Prediction of Central Post-Stroke Pain by Quantitative Sensory Testing

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Objective: Among patients with acute stroke, we aimed to identify those who will later develop central post-stroke pain (CPSP) versus those who will not (non-pain sensory stroke [NPSS]) by assessing potential differences in somatosensory profile patterns and evaluating their potential as predictors of CPSP.
Methods: In a prospective longitudinal study on 75 acute stroke patients with somatosensory symptoms, we performed quantitative somatosensory testing (QST) in the acute/subacute phase (within 10 days) and on follow-up visits for 12 months. Based on previous QST studies, we hypothesized that QST values of cold detection threshold (CDT) and dynamic mechanical allodynia (DMA) would differ between CPSP and NPSS patients before the onset of pain. Mann–Whitney *U*-tests and mixed analysis of variances with Bonferroni corrections were performed to compare z-normalized QST scores between both groups.
Results: In total, 26 patients (34.7%) developed CPSP. In the acute phase, CPSP patients showed contralesional cold hypoesthesia compared to NPSS patients ($p = 0.04$), but no DMA differences. Additional exploratory analysis showed NPSS patients exhibit cold hyperalgesia on the contralesional side compared to the ipsilesional side, not seen in CPSP patients ($p = 0.011$). A gradient-boosting approach to predicting CPSP from QST patterns before pain onset had an overall accuracy of 84.6%, with a recall and precision of 75%. Notably, both in the acute and the chronic phase, approximately 80% of CPSP and NPSS patients showed bilateral QST abnormalities.
Interpretation: Cold perception differences between CPSP and NPSS patients appear early post stroke before pain onset. Prediction of CPSP through QST patterns seems feasible.

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Central post-stroke pain (CPSP) is a severe form of neuropathic pain that is often refractory to treatment[1] affecting approximately 8% to 10.5% of patients after stroke.[2,3] It occurs within weeks to months in patients with lesions in the central somatosensory system, including the thalamus,[4–7] brainstem, pons, and somatosensory cortices.[8] In patients with thalamic stroke, prevalence has been reported to be 18% and in those with a lateral medullary infarction 25%,[9,10] although reported estimates of prevalence vary widely. Pain localization is typically associated with sensory abnormalities in body parts corresponding to the affected brain area.[1] Besides spontaneous and/or evoked pain, impaired temperature perception and nociception have been reported.[11] This has led to the assumption that lesions of the lateral spinothalamic tract (STT) and/or its central projections to the cortex are a prerequisite for the development of CPSP.[12–14] Consistent with this assumption, studies have shown differences in the location of thalamic lesions in patients with and without pain, with lesions in CPSP patients often involving the ventral posterior nucleus and the anterior pulvinar nucleus, where the STT is thought to terminate.[5–7,15] Despite such subtle differences in lesion locations between groups, it is currently unclear why some patients with a stroke in the somatosensory system later develop CPSP, whereas others do not.[16]

Few studies have examined patients in the acute phase after stroke before the onset of pain.[2,9,11] Klit et al.[11] reported that a combination of reduced sensation to pinprick or cold, and evoked pain or dysesthesia when comparing the affected to the unaffected body parts, increases the risk of developing CPSP.[11] What has been missing is a standardized and quantifiable assessment of clinical and specific sensory symptoms in the pre-pain phase, which would allow an easier transfer of results to clinical practice. It would be useful to provide a clinician treating patients who are at risk of potentially developing CPSP (ie, patients with somatosensory stroke) with criteria to predict whether an individual patient will develop pain or not.

To address this need, we conducted a prospective longitudinal study in patients with acute somatosensory stroke as part of a larger prospective clinical trial,[17] which, in addition to a detailed clinical assessment and magnetic resonance (MR) imaging, standardized quantitative sensory testing (QST) was performed.[18] QST was conducted in the acute/subacute phase "before pain" and follow-up exams were repeated at different time points up to 12 months.

Based on 2 previous QST studies in chronic CPSP patients,[19,20] we hypothesized that the QST parameters, cold detection threshold (CDT) and dynamic mechanical allodynia (DMA), differ already in the acute stage of stroke between patients who will later develop CPSP and those who will not (non-pain sensory stroke [NPSS]). In addition, we performed an exploratory analysis of all QST parameters bilaterally in the acute and chronic phases after stroke.

Materials and Methods

Subjects

Patients with an acute ischemic or hemorrhagic stroke affecting the somatosensory system were enrolled at the Charité-Universitätsmedizin Berlin, Germany between 2010 and 2016. The study was approved by the local ethics committee (EA4/003/10) and informed consent was obtained from all participants before inclusion.

Inclusion criteria were age between 18 and 85 years and a transient or persistent somatosensory deficit with a corresponding magnetic resonance imaging (MRI)-proven acute unilateral stroke within central parts of the somatosensory system (ie, medulla oblongata, pons, thalamus, internal capsule, or somatosensory cortices). A transient somatosensory deficit was defined as a sensory symptom that was present in the acute phase at presentation but recovered spontaneously or after treatment. A persistent somatosensory deficit was defined as a sensory symptom that did not recover during the period of the study. Exclusion criteria are detailed in the supplementary methods. The neurological examination comprised detailed sensory and motor testing to diagnose the underlying etiology. In patients who reported pain, pain intensity, pain quality, pain course, and pain duration were assessed with validated pain questionnaires (see below).

According to Klit et al.,[1] CPSP was defined as pain that occurred as a direct result of a stroke to the central somatosensory system, confirmed by MRI, in the body area corresponding to the somatosensory deficit (eg, hypoesthesia, paresthesia). Other causes of pain, such as nociceptive or peripheral neuropathic pain (complex regional pain syndrome, joint abnormalities, spasticity, and pain types unrelated to the injury), were excluded or considered highly unlikely. Therefore, according to the criteria recently set out by Rosner et al.,[22] all our CPSP patients fulfilled the criteria for "definite CPSP." Hyperalgesia and allodynia, which emerged only during clinical examination, but were not perceived in daily life, were not classified as CPSP. It is conceivable that some NPSS patients share characteristics of hypersensitivity without developing manifest CPSP.[1,21,22]

CPSP most commonly occurs within the first few months after a stroke,[2,11,23] therefore, in-person follow up for the diagnosis of CPSP was chosen to be at least 6 months after the stroke. Classification of a patient as CPSP (or NPSS) was done retrospectively in the following 12 months when either pain occurred, meeting the above-mentioned criteria of CPSP, or no pain occurred (NPSS).

Clinical Data and Assessment

Each patient underwent a semi-structured interview for medical history and a neurological examination (see supplementary methods), including stroke severity assessment (National Institutes of Health

Stroke Scale [NIHSS],[24] modified Rankin Scale [mRS],[25] and Barthel index [BI][26]) as well as QST and MRI. Patient-reported outcomes were assessed by validated questionnaires (12-item Short Form Health Survey,[27] Pittsburgh Sleep Quality Index,[28] Geriatric Depression Scale 30[29]). In patients who reported pain, the painDETECT Questionnaire (PD-Q), the German pain questionnaire and the pain perception scale were administered.[30–32]

QST

QST is a standardized, non-invasive method approved by the German Research Network on Neuropathic Pain (DFNS),[33] which evaluates somatosensory function using normative values from a healthy population, adjusted for age, sex, and test location.[18]

Our study aimed to capture QST data (1) in the acute/subacute stage within 10 days after stroke before pain development and (2) in the chronic stage after pain development in the CPSP group or NPSS group. As the onset of pain in CPSP is variable and to capture patients before and after the onset of pain, a total of 5 QST assessments were planned to be conducted in regular intervals up to 180 days post stroke. Because of the clinical nature of the study, flexibility in the timings was allowed and, therefore, some QST assessments were conducted close to a year following the stroke. Among all the QST measurements, we included 2 per patient for our main analysis, which was operationally defined in the following way: (1) "acute QST before pain", which is the earliest QST value per patient that occurred "before pain" for CPSP patients, and overall not later than 10 days after stroke. It was performed in the area with the most pronounced sensory symptom reported by the patients. (2) "Chronic QST after pain", which is the latest available QST value in the chronic phase that, in CPSP patients, must have been obtained after pain has occurred. In CPSP patients, QST was performed in the area with the most pronounced neuropathic pain, and in NPSS patients, in the area of the most prominent non-painful sensory symptom.

Both acute and chronic QST visits were conducted at similar time points for both CPSP and NPSS patients (Table S1).

Examinations targeted the somatosensory system's most affected area (face, hand, or foot), covering both ipsilesional and contralesional sides, in sequence. In patients where the area with the most pronounced neuropathic pain or non-painful sensory symptom was outside the face, hands or feet, the nearest area was chosen. QST parameters are denoted as "$_c$" for contralesional (eg, $_c$CDT) and "$_i$" for ipsilesional (eg, $_i$CDT), with side-to-side differences labelled "$_{sd}$" (eg, $_{sd}$CDT). Side-to-side differences are calculated by subtracting the raw or log-transformed ipsilesional values from the contralesional values and then dividing by the standard deviation (SD) of the left–right difference based on the DFNS reference values (please see supplementary methods).[18] The formula used was as follows: (contralesional − ipsilesional)/SD of left–right difference. All assessments were conducted by 2 DFNS-trained examiners.

In a QST exam, the following parameters are determined: CDT and warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensations (PHS), cold (CPT) and heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), DMA, wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT).[18]

Statistical Analysis

Statistical analysis was conducted in R 4.2.2 (2022.10.31)[34] with RStudio. Data normality was assessed through skewness, kurtosis, histograms, and the Shapiro–Wilk test. Normally distributed metrics are reported as mean ± SD, and non-normally distributed as median and inter-quartile range (IQR). Group comparisons (CPSP vs NPSS) used Pearson's chi-square test for categorical variables and the Mann–Whitney U test for non-normally distributed ordinal/quantitative data, with Cliff's delta indicating effect size. Comparison between patients and the reference values from the healthy reference collective was conducted as previously suggested (see supplementary methods for more details).[35] Bonferroni correction was applied to adjust for multiple comparisons. For the hypothesis driven analysis, significance was set at $p \leq 0.05$ (Bonferroni corrected, corresponding to $p \leq 0.025$ uncorrected). For the exploratory part of our study, the Bonferroni corrected significance level $p \leq 0.05$ corresponded to uncorrected $p \leq 0.004$. In the tables, we also report the uncorrected p values highlighting parameters with $p \leq 0.05$ (uncorrected).

Longitudinal data analysis, addressing non-normality and outliers, applied robust statistical methods from the WRS2 (1.1–4) package in R,[36] including median-based imputation for missing values. A mixed-design was evaluated using robust analysis of variance (bwtrim), focusing on within- and between-subject effects, and exploring "Group" and "Time" interactions (sppbi). Robustness was further ensured by using the "mom" M-estimator for individual contrasts and bootstrap resampling (nboot = 10,000) to validate findings.

Logistic regression was performed to assess possible indicators for the development of CPSP. The *finalfit* (1.0.7) package was used in R to produce the final regression tables and odds ratio figure.[37] First univariate binary logistic regression examined various variables (age, sex, neurological scores—BI, mRS, NIHSS, health quality, and QST parameters) independently. In a second step, we ran a multivariate model with all QST variables that significantly differed between the groups in the univariate regression $p \leq 0.05$, correcting for NIHSS and sex.[38]

In a third step we calculated variance inflation factors (VIF) and correlation matrices to assess multicollinearity of the QST parameters included in model 1. We ran a second multivariate model with reduced numbers of QST parameters, we chose $_c$CDT, $_{sd}$CPT, and $_{sd}$HPT based on differences between the 2 groups. We excluded $_{sd}$CDT, $_{sd}$TSL, $_c$TSL, and $_c$WDT because of a high VIF (>8), and $_c$CPT because of collinearity with $_{sd}$CPT. In the end, $_c$CDT, $_c$PPT, $_{sd}$CPT, and $_{sd}$HPT were included in the final model, correcting for NIHSS and sex. Model efficacy was evaluated using Nagelkerke's R^2, with model comparison based on Akaike information criterion (AIC) and C-statistic.

Prediction of CPSP

Python (3.11.5) and scikit-learn[39] were used to train a GradientBoostingClassifier algorithm to classify patients before occurrence of pain into CPSP and NPSS groups using the QST parameters. Gradient boosting supervised machine learning is a robust ensemble approach combining several decision tree "weak learners" into a single strong learner in an iterative fashion. Predictions from all the trees are combined through a weighted majority vote to produce a final prediction.[40] All QST variables from the contralesional side and side-to-side differences were initially included in the classifier. In the final classifier, QST variables were chosen based on feature importance, Shapley additive explanations (SHA) values, and those that were significantly different between CPSP and NPSS patients. The hyperparameters of the algorithm were optimized using GridSearchCV. The GridSearchCV object was configured with the GradientBoostingClassifier as the base estimator, and the evaluation metric was set to the weighted F1 score. Leave-one-out cross-validation (LOOCV) was used to ensure robust model assessment. The optimal configuration, comprising 180 trees, a learning rate of 0.1, "log_loss" as the loss function, and a maximum tree depth of 3, was then used for the final classifier. The accuracy, recall, precision, receiver operating characteristic curve (ROC)-area under curve (AUC), F1 scores, and confusion matrix of this model are reported. Furthermore, permutation importance was used to determine, which QST variables contributed the most to the classification of pain patients.

Results

Cohort Description

Of 115 patients screened after acute unilateral somatosensory stroke, 75 were included; 26 developed CPSP and 49 did not (NPSS) (Fig S1). Six CPSP patients (because of incomplete data or pain before the first QST) and 4 NPSS patients (because of lacking early QST data) were excluded from the pre-pain and prospective QST analyses. The final QST analysis involved 20 CPSP and 45 NPSS patients. For the hypothesis-driven analysis focusing on pre-pain QST, 18 CPSP and 38 NPSS patients were evaluated, excluding 9 subjects previously published to prevent data overlap.[19] An overview of clinical characteristics and results of questionnaires is provided in Table 1.

Sensory deficits were localized unilaterally in the body and/or face on the contralesional side to the stroke. One patient with a left-sided medullary stroke lesion reported unilateral sensory deficits on the right side of the body with left-sided involvement of the face. Results of the non-quantitative clinical examination of sensory symptoms are reported in Table S2. The lesion distribution of the patients is given in Table S3.

Pain Features

Patients developed CPSP within 8 months (mean = 60.6, SD = 64.2 days) following stroke. A detailed analysis of pain onset is reported in Table 1. Pain localization is displayed in Figure 1. Average pain intensity was 4.1 ± 1.9 (SD) and maximum pain intensity was 6.3 ± 2.1 (mean ± SD) on a scale of 0 to 10 (worst pain imaginable). The mean PD-Q score was 12.4 ± 6.7 (SD). Common pain descriptors included burning (n = 12), pressing (n = 9), stinging (n = 8), throbbing (n = 8) or knocking (n = 7), severe (n = 10), and annoying (n = 9).

QST

The hypothesis-driven group comparisons and the exploratory group comparisons are provided below. The analyses of individual QST values compared to the DFNS reference collective are presented in the Tables S4, S5, and Figure S2 and described in the supplementary results. QST was performed in the acute phase on the hand (n = 58), face (n = 2), foot (n = 1) and other areas (n = 4). In the chronic phase, QST was performed on the hand (n = 61), face (n = 1), foot (n = 1) and other areas (n = 2).

QST in the "Acute Phase" of Stroke before Eventual Pain. QST was performed within 1 to 10 days after stroke (mean = 3.9, SD = 2.0 days).

CDT and DMA (Hypothesis Driven Comparison). Based on the aforementioned hypotheses, we expected CPSP patients to show differences in CDT and DMA compared to NPSS patients before pain occurred. CPSP patients showed contralesional hypoesthesia to cold compared to NPSS patients ($_{c}$CDT U = 475, $p = 0.04$ Bonferroni corrected) with a medium effect size Cliff's delta = −0.39 (Table 2). This confirms that NPSS patients had a consistently lower CDT (ie, more positive z scores) than CPSP patients. DMA did not differ significantly between the 2 groups ($U = 368$, $p = 0.54$).

Exploratory Comparisons of all QST Parameters in the Pre-Pain Phase. A marked side-to-side difference in cold pain threshold ($_{sd}$CPT U = 682, $p < 0.005$, Bonferroni corrected), was noted with a large effect size Cliff's delta = −0.55, which was because of NPSS patients having heightened sensitivity to cold pain on the contralesional side, in contrast to CPSP patients, who had preserved thresholds. Although more differences in QST values were noted between the 2 groups based on uncorrected p-values (Tables 3–5), only $_{sd}$CPT survived Bonferroni correction. Results are detailed in Tables 3–5.

QST in the Chronic Phase after Stroke. The QST exams in the chronic post-stroke phase were performed between 93 and 361 days (mean = 200.7, SD = 43.6) after the

TABLE 1. Demographics and Clinical Data

Diagnosis		CPSP	NPSS	Total	*p*
Total	n (%)	26 (34.7)	49 (65.3)	75	
Age (yr)	Median (IQR)	63.0 (55.5 to 69.5)	65.0 (56.0 to 70.0)	65.0 (55.5 to 70.0)	0.660
Sex	Female/n (%)	15 (57.7)	15 (30.6)	30 (40.0)	**0.028**
	Male/n (%)	11 (42.3)	34 (69.4)	45 (60.0)	
Thrombolysis	No/n (%)	18 (69.2)	40 (81.6)	58 (77.3)	0.255
	Yes/n (%)	8 (30.8)	9 (18.4)	17 (22.7)	
Etiology	Hemorrhagic/n (%)	1 (3.8)	2 (4.1)	3 (4.0)	1.000
	Ischemic/n (%)	25 (96.2)	47 (95.9)	72 (96.0)	
Lesion side	Left/n (%)	9 (34.6)	24 (49.0)	33 (44.0)	0.406
	Right/n (%)	16 (61.5)	24 (49.0)	40 (53.3)	
	Bilateral/n (%)	1 (3.8)	1 (2.0)	2 (2.7)	
Lesion location	Brainstem/n (%)	6 (23.1)	5 (10.2)	11 (14.7)	0.191
	Cortex/n (%)	7 (26.9)	8 (16.3)	15 (20.0)	
	Thalamus/n (%)	13 (50.0)	35 (71.4)	48 (64.0)	
	Pathways/n (%)		1 (2.0)	1 (1.3)	
Lesion volume (ml)	Mean (SD)	1.8 (3.3)	1.3 (3.3)		0.506
Assessment scales					
First NIHSS	Median (IQR)	3.0 (2.0 to 5.0)	2.0 (1.0 to 2.0)	2.0 (1.0 to 3.0)	**0.001**
First mRS	Median (IQR)	2.0 (1.0 to 3.8)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	**0.001**
First Barthel index	Median (IQR)	90.0 (61.2 to 100.0)	100.0 (100.0 to 100.0)	100.0 (90.0 to 100.0)	**0.002**
Pain occurrence within					
≤1 week	n (%)	5 (19.2)	0		
>1 week to ≤1 month	n (%)	8 (30,8)	0		
>1 month to ≤3 months	n (%)	7 (26.9)	0		
>3 months to ≤8 months	n (%)	6 (23.1)	0		

BMI = body mass index; CPSP = central post-stroke pain; CPSP = central post-stroke pain; CVD = cardiovascular disease, GDS = geriatric depression scale; IQR = interquartile range; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke scale; NPSS = non-pain sensory stroke; SD = standard deviation. Bold values indicate statistical significance with $p < 0.05$.

onset of stroke. The time interval between the acute QST (before pain) and chronic QST (after pain) was very similar in both groups (CPSP mean = 199.4, SD = 53.7, NPSS mean = 195.7, SD = 38.7 days) and did not differ significantly (see Table S1).

Although we observed group differences in individual QST parameters, these differences did not survive Bonferroni correction. Results are detailed in Tables 3–5. Combinations of sensory abnormalities are presented in the supplementary results and Tables S6 and S7.

Longitudinal Analysis of QST Parameters. No significant group and time interactions were observed on the contralesional side (Table S8). Significant interactions were observed ipsilesionally in the ¡HPT (F [1, 48] =6.5, $p = 0.042$ after Bonferroni correction). Bootstrapping revealed that only the interaction for iHPT remained

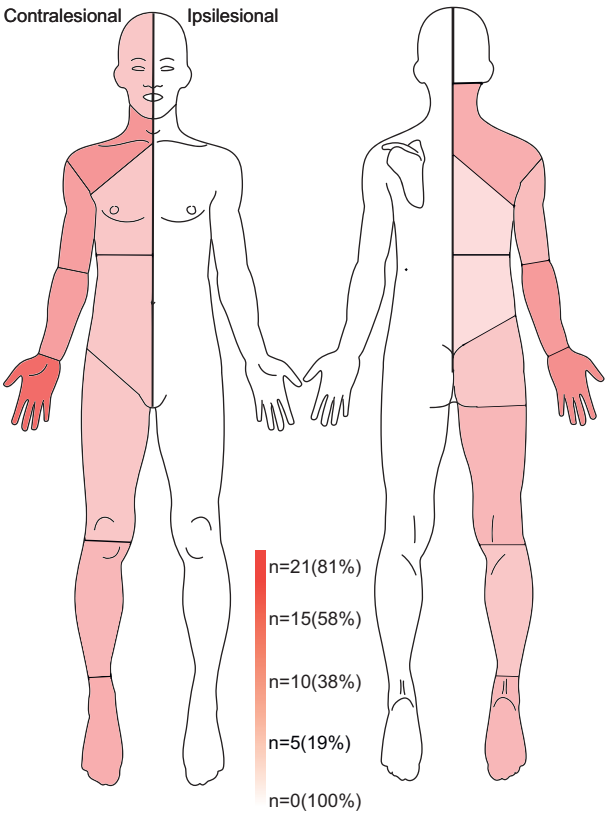


FIGURE 1: Pain localization. Pain localization of patients with central post stroke pain (CPSP) (n = 26). All unilateral right-sided infarcts with clinical symptoms have been flipped to the left side so that all symptoms are depicted on the same body side. Pain contralesional to the stroke lesion manifested in the face (n = 4), perioral region (n = 8), shoulder and upper arm (n = 10), forearm (n = 12), hand (n = 21), chest and abdomen (n = 3), buttock (n = 5), thigh (n = 4), lower leg (n = 7) and foot (n = 8).

significant ($p = 0.004$). This result was likely driven by the CPSP group, which showed a significant loss of function in ipsilesional heat pain perception between acute and chronic phases (iHPT t [19] =3.31, $p = 0.004$) that was not evident in NPSS patients. This indicates that a progressive loss of ipsilesional heat pain perception might be specific to the CPSP group.

Bilateral QST Abnormalities. We observed bilateral QST abnormalities compared to the DFNS reference values. In the acute setting, bilateral sensory loss was prominent in CPSP patients, whereas bilateral sensory gain was dominant in NPSS patients. In the chronic stage, the ipsilesional values overall approached the values of the contralesional side (for details see Fig S2A,B and Tables S4 and S5).

Predictor Analysis. Univariate binary logistic regression was conducted to assess the influence of various factors on the development of CPSP, including sex, age, neurological impairment, sleep quality, quality of life, depression, and QST parameters acutely post-stroke. The variables found to be significant predictors for later development of CPSP are displayed in Table S2.

Subsequently, a multivariate logistic regression analysis was performed, incorporating significant parameters from the univariate logistic regression. The analysis revealed that hyposensitivity to blunt pressure ($_c$PPT: odds ratio [OR] = 0.23, 95% confidence interval [CI] = 0.04–0.70, $p = 0.034$) was a significant predictor. Nagelkerke's R^2 for the multiple logistic regression was 68.7%, indicating a good fit of the model.

To further streamline the model, a reduced analysis was conducted, including NIHSS, sex, $_c$CDT, $_c$PPT,

TABLE 2. Hypothesis Driven Analysis of QST Parameters

Diagnosis		CPSP	NPSS	p_{uncorr}	p_{adj}	d
Acute setting						
Total n (%)		18 (32.1)	38 (67.9)			
$_c$CDT	Median (IQR)	−1.5 (−3.5 to −0.5)	−0.2 (−1.3 to 0.2)	0.020	**0.04**	**−0.39**
$_c$DMA	Median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.538	1.00	

The hypothesis was tested that $_c$CDT is lower in patients who later develop CPSP. Mann–Whitney *U* tests were performed in the acute setting (on average 3.9 [1–10] days after stroke) excluding patients, which were included in the study by Krause et al.[19] DMA has been log transformed. Blue color means "relative loss of function" compared to DFNS reference values (based on the statistical comparisons given in Table S4). Effect sizes reported are Cliff's d, delta ranges from −1 to 1 and 0 indicates no difference, a positive delta suggests that the CPSP has larger values whereas a negative delta suggests the NPSS group has larger values. Magnitude is assessed as d < 0.33 "small", d < 0.47 "medium", d > 0.47 "large". p_{uncorr}, uncorrected *p*-values; p_{adj} Bonferroni corrected *p*-values.
QST on the contralesional side is indicated with "$_c$" (eg, $_c$CDT).
CDT = cold detection threshold; CPSP = Central post-stroke pain; DMA = dynamic mechanical allodynia; DFNS = German Research Network on Neuropathic Pain; NPSS = non-pain sensory stroke. Bold values indicate statistical significance with $p < 0.05$.

TABLE 3. QST Parameters in Acute (Pre-Pain) Phase and Chronic Phase: Contralesional Side

				Between group comparison							
		Acute					Chronic				
Diagnosis		CPSP	NPSS	p_{uncorr}	p_{adj}	d	CPSP	NPSS	p_{uncorr}	p_{adj}	d
Total n (%)		20 (30.8)	45 (69.2)				20 (30.8)	45 (69.2)			
$_{c}$CDT	Median (IQR)	−1.3 (−3.0 to −0.4)	−0.2 (−1.1 to 0.2)	**0.010**	0.130	−0.40	−0.8 (−2.5 to −0.3)	−0.1 (−0.8 to 0.4)	**0.007**	0.091	−0.43
$_{c}$WDT	Median (IQR)	−1.8 (−2.9 to −0.6)	−0.7 (−1.9 to 0.0)	0.059	0.767		−2.2 (−2.9 to −0.7)	−0.6 (−1.5 to 0.4)	**0.014**	0.182	−0.39
$_{c}$TSL	Median (IQR)	−1.4 (−2.5 to −0.7)	−0.7 (−1.4 to 0.2)	**0.019**	0.247	−0.37	−1.7 (−2.4 to 0.1)	−0.6 (−1.1 to 0.1)	0.064	0.832	
$_{c}$CPT	Median (IQR)	−0.5 (−0.9 to 0.7)	1.2 (−0.4 to 2.2)	**0.006**	0.078	−0.43	−0.3 (−0.9 to 1.4)	1.0 (−0.2 to 2.0)	**0.030**	0.390	−0.35
$_{c}$HPT	Median (IQR)	−1.2 (−1.5 to −0.5)	−0.1 (−1.1 to 0.9)	**0.043**	0.559	−0.32	−0.9 (−1.3 to 0.6)	0.0 (−0.9 to 1.5)	**0.046**	0.598	−0.32
$_{c}$PPT	Median (IQR)	−1.2 (−2.4 to −0.6)	−0.3 (−1.2 to 0.5)	**0.005**	0.065	−0.45	−1.2 (−1.9 to 0.4)	−0.5 (−1.2 to 0.5)	0.053	0.689	
$_{c}$MPT	Median (IQR)	0.6 (−0.9 to 2.4)	1.2 (0.0–2.3)	0.309	1.000		1.5 (−0.7 to 3.4)	1.7 (0.4 –2.8)	0.446	1.000	
$_{c}$MPS	Median (IQR)	0.2 (−1.1 to 1.5)	1.3 (0.1–2.3)	**0.048**	0.624	−0.31	1.4 (−0.3 to 2.0)	1.2 (0.5 –2.5)	0.233	1.000	
$_{c}$WUR	Median (IQR)	0.4 (−0.4 to 0.7)	−0.1 (−0.7 to 0.5)	0.564	1.000		0.0 (−0.6 to 0.8)	−0.3 (−0.7 to 0.6)	0.649	1.000	
$_{c}$MDT	Median (IQR)	−1.6 (−2.9 to 0.3)	−0.7 (−2.7 to 0.0)	0.546	1.000		−1.0 (−1.9 to −0.4)	−0.3 (−1.5 to 0.6)	**0.047**	0.611	−0.31
$_{c}$VDT	Median (IQR)	−0.5 (−1.2 to 0.8)	0.8 (−1.0 to 0.9)	0.089	1.000		0.1 (−1.1 to 0.5)	0.8 (0.1 to 0.9)	**0.010**	0.130	−0.40
$_{c}$PHS	0	16 (80.0)	34 (75.6)	0.217	1.000		16 (84.2)	42 (97.7)	0.082	1.000	
	1	1 (5.0)	7 (15.6)				1 (5.3)	0 (0.0)			
	2	1 (5.0)	0 (0.0)				0 (0.0)	0 (0.0)			
	3	0 (0.0)	3 (6.7)				2 (10.5)	1 (2.3)			
(Missing)		2 (10.0)	1 (2.2)								
$_{c}$DMA	Median (IQR)	0.0 (−0.1 to 0.0)	0.0 (0.0 to 0.0)	0.386	1.000		0.0 (0.0–0.0)	0.0 (0.0 –0.0)	0.611	1.000	

QST on the contralesional side is indicated with "$_{c}$" (eg, $_{c}$CDT).

Explorative analysis of QST parameters on the contralesional side using Mann–Whitney *U* test in the acute phase and chronic phase. Blue color means "relative loss of function" compared to DFNS reference values; orange color means "relative gain of function" compared to reference values (based on the statistical comparisons given in Tables S4/S5). The *p*-values given here refer to the statistical comparison between CPSP and NPSS. p_{uncorr}, uncorrected *p*-values; p_{adj} Bonferroni corrected *p*-values. Effect sizes reported are Cliff's d, delta.

CDT = cold detection threshold; CPSP = Central post-stroke pain; CPT = cold pain threshold; DMA = dynamic mechanical allodynia; DFNS = German Research Network on Neuropathic Pain; HPT = heat pain threshold; IQR = interquartile range; MDT = mechanical detection threshold; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; NPSS = non-pain sensory stroke; PHS = paradoxical heat sensations (0–3); PPT = pressure pain threshold; TSL = thermal sensory limen; VDT = vibration detection threshold; WDT = warm detection threshold; WUR = wind up ratio. Bold values indicate statistical significance with $p < 0.05$.

$_{sd}$CPT, $_{sd}$HPT, and $_{c}$VDT. This led to an improved AIC from 60.5 to 51.5, indicating a better fit of the reduced model, although the c-statistic decreased slightly suggesting that the full model had better discrimination. Nagelkerke's R^2 also reduced slightly from 68.7% to 65.1%. The results indicated that $_{c}$PPT (0.24, 95% CI = 0.07–0.56, $p = 0.006$), and $_{sd}$CPT (0.54, 95% CI = 0.28–0.89, $p = 0.029$) remained significant predictors (Fig 2C). After adjusting for sex, NIHSS, and the mentioned QST parameters, a lower PPT (corresponding to a higher z-score of cPPT) is associated with a 76% reduction in the odds of developing CPSP.

Classification of CPSP and NPSS Patients before Pain Onset. We used a gradient boosting classifier with LOOCV to categorize CPSP (n = 20) versus NPSS (n = 45) patients before the onset of pain in the acute phase (Fig 2). The model correctly classified 15 of 20 CPSP patients, and 40 of 45 NPSS patients, resulting in an accuracy of 84.6% and an AUC-ROC of 0.85. Both precision and recall were 75%, indicating balanced classification capabilities, further supported by a consistent F1 score of 75%. Feature importance identified the QST parameters $_{sd}$HPT and $_{c}$PPT, which aligned with the statistical differences observed between the groups.

TABLE 4. QST Parameters in the Acute (Pre-Pain) Phase and Chronic Phase: Ipsilesional Side

		Acute		Between group comparisons			Chronic		Between group comparisons		
Diagnosis		CPSP	NPSS	p_{uncorr}	p_{adj}	d	CPSP	NPSS	p_{uncorr}	p_{adj}	d
Total n (%)		20 (30.8)	45 (69.2)				20 (30.8)	45 (69.2)			
¡CDT	Median (IQR)	−0.2 (−1.2 to 0.4)	0.1 (−0.9 to 0.9)	0.328			−0.5 (−1.8 to −0.1)	−0.0 (−1.0 to 0.5)	**0.046**	0.598	−0.32
¡WDT	Median (IQR)	−0.1 (−0.9 to 0.6)	−0.2 (−1.2 to 1.0)	0.925			−1.1 (−1.7 to −0.4)	−0.3 (−0.9 to 0.6)	**0.036**	0.468	−0.34
¡TSL	Median (IQR)	0.1 (−0.6 to 0.9)	−0.1 (−0.7 to 0.7)	0.505			−0.5 (−1.2 to 0.1)	−0.2 (−0.8 to 0.5)	0.200		
¡CPT	Median (IQR)	0.2 (−0.7 to 1.3)	−0.1 (−0.7 to 1.0)	0.696			0.4 (−0.6 to 1.1)	0.4 (−0.5 to 1.5)	0.557		
¡HPT	Median (IQR)	0.7 (−0.6 to 1.8)	−0.3 (−0.8 to 0.9)	0.288			−0.7 (−1.2 to −0.2)	−0.0 (−0.9 to 1.3)	**0.018**	0.234	−0.38
¡PPT	Median (IQR)	−0.9 (−1.6 to −0.2)	−0.4 (−1.4 to 0.6)	0.170			−0.7 (−2.1 to −0.0)	−0.5 (−1.6 to 0.5)	0.238		
¡MPT	Median (IQR)	1.2 (0.2–2.8)	1.3 (0.3–2.7)	0.798			2.0 (0.3–3.0)	1.6 (0.4–2.9)	0.853		
¡MPS	Median (IQR)	1.4 (0.2–1.9)	1.5 (0.0–2.6)	0.629			0.9 (0.4 to 2.1)	1.1 (0.6–2.6)	0.274		
¡WUR	Median (IQR)	−0.7 (−1.0 to 0.2)	−0.2 (−0.8 to 0.7)	0.319			−0.5 (−0.8 to 0.1)	−0.4 (−0.9 to 0.2)	0.917		
¡MDT	Median (IQR)	−0.8 (−1.4 to −0.3)	−0.4 (−1.5 to 0.6)	0.422			−0.7 (−1.8 to 0.4)	−0.3 (−1.7 to 0.6)	0.491		
¡VDT	Median (IQR)	−0.0 (−0.7 to 0.8)	0.8 (0.1 –0.9)	**0.039**	0.507	−0.32	0.1 (−1.0 to 0.7)	0.8 (0.2–1.1)	**0.020**	0.260	−0.36
¡PHS	0	19 (95.0)	40 (88.9)	1.000			17 (89.5)	43 (100.0)	0.090		
	1	1 (5.0)	3 (6.7)				1 (5.3)	0 (0.0)			
	2	0 (0.0)	1 (2.2)				0 (0.0)	0 (0.0)			
	3	0 (0.0)	0 (0.0)				1 (5.3)	0 (0.0)			
	(Missing)	0 (0.0)	1 (2.2)								
¡DMA	Median (IQR)	0.0 (0.0 –0.0)	0.0 (0.0 –0.0)	0.547			0.0 (0.0 –0.0)	0.0 (0.0–0.0)	0.382		

QST on the ipsilesional side is indicated with "¡" (eg, ¡CDT).

Explorative analysis of QST parameters on the ipsilesional side using Mann–Whitney *U* tests. Blue color means "relative loss of function" compared to DFNS reference values; orange means "relative gain of function" compared to reference values (based on the statistical comparisons given in Tables S4/S5). The *p*-values given here refer to the statistical comparison between CPSP and NPSS. p_{uncorr}, uncorrected *p*-values; p_{adj} Bonferroni corrected *p*-values. Effect sizes reported are Cliff's d, delta.

CDT = cold detection threshold; CPSP = central post-stroke pain; CPT = cold pain threshold; DMA = dynamic mechanical allodynia; DFNS = German Research Network on Neuropathic Pain; HPT = heat pain threshold; IQR = interquartile range; MDT = mechanical detection threshold; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; NPSS = non pain sensory stroke; PHS = paradoxical heat sensations (0–3); PPT = pressure pain threshold; QST = quantitative sensory testing; TSL = thermal sensory limen; VDT = vibration detection threshold; WDT = warm detection threshold; WUR = wind up ratio. Bold values indicate statistical significance with $p < 0.05$.

Discussion

Main Findings

With the aim of identifying potential predictors of CPSP, we present the results of the first prospective and longitudinal evaluation of QST profiles in patients with acute somatosensory stroke. Of the 75 study participants, 26 (34.7%) developed CPSP within 8 months. Before the onset of pain, CPSP patients had more severe cold hypoesthesia compared to NPSS patients, confirming 1 of our 2 hypotheses. Additional exploratory analysis showed that almost all thermal QST parameters differed between CPSP and NPSS patients on the symptomatic side or in the side-to-side differences before pain onset, with the side-to-side difference of cold pain perception, remaining significant after Bonferroni correction. Using a gradient-boosting approach, we were able to correctly classify future CPSP patients before they developed pain, with an overall accuracy of 84.6%, a recall of 75%, and a precision of 75%. Another notable finding is that approximately 80% of patients with unilateral somatosensory stroke (both CPSP and NPSS) had bilateral sensory QST changes (>2 SD from reference values) in both the acute and chronic phases.

CPSP after Somatosensory Stroke

In our cohort, 34.7% of stroke patients developed CPSP, a rate higher than reported in most previous

TABLE 5. QST Parameters in the Acute (Pre-Pain) Phase and Chronic Phase: Side-to-Side Differences

		Between group comparisons									
		Acute					Chronic				
Diagnosis		CPSP	NPSS	p_{uncorr}	p_{adj}	d	CPSP	NPSS	p_{uncorr}	p_{adj}	d
Total n (%)		20 (30.8)	45 (69.2)				20 (30.8)	45 (69.2)			
$_{sd}$CDT	Median (IQR)	−1.1 (−2.8 to −0.1)	−0.8 (−1.4 to 0.7)	0.118			−0.6 (−1.4 to 0.6)	−0.0 (−1.0 to 0.6)	0.388		
$_{sd}$WDT	Median (IQR)	−1.5 (−3.0 to −0.5)	−0.8 (−2.1 to 0.4)	0.121			−0.6 (−2.0 to 0.1)	−0.6 (−1.3 to 0.3)	0.459		
$_{sd}$TSL	Median (IQR)	−1.9 (−3.2 to −0.5)	−0.8 (−1.7 to 0.2)	**0.030**	0.328	−0.34	−1.0 (−2.4 to 0.6)	−0.6 (−1.6 to 0.4)	0.609		
$_{sd}$CPT	Median (IQR)	−0.4 (−1.1 to 0.2)	1.2 (0.0 to 2.3)	**0.0005**	**0.005***	−0.55	−0.1 (−0.7 to 0.7)	0.3 (−0.1 to 1.6)	0.075		
$_{sd}$HPT	Median (IQR)	−2.0 (−3.1 to −0.2)	−0.1 (−0.9 to 0.5)	**0.012**	0.131	−0.40	−0.4 (−1.0 to 0.3)	0.0 (−0.9 to 0.8)	0.631		
$_{sd}$PPT	Median (IQR)	−0.6 (−1.5 to 0.6)	0.0 (−0.6 to 0.6)	0.112			−0.2 (−1.4 to 0.5)	0.1 (−0.8 to 0.7)	0.241		
$_{sd}$MPT	Median (IQR)	−0.6 (−2.1 to 0.1)	0.0 (−1.2 to 1.9)	0.090			−0.1 (−2.4 to 1.3)	0.0 (−0.9 to 0.9)	0.467		
$_{sd}$MPS	Median (IQR)	−1.0 (−3.1 to 0.3)	−0.5 (−1.3 to 0.2)	0.280			−0.2 (−0.9 to 0.7)	−0.1 (−0.4 to 0.7)	0.486		
$_{sd}$WUR	Median (IQR)	0.6 (−0.1 to 1.7)	0.2 (−0.6 to 1.0)	0.056			0.3 (0.1 to 0.6)	0.2 (−0.2 to 0.6)	0.330		
$_{sd}$MDT	Median (IQR)	−1.3 (−3.6 to 1.4)	−0.7 (−2.3 to 0.3)	0.842			−1.6 (−1.9 to −0.8)	0.3 (−1.8 to 1.4)	**0.025**	0.276	−0.35
$_{sd}$VDT	Median (IQR)	−0.1 (−1.3 to 0.0)	0.0 (0.0–0.0)	0.068			0.0 (−1.1 to 0.0)	0.0 (0.0–0.0)	0.348		

QST side-to-side differences are indicated with "$_{sd}$" (eg, $_{sd}$CDT).

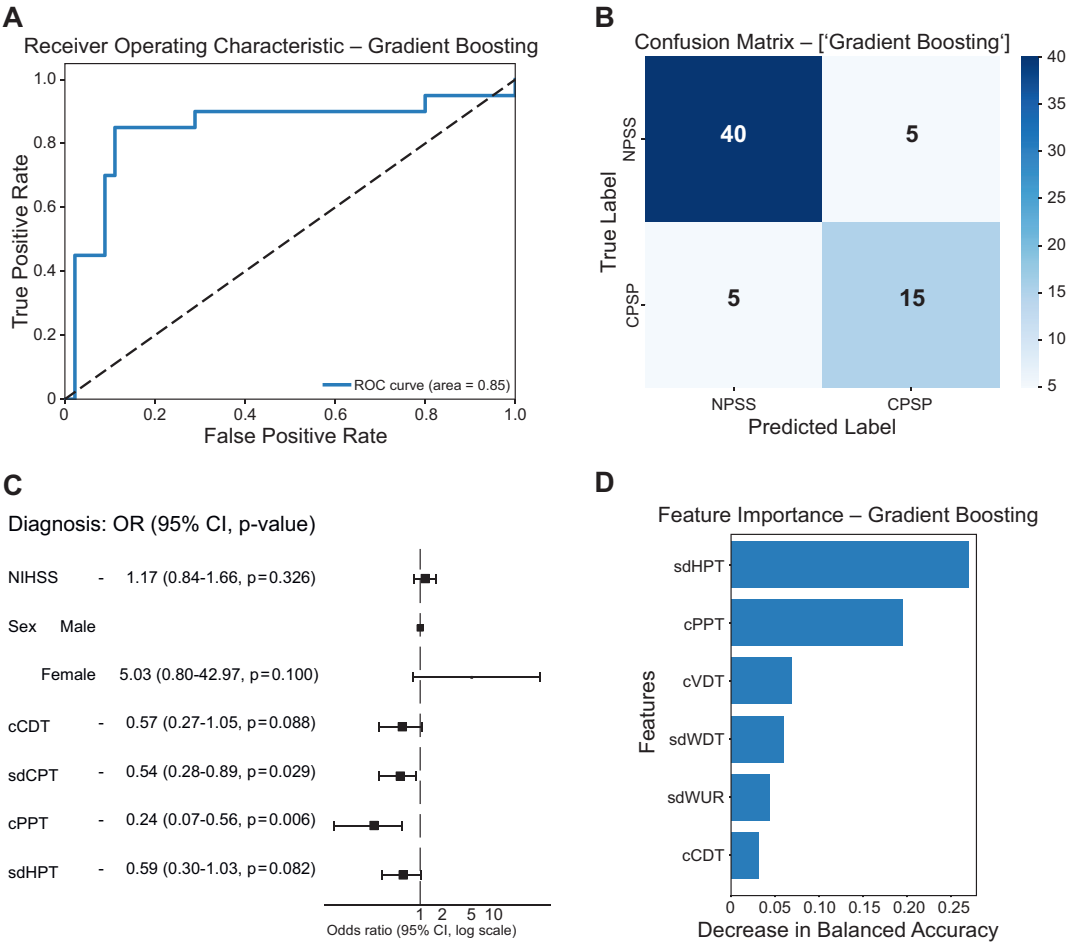
Explorative analysis of QST parameters for side-to-side differences using Mann–Whitney *U* tests. Blue color means "relative loss of function" compared to DFNS reference values; orange color means "relative gain of function" compared to DFNS reference values (based on the statistical comparisons given in Tables S4/S5). The *p*-values given here refer to the statistical comparison between CPSP and NPSS. p_{uncorr}, uncorrected *p*-values; p_{adj} Bonferroni corrected *p*-values. Effect sizes reported are Cliff's d, delta.

CDT = cold detection threshold; CPSP = central post-stroke pain; CPT = cold pain threshold; DMA = dynamic mechanical allodynia; DFNS = German Research Network on Neuropathic Pain; HPT = heat pain threshold; IQR = interquartile range; MDT = mechanical detection threshold; MPS = mechanical pain sensitivity; MPT = mechanical pain threshold; NPSS = non pain sensory stroke; PHS = paradoxical heat sensations(0–3); PPT = pressure pain threshold; QST = quantitative sensory testing; TSL = thermal sensory limen; VDT = vibration detection threshold; WDT = warm detection threshold; WUR = wind up ratio. Bold values indicate statistical significance with $p < 0.05$. *Indicates statistical significance after Bonferroni correction.

somatosensory stroke studies,[23] although some studies have reported prevalence exceeding 50% in patients with thalamic or medullary stroke.[41] Theoretically, this higher rate may have been because of a higher dropout rate among NPSS patients, however, even assuming that all dropouts of the study did not develop pain, the rate would still be 27.7%. The time delay between stroke onset and onset of pain ranged between 1 week and 8 months (Table 1), with most patients developing pain within 1 month, which agrees with previous observations.[41] The age and sex distribution of all included patients with somatosensory stroke (65 [55.5–70] years, female:male 1:1.5) were within the expected range at our institution.[42] Female sex as well as the severity of stroke (NIHSS) were associated with higher risk of CPSP in a univariate analysis, however, in the multivariate regression model NIHSS and sex were no longer significant predictors of CPSP. A study by Hansen et al.[2] has also reported that patients with CPSP were more often female, however, other studies have reported no sex differences, or a higher male to female ratio.[2,43,44] Regarding stroke severity, given the overall low NIHSS in our cohort, it seems plausible that it is not the increasing severity of stroke, but rather the specific site(s) of damage that is relevant for the development of CPSP. However, because we have not included severely affected stroke patients, our results might not extend to patients with severe stroke.

QST in Acute/Subacute Stroke

Although a few prior studies have performed sensory exams in acute stroke patients who later developed pain,[11] this study is the first to apply quantitative somatosensory testing. We found substantial differences between CPSP and NPSS patients in the acute/subacute "pre-pain" stroke phase, specifically we found compelling evidence for an increased CDT in CPSP patients. In exploratory analyses we found that CPSP patients differed from NPSS patients in almost all thermal and nociceptive parameters, which further supports previous interpretations that CPSP is



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Classifier	Accuracy	ROC_AUC	Recall	Precision	F1	Balanced Accuracy	Weighted F1
Gradient Boosting	84.6	0.85	75.0	75.0	75.0	81.9	84.6

FIGURE 2: Prediction of pain occurrence from the acute setting QST parameters. QST on the contralesional side is indicated with "$_{c}$" (eg, $_{c}$CDT). Side-to-side differences between the ipsilesional and the contralesional side are indicated with "$_{sd}$" (eg, $_{sd}$CDT). Gradient boosting classification (with leave-one out cross validation) based on QST findings in acute stage to predict pain occurrence. (A) ROC curve of the gradient boosting classifier. (B) Confusion matrix. (C) Odds ratio plot of the logistic regression. (D) Feature importance showing the contribution of the 6 QST features included in the classifier model. CDT, cold detection threshold; CPSP, central post-stroke pain; CPT, cold pain threshold; HPT, heat pain threshold; NIHSS, National Institutes of Health Stroke scale; PPT, pressure pain threshold; QST, quantitative sensory testing.

primarily a deficit in processing of protopathic information, rather than a deficit in epicritic information processing.[45] Overall, loss of function occurred much more frequently in CPSP patients and gain of function more frequently in NPSS patients.

When comparing the acute QST values in our study with the reference values of the DFNS cohort, CPSP patients showed overall a significant loss of temperature and mechanical perception, as well as hypoalgesia to pressure pain. NPSS patients, on the other hand, generally showed a loss of temperature and mechanical perception, but also a pronounced hyperalgesia to cold and mechanical pain. For example, only in the latter group did cold pain perception ($_{c}$CPT, $_{sd}$CPT) and mechanical pain perception and sensitivity ($_{c}$MPT, $_{c}$MPS) deviate from the DFNS reference values as gain of function. This indicates a tendency for hyperalgesia to cold and mechanical stimuli on the contralesional side in NPSS patients. It is important to emphasize that these results represent comparisons on the group level, however, as discussed below there is also some interindividual heterogeneity within the groups.

It is conceivable that edema may have affected patients' sensory perception,[46] however, given the very similar time points of the QST-exams, this would have affected both groups equally. To better account for a potential influence of edema, future studies might include MRI assessments such as quantitative T2 imaging and diffusion imaging.[47]

Toward Pain-Prediction

The exploratory findings that almost all temperature based QST measures differed between CPSP and NPSS patients before pain developed with 1 of them ($_{sd}$CPT) remaining significant after Bonferroni correction, provide further evidence that prediction of pain based solely on sensory examination might be possible. Beyond such group comparisons, the goal is that the clinician who treats a patient with somatosensory stroke gets tools at hand for the individual prediction of CPSP. To predict CPSP we used gradient boosting with LOOCV, which combines the predictions of several "weak" decision trees into a single strong learner in an iterative fashion and has been shown to be a powerful approach for classifying patients because of its high predictive accuracy and flexibility through hyperparameter optimization. This approach to predict CPSP resulted in a good overall accuracy of 84.6%.

Feature importance identified the difference in HPT between the contralesional and ipsilesional sides as the most significant contributor to the model. When comparing HPT values in CPSP patients with the reference values, 52.6% of patients exhibited heat pain hypoalgesia on the contralesional side compared to the ipsilesional side. At first glance, this may seem to contradict previous research suggesting that the presence of hyperalgesia (to brush, touch, cold, or pinprick) in a standardized clinical examination within 4 days after stroke onset predicts the development of CPSP.[11] However, previous studies, including this study find evidence for both hypoalgesia and hyperalgesia in different CPSP patients. Therefore, in addition to hypoalgesia in many patients, we also find hyperalgesia to heat pain in 15.8% and to mechanical pain in 35% of CPSP patients on the contralesional side.[11] In a previous study, both heat pain hypoalgesia as well as heat hyperalgesia were observed in central pain conditions (although not specifically in CPSP).[48] These results indicate that individual QST features can be heterogeneous in patients with CPSP, whereas patterns of symptoms, for example, identified by machine learning, might be more informative for predicting who might develop pain.

The second most important feature in the gradient boosting approach was ¿PPT, which was also a significant predictor in the logistic regression analysis. Our findings reveal that 35% of CPSP patients have a hypoalgesia to pressure pain. Previously in central neuropathic pain patients, the frequency of pressure pain hypoalgesia has been reported to be 14%, with 16% showing a hyperalgesia.[48]

Overall, we believe that these results represent an important step toward clinically meaningful pain prediction. Single abnormal QST values are variable, but our machine learning results indicate that the prediction of CPSP can be much improved by using a combination of 6 QST parameters. In the future, a clinician might use a simple app (eg, on a smartphone) to make these predictions after determining 6 QST values. As a next step, we call for a confirmatory multicenter study, the results of which could be the basis for future clinical trials on pain prevention in CPSP patients. Such a trial might also consider results of a recent study that, based on data from the United Kingdom Biobank, has shown a set of biopsychosocial factors, including sleep, neuroticism, mood, life stressors, and body mass index to be sufficient to predict the development and spread of chronic pain.[49]

Bilateral Sensory Deviations

Both patient groups showed perception deficits compared to the reference values from the DFNS, not only on the contralesional side, but also on the ipsilesional side, acutely and at the last QST follow-up. The ipsilesional side is often labelled as "unaffected" by the stroke and serves as a sensory control area in many studies.[11,20] However, we and others have previously shown that bilateral perception deficits occur in the chronic stage post-stroke.[19,50–52] These bilateral sensory symptoms were not limited to subjects with medulla or paramedian pons lesions, where bilateral facial and perioral symptoms are known to occur, but occurred also in patients with lesions in the other brain areas and were also observed on the extremities. One possible explanation includes sensory pathways that do not decussate in the spinal cord.[52,53] Another explanation could be subclinical involvement of the peripheral nervous system because of concomitant diseases including diabetes mellitus, arterial hypertension, and adiposity,[54] despite having excluded patients with peripheral polyneuropathy. However, these explanations do not easily explain that in the CPSP group we also see a change over time, for example, in heat pain perception on the ipsilesional side that is not evident in the NPSS group. Similarly, in a case series of 6 patients with CPSP, patients developed symptoms in contralateral (ie, ipsilesional) counterparts of the body areas where initial pain was most severe.[52]

Pathophysiological Implications

Three aspects of the QST differences between CPSP and NPSS patients in the acute and chronic phases of stroke are striking. (1) Most marked differences appear to occur for temperature-related parameters, particularly in relation to cold perception. (2) For almost all sensory parameters, CPSP patients show a relative loss of function compared to NPSS patients in both the acute and chronic stages. (3) Although both groups exhibit frequent bilateral

sensory abnormalities, the ipsilesional side developing QST abnormalities over time might be specific to the CPSP group (see previous paragraph).

In line with previous literature, we show that in CPSP patient temperature related parameters are primarily affected. Lesion studies have demonstrated that in pain patients thalamic lesions often affect the ventral posterior lateral nucleus of the thalamus, where the STT is thought to terminate,[5,7] as well as the anterior nucleus pulvinaris.[6] Furthermore, a case report has indicated that the delayed onset of CPSP after thalamic hemorrhage could be because of perilesional neural degeneration of the STT.[55] The authors used diffusion tensor imaging, which revealed progressive thinning and tearing of the STT as the patient's pain symptoms progressed.[55] The involvement of pathways processing protopathic information (eg, the STT) has been suggested to be a necessary but not sufficient condition for CPSP.[7]

Overall, the QST findings in our CPSP patient cohort—both in the acute and chronic phase—indicate loss of function in most parameters, especially regarding protopathic sensation. However, there is heterogeneity among individuals, with some patients exhibiting gain of function. It seems more likely that combinations of symptoms could cluster patients together, as shown in peripheral neuropathy.[56] Loss of function for pain parameters such as heat and pressure pain seems surprising as one might expect higher rates of evoked pain. Previous studies have reported gain of function, for example, up to 40% of patients experienced early evoked pain or dysesthesia.[11] Consistently, among our CPSP patients, a subgroup shows signs of "gain of function"—15.8% of our CPSP patients show heat pain hyperalgesia and 35% have hyperalgesia to mechanical pain. Therefore, it seems that the currently popular and plausible explanation that because of central sensitization following damage to pathways carrying protopathic information, neuronal hyperexcitability gradually develops into spontaneous central pain, either cannot be easily translated into "gain of function" symptoms or might have to be modified. Although we cannot draw firm pathophysiological conclusions from our data, the interindividual heterogeneity of sensory symptoms observed may suggest that different sensory constellations may eventually converge on a common pathway leading to central neuropathic pain. Ongoing functional and structural neuroimaging studies may help to solve this puzzle. For example, it will be interesting to repeat the study of a small group of 8 CPSP patients in whom a peripheral lidocaine nerve block abolished both, perception of peripheral input as measured by QST and pain, using functional neuroimaging to potentially identify a common pathway.[57]

Limitations

Our study's limitations include reliance on DFNS reference data instead of a local control group, which may overlook center and examiner variability. Although QST examiners were DFNS-trained, their awareness of participants' pain status could introduce bias, importantly, however, this does not apply to the predictive QST findings in the acute stage as all included patients did not report pain at this exam and, of course, neither patients nor the examiner could know about the (later) pain status. Our strict inclusion and exclusion criteria mean that our study population is carefully selected and well defined, but this also leads to a relatively small and unbalanced sample size. However, this reflects the reality in clinical practice, because most patients with somatosensory stroke do not develop pain. Regarding the bilateral QST findings, it is possible that stroke patients differ a priori from healthy individuals (eg, having subclinical alterations even before the stroke). A limitation of QST is that it is a demanding examination requiring patient input. Therefore, we excluded patients with more severe strokes, with aphasia, or neglect. Therefore, these results might not extend to patients with severe stroke. Although every attempt was made to keep QST timings consistent, the clinical nature of the study introduced variability in the timing of the assessments. We followed a clear operational rule for selecting the "before pain" and "after pain" assessments, and we observed no statistical differences in the QST timings between the 2 groups. The observation time was limited to 12 months, because CPSP mainly occurs within the first few months after a stroke.[1,2,23] However, a later onset of CPSP in the NPSS patients cannot be ruled out.[13,41] Last, the risk of overfitting in our classification model because of the small sample size necessitates cautious interpretation and validation in larger studies.

Conclusions

Our study is pioneering in prospectively applying QST to acute somatosensory stroke patients and identifying early sensory differences predictive of CPSP development. Notably, differences in cold perception between CPSP and NPSS patients shortly after stroke were found to be significant. Early classification of impending CPSP based on QST-patterns seems possible. Both NPSS and CPSP patients showed bilateral sensory changes in the acute and chronic post-stroke stages. The early post-stroke phase is critical, highlighting the importance of timely interventions. Integrating clinical assessments with QST can enhance the identification of patients prone to central neuropathic pain, enabling early therapeutic measures to mitigate pain chronification.

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Author Contributions

T.K., A.V., and G.J.J. were responsible for the conception and design of the study; S.A., E.P., J.M., K.V., E.A., X.C., T.K., S.H., A.V., and G.J.J. were responsible for the acquisition and analysis of data; S.A., E.A., J.M., A.V., and G.J.J. were responsible for the drafting a significant portion of the manuscript or figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

Data are available on reasonable request. The analysis code will be made available on github, epanagoulas/SOSENS.

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