in stroke patients. To our knowledge, selective attenuation of the N150 amplitude has not been reported before. Attenuation of the N150 peak may be related to lesions of the insula and anterior cingulated cortices. In addition, in previous studies, attenuation of the N150-P200 complex has been related to distraction and decreased states of arousal [5,65]. The reduction in N150, therefore, might be explained by a (functional) loss of brain structures responsible for its generation and/or by reduced cognitive (attentional) capacities resulting from the brain lesion [46].

Latency shifts of the N150 and P200 have been reported before but not in relation to stroke or pain. Moreover, latency shifts have been reported inconsistently. In the current study, increased N150 and P200 latencies were observed in all stroke patients as opposed to healthy controls. In addition, the P200 and the N150-P200 peak-to-peak latencies were significantly more increased in patients with PSSP. Since calculation or memorization tasks have not been shown to affect the latency of N150 or P200 components [65], loss of attentional capabilities cannot account for the observed differences between groups. However, the selective increase in P200 latencies in patients with PSSP may be explained by a disturbance in the perception of stimulus intensity, since the perception of stimulus intensity has previously been negatively correlated with the P200 latency [53,55]. Since the difference in P200 latency was also observed in the sub-analysis in which PSSP and PF patients were matched for lesion size and location, it seems likely that the abnormality in the P200 latency is related to the presence of PSSP.

4.4. P300

The P300 has been implicated in various cognitive processes, such as attention and distraction and target/non-target responses [7]. Its latency provides an indirect indication of the duration of the processes involved in stimulus discrimination [28]. Moreover, the P300 latency has been shown to be increased in patients with chronic pain [56], indicating that chronic pain may interfere with cognitive processes. The P300 amplitude has been related to stimulation intensity and subjective ratings of stimulus intensity at both painful and non-painful stimulation levels [18,61]. In response to painful electrical stimulation, the P300 may reflect an attention component, a pain component and a stimulus intensity component [4]. In the current study, reduced P300 amplitudes and increased P300 latencies were observed in all stroke patients. Therefore, the changes in P300 likely represent a cognitive deficit in the discrimination of stimuli associated with the brain lesion but with no direct relation to PSSP.

4.5. Limitations

This study was the first to assess the cortical processing of somatosensory stimuli in patients with PSSP, and the results should therefore be interpreted with caution. Since this was a cross-sectional study, no conclusions can be drawn on any causal relation between the reported differences in somatosensory processing and the presence of pain.

One of the limitations of this study is the small sample size, which was predominantly due to the demands on cognitive and somatosensory functions necessary for the experimental set-up.

As a result, several factors, such as age, gender and depression, which have previously been related to EP amplitude or latency, were slightly different between groups. However, based on additional regression and correlation tests using the HC data, age and gender were not considered to form a relevant source of confounding for the current results. In addition, although the incidence of depressive symptoms in patients with PSSP was higher than in the PF patients, depressive symptoms were not severe [68] and no group differences were observed for EP components previously related to major depression [36]. The influence of analgesic medication [2,3,43,54] and antidepressants [16, 45,62] was not considered to form a relevant source of confounding either, although confounding could not entirely be ruled out as a result of the sample size.

Another limitation is the fact that lesion characteristics could not be determined in several patients due to the unavailability of a CT or MRI brain scan. Moreover, high resolution scans were not available for any patient, so that lesion characteristics could only roughly be determined and diffuse white matter lesions might have remained undetected. To at least grossly evaluate the level of confounding introduced by lesion characteristics, a sub-analysis was performed in which PSSP ($n = 4$) and PF ($n = 4$) patients were matched for lesion size and location. Although no difference was observed for the N90 latency comparing the PSSP and

PF groups, in this sub-analysis, PSSP was still related to increased P200 and N150-P200 latencies. Despite the small number of subjects in the sub-analysis, these results at least suggest that lesion characteristics alone cannot explain the observed differences between PSSP and PF groups, and that the observed abnormalities in evoked potential characteristics in PSSP patients may be related to the central effects of persistent nociceptive pain.

5. Conclusion

The present study showed that the cortical processing of somatosensory stimuli was generally reduced in patients with stroke, which may be related to attentional deficits and to deficits in the discrimination of stimuli as a result of the brain lesion. These deficits may put stroke patients at risk of developing any type of pain after stroke, since patients may not be able to adequately react to potentially harmful stimuli. In addition, in patients with PSSP, loss of somatosensory function was more severe and the cognitive processing of somatosensory stimuli was affected. This seemed to occur independent of lesion size and location and may, therefore, be related to the central effects of chronic pain. However, since this was an explorative study in a small number of patients, our findings should be confirmed in a larger study.

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