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ORIGINAL ARTICLE

Somatosensory and trigeminal pathway abnormalities in Chinese patients with trigeminal neuralgia

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Abstract

This study aimed to evaluate somatosensory function in Chinese patients with trigeminal neuralgia (TN) using a standard quantitative sensory testing (QST) battery and electrophysiological tests consisting of contact heat-evoked potentials (CHEPs) and blink reflex (BR). Twenty patients with TN and 20 sex- and age-matched healthy controls were recruited for this study. A standard QST protocol recommended by the German Research Network on Neuropathic Pain was carried out on the patients' painful and contralateral faces, the controls' right faces, and all participants' right hands. The CHEPs and BR were recorded at the Cz electrode and bilateral lower bellies of the orbicularis oculi, respectively, with thermal stimuli applied to both sides of the patient's face and the control's right face. The cold detection threshold, heat pain threshold, and mechanical pain threshold on the painful face were lower than those of healthy controls ($P<0.05$), whereas the cold pain threshold and mechanical detection threshold were higher ($P<0.05$) on the painful faces than those of the contralateral faces from patients or healthy controls. Mechanical pain sensitivity was higher in both test sites than in healthy controls ($P<0.05$). Significantly longer *N* latencies ($P<0.05$) and lower *N*–*P* amplitudes ($P<0.01$) were detected in the patients' painful sites than in the contralateral sites and those of healthy controls. Comprehensive somatosensory abnormalities were found in painful facial sites in patients with TN, suggesting disturbances in the processing of somatosensory stimuli. Deficiencies in electrophysiological tests further revealed unilaterally impaired function of the trigeminal pathway in TN patients.

Keywords Trigeminal neuralgia · Quantitative sensory testing · Contact heat-evoked potentials · Blink reflex · Orofacial pain

Abbreviations

TN	Trigeminal neuralgia
QST	Quantitative sensory testing
CHEPs	Contact heat-evoked potentials
BR	Blink reflex
CDT	Cold detection threshold
WDT	Warm detection threshold
TSL	Thermal sensory limen
PHS	Paradoxical heat sensation
CPT	Cold pain threshold
HPT	Heat pain threshold
MDT	Mechanical detection threshold
MPT	Mechanical pain threshold
MPS	Mechanical pain sensitivity
DMA	Dynamic mechanical allodynia
WUR	Wind-up ratio
VDT	Vibration detection threshold
PPT	Pressure pain threshold
EEG	Electroencephalogram

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Introduction

Trigeminal neuralgia (TN) is a severely painful disease of the orofacial area and is characterized by painful paroxysmal attacks in the distribution region of the trigeminal nerve [1, 2]. Traditionally, TN has been recognized as a neuropathic pathology without clinically apparent neurological deficits through chairside examinations. In the current diagnostic criteria, TN diagnosis is mainly based on medical history and requires the exclusion of other dental and neurological problems [3–5]. This diagnostic criterion lacks auxiliary/laboratory evidence, requires special training, and has abundant clinical experience. In recent years, several studies have discovered neurological abnormalities in TN using more elaborate and quantitative laboratory tests, such as quantitative sensory testing (QST) [6–8] and electrophysiological tests [9–11], which may improve the diagnostic efficacy of TN.

Furthermore, QST is a psychophysiological method used to measure the sensory function of different afferent nerve fibers [12–14]. Abnormal QST results could reveal fiber-specific mechanisms underlying pain conditions [15–17]. Previous studies have found that TN patients present subclinical higher thermal and touch detection thresholds and lower thermal and mechanical pain thresholds on the painful side of the face [18, 19]. Another study reported generally increased touch detection thresholds and bilateral decreased thermal and mechanical pain thresholds, indicating peripheral and central neural pathological involvement in TN [6]. However, these conclusions were based on small sample case numbers and non-comprehensive QST parameters [7, 8], and few studies have measured sensory function in the extra-trigeminal region. A standardized and validated QST protocol was developed by the German Research Network on Neuropathic Pain (DFNS) [16, 17], comprising a comprehensive QST battery to measure human sensory functions. We hypothesized that a more comprehensive somatosensory abnormality might be detected by applying this protocol both in the trigeminal and extra-trigeminal regions in patients with TN.

Electrophysiological studies, such as evoked brain potentials and brainstem reflexes, can also assess the function of different neural pathways [20]. Previous studies applied electric or laser stimuli to the facial skin of patients with TN to evoke potentials and found that they were characterized by delayed evoked potential latencies and decreased evoked potential amplitudes, but normal blink reflex (BR) or jaw-jerk reflex [10, 20, 21]. Recently, contact heat-evoked potentials (CHEPs) have been developed [22–24] that deliver heat stimuli to the skin and selectively activate thermal pathways similar to the pain pathway. To the best of our knowledge, no CHEP studies have assessed small fiber nerve function in patients with TN.

In this study, we aimed to assess the somatosensory function and electrophysiological characteristics of clinically diagnosed patients with TN using QST, CHEPs, and BR. We hypothesized that a quantitatively and comprehensively damaged somatosensory function in patients was presented using these laboratory tests.

Materials and methods

Ethics

This study is part of a population study on sensory function changes in Chinese patients with orofacial pain and was approved by the Ethics Committee for Biomedical Sciences at Peking University School of Stomatology (PKUSSIRB-2013012). This study was conducted in accordance with the principles of the Declaration of Helsinki. Signed informed consent forms were obtained from all the participants before entering the study.

Participants

Twenty patients with TN were recruited from the maxillofacial department of Peking University School of Stomatology. The inclusion criteria were as follows: (1) clinically diagnosed with TN by a specialist according to the International Classification of Headache Disorders 3rd edition beta (ICHD-3 beta), (2) apparent pain intensity, evaluated using a numerical rating scale (NRS-100, where 0 represents pain-free and 100 represents the maximal pain that could be imagined), and > 30 for recent pain attacks. The exclusion criteria were as follows: (1) bilateral TN or background pain; (2) clinically detected apparent sensory or reflex abnormalities in the facial region; (3) prior surgery for TN or other surgery and trauma in the facial region; (4) craniocerebral occupying lesions detected by magnetic resonance imaging (MRI) or computed tomography (CT); (5) recent intake of analgesics, anesthetics, and psychotropic drugs; (6) other chronic pain disorders; (7) systemic diseases such as severe diabetes and heart diseases; (8) psychiatric diseases or communication barriers, and (9) female participants in the menstrual period to avoid the potential influence of fluctuating sex hormones or menstrual pain.

Twenty age- and sex-matched pain-free volunteers were recruited as the control group from Peking University and the neighboring community through flyers, posters, and social media. Controls were screened according to the aforementioned exclusion criteria.

Test environment and process

The entire test was conducted in a quiet room with a controlled temperature of 21–23 °C and no direct sunlight. Participants were asked to lie on a dental chair, stay relaxed, lightly close their eyes, and avoid clenching their teeth. The sequence of the tests is shown in Fig. 1. The content of each test was explained to participants before the application. All the tests were performed by the same trained dentist. All stimuli applied to the patients avoided trigger points.

Demography and pain characteristics

Basic demographics of all participants and the pain characteristics of the patients were documented by a clinical inventory, including the affected trigeminal branches, disease course (from the first onset), pain description, and the pain intensity of recent attacks using the NRS-100.

Quantitative sensory testing

The standard QST protocol established by DFNS [15, 17] was used in this study, which consists of seven tests including 13 parameters, covering all fiber types innervating thermal and mechanical senses, and examining both peripheral and central nociception.

2.5.1. We used a thermal sensory analyzer (Medoc Pathway, Ramat Yishai, Israel) with ATS thermode (Medoc: 30 mm 30 mm, square surface) to assess the cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), and heat pain threshold (HPT). The CDT, WDT, CPT, and HPT were measured three times, and the averages were used as the final values [25]. For the TSL test, the temperature first increased, and the participants pressed a button when they perceived a change. The number of PHS during the TSL was recorded as previously described. The temperature baseline was set at 32 °C and ramped at 1 °C/s with cut-off temperatures of 0 °C and 50 °C [25].

2.5.2. For the mechanical detection threshold (MDT), von Frey filaments (Semmes–Weinstein monofilaments, Touch-Test™ Sensory Evaluator, North Coast Medical, Morgan Hill, CA, USA) were used. Five repeated measurements were recorded in a sequence of increasing and decreasing stimulus intensities, and the final value was the geometric average of all measurements [27–29]. Seven weighted pinpricks validated in our previous work [25–27] were used for the mechanical pain threshold (MPT). Similar to the MDT, the MPT was measured using the method of limits.

2.5.3. Mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA) were assessed using stimulation–response assessment, as previously described [27–29]. Pinprick stimulators were used to measure the MPS. Three tactile stimulators were used for DMA: a cotton wisp (~ 3 mN), a cotton wool tip (Q-tip, ~ 100 mN) attached to a flexible handle, and a disposable toothbrush (Top Dent®, Meda AB, Solna, Sweden, ~ 200–400 mN) [27–29]. A series of 10 different stimuli was applied, and the participants chose a pain rating for each stimulus from 0 to 100 with the endpoint '0' indicating "no pain" and '100' indicating the "most intense pain imaginable". This series was repeated three times in different orders [27–29]. The wind-up ratio (WUR) was measured as the perceived pain intensity of a sequence of 10 identical pinprick stimuli repeated at 1 Hz divided by the pain intensity of a single stimulus presentation [27–29].

2.5.4. The vibration detection threshold (VDT) was measured using a graded tuning fork (64 Hz, 0–8 scale, Rydel–Seiffer). Participants reported that they could no longer feel the sensation on a 0–9 scale [27–29].

2.5.5. For the pressure pain threshold (PPT), a computerized pressure Algometer (AlgoMed, Medoc) with a probe covered with rubber and a surface area of 1 cm^2 was used. Participants were instructed to press a button when pressure pain was felt under a constant application rate of 30 kPa/s [27–29].

Next, WUR, VDT, and PPT were measured in triplicate and averaged to determine the final values.

The QST stimuli were applied to both sides of the patient's face and the control's right face. The CDT, WDT, TSL, PHS, HPT, CPT, MDT, MPT, MPS, and WUR

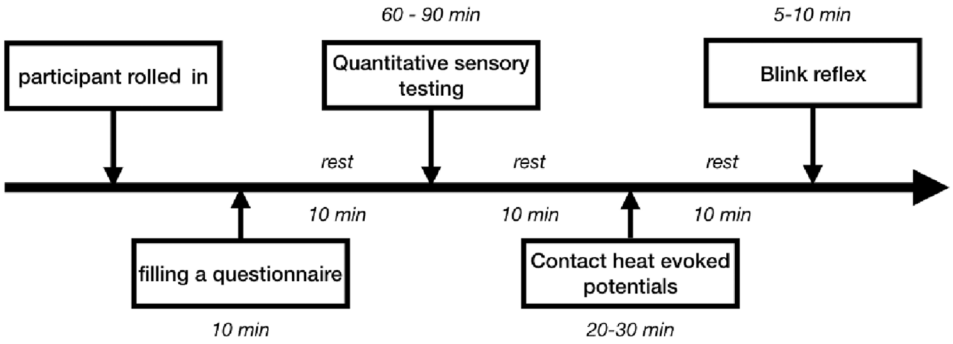

Fig. 1 Flow chart of the whole test. The whole test lasted 2–3 h based on the number of test sites and the compliance of the participants

stimuli were delivered to the skin innervated by the affected nerve on the painful face, that is, on the forehead (if V1 is affected), medial cheek (if V2 is affected), or the skin on the lower edge of the mandible (if V3 is affected). The VDT stimuli were delivered to the nearest bone mark according to the affected branch, that is, on the orbital rim, zygomatic process, or lower edge of the mandible, and the ulnar styloid process on the hand. PPT stimuli were applied to the bellies of the temporalis and masseter muscles. For extra-trigeminal region assessment, the QST was tested on the right hand of all participants.

Z scores of QST results

Z-score transformations for the patients' QST data were performed in comparison to controls, as previously described [25, 27]. *Z* scores > 0 indicate a gain of function or greater sensitivity to corresponding stimuli, and *z* scores < 0 indicate loss of function or decreased sensitivity to corresponding stimuli [25, 27]. Sensory abnormalities for each parameter were defined as *Z* scores outside the 95% confidence interval of the controls (*Z* score < -1.96 or *Z* score > 1.96). The frequency of the sensory abnormalities was also assessed.

Electrophysiological tests

A CHEP stimulator (Medoc Ltd., Ramat Yishai, Israel) with a thermode area of 573 mm^2 was used to deliver CHEP stimuli. The thermode heating rate was 70 °C/s and the cooling rate was 40 °C/s. The baseline temperature was set at 32 °C, and 25–30 stimuli were presented at random intervals of 10–15 s. The destination temperature was set at 51 °C to provide a robust peak value from the maximal negative wave to the maximal positive wave (N–P wave) of CHEPs for the Aδ fiber pathway, according to previous studies [28] and our pilot experiment. The latencies and amplitudes of the N–P waves were then averaged across all replications of each stimulus condition. The CHEP stimuli were delivered to the angulus oris bilaterally on the patient's face and one right face of the controls. The CHEPs were recorded from a surface electrode placed on the Cz site following the 10–20 international electroencephalogram (EEG) system and referenced using an Fpz electrode [23]. A ground wrist electrode was placed on the right hand. A 0.1–100 Hz bandpass filter was applied. The impedance of all electrodes was maintained below 5 Ω, and the EEG signal was recorded using an EMG/EEG recording system (Keypoint, Dantec, Denmark).

The same thermode and EMG/EEG recorder used for the CHEPs were used for contact heat-evoked BR, as previously described. The destination temperature was set at 55 °C, and the stimuli were repeated three times at 20-s intervals. The BR stimuli were delivered to the skin near the inferior orbital hole bilaterally on the patient's face and one right face of the controls. Next, R2 (the same side of the stimulus) and R2' (the contralateral side of the stimulus) signals were recorded bilaterally from the lower belly of the orbicularis oculi and referenced from the skin, 1 cm outside the lateral canthus. The bilateral latencies of the BR waves were then averaged from all repeated stimulus presentations.

Statistics

All statistical analyses were performed using SPSS software (version 20.0; IBM, Armonk, New York City, USA). Graphs were created using SPSS and Excel 2016 software for Mac (Microsoft Corp., Redmond, Washington, USA). Fisher's exact test was used to compare the categorical data. For continuous data, the Kolmogorov–Smirnov test was conducted to test for normal distribution. If the normal distribution was not met, a standard logarithmic transformation was performed. A paired *t* test was performed to compare QST data, CHEPs, and BR results between the painful and contralateral sides of the patients. An unpaired *t* test was performed to compare QST data, CHEPs, and BR results between patients and controls. Two-way ANOVA was used to examine the impact of disease, sex, and disease × sex interaction on all parameters. *P* values were 2-tailed with a significance level of 0.05.

Results

Demographic and pain characteristics

The demographic data and pain characteristics of the recruited participants are shown in Table 1. The most affected trigeminal nerve branch was the second branch (V2), accounting for 75% (15/20) of all patients, followed by the third branch (V3, 20%, 4/20), and the first branch (V1, 5%, 1/20). The pain was described as "pinching", "cutting", and "electric shock, reflecting acute pain. The pain history was 6.4 ± 4.6 months (mean ± SD), and the pain intensity was moderate to severe (54.1 ± 18.1, 0–100 NRS).

Quantitative sensory testing results

Comparisons between the sites and groups are presented in Table 2. The results for each QST parameter are presented in Table 3. The CDT ($t = -5.073$, $P < 0.001$), HPT ($t = -2.653$, $P < 0.05$), and MPT ($t = -3.752$, $P < 0.01$) of the painful side of the patients were significantly lower than those of the contralateral side. The CPT ($t = 4.588$, $P < 0.001$) and MDT ($t = 4.046$, $P < 0.001$) of the painful side of the patients were significantly higher than those of the contralateral side. The CDT ($t = -4.293$, $P < 0.001$), HPT ($t = -2.774$, $P < 0.01$), and MPT ($t = -2.417$,

Table 1 Demographic and pain characteristics of participants

Groups	TN patients	Pain-free controls	*P*
Sample size (*n*)	20	20	–
Age (years, mean ± SD)	47.7 ± 12.2	45.6 ± 12.7	0.6176[a]
Sex (M:F)	8:12	8:12	1.000[b]
Affected branch (V1:V2:V3)[c]	1:15:4	–	–
Pain history (months, mean ± SD)	6.4 ± 4.6	–	–
Pain description	10	–	–
Pinching	3	–	–
Cutting	2	–	–
Electric shock-like	5	–	–
Others[d]			
Pain intensity (mean ± SD)[e]	54.1 ± 18.1	–	–

The clinically diagnosed trigeminal neuralgia patient group showed severe acute pain characteristics mostly affecting the second branch of the trigeminal nerve

[a]Unpaired *t* test

[b]Fisher's exact test

[c]V1: the first branch of trigeminal nerve, ophthalmic nerve; V2: the second branch of trigeminal nerve, maxillary nerve; V3: the third branch of trigeminal nerve, mandibular nerve

[d]Others were described as aching pain, throbbing pain, scurrying pain, wind blowing-like pain and acute pain in Chinese

[e]Numeric rating scale (0–100, "0" = pain free, "100" = the most severe pain one can imagine)

Table 2 Comparisons of QST parameters among groups

Comparisons		CDT	WDT	TSL	CPT	HPT	MDT	MPT	MPS	WUR	VDT	PPTM	PPTT	PPTH
PF vs CF	t^a	**− 5.073**	1.622	0.6382	**4.588**	**− 2.653**	**4.046**	**− 3.752**	1.942	0.6174	0.8482	0.9431	0.2536	–
	P^a	**< 0.001**	0.1212	0.531	**< 0.001**	**< 0.05**	**< 0.001**	**< 0.01**	0.0671	0.5443	0.4069	0.3575	0.8026	–
PF vs Controls	t^b	**− 4.293**	**2.343**	**2.544**	**2.143**	**− 2.774**	**5.119**	**− 2.417**	**3.181**	1.195	1.1511	0.8631	0.4459	–
	P^b	**< 0.001**	**< 0.05**	**< 0.05**	**< 0.05**	**< 0.01**	**< 0.001**	**< 0.05**	**< 0.01**	0.2393	0.1391	0.3935	0.6582	–
CF vs Controls	t^b	− 0.167	1.415	1.939	0.1295	− 1.609	1.489	− 0.155	**2.456**	0.7553	0.8083	1.5	0.3577	–
	P^b	0.8683	0.1652	0.06	0.8976	0.1159	0.1447	0.8776	**< 0.05**	0.4547	0.424	0.1418	0.7225	–
RH	t^b	0.5222	1.683	0.9895	1.654	0.1583	1.573	0.7739	1.316	1.82	1.388	–	–	1.718
	P^b	0.6045	0.1007	0.3287	0.1064	0.8751	0.124	0.4438	0.1961	0.0766	0.1733	–	–	0.094

CDT cold detection threshold, *WDT* warm detection threshold, *TSL* thermal sensory limen, *CPT* cold pain threshold, *HPT* heat pain threshold, *MDT* mechanical detection threshold, *MPT* mechanical pain threshold, *MPS* mechanical pain sensitivity, *WUR*: wind-up ratio, *VDT* vibration detection threshold, *PPTM* pressure pain threshold at the masseter, *PPTT* pressure pain threshold at the temporalis, *PPTH* pressure pain threshold at the right hand. The results of paradoxical heat sensation (PHS) and dynamic mechanical allodynia (DMA) were not listed since they were 0 in all participants. Before *t* test comparisons, a standard logarithmic transformation was performed for the MDT, MPT, MPS, and WUR measures to meet the normal distribution. PF: the painful side of the patients' face. CF: the contralateral side of the patients' face. RF: the controls' right face. RH: the comparison between the QST results from the right hand of the patients and the controls. The results in bold indicate significant differences in the comparison. a: Paired t test. b: Unpaired t test

$P < 0.05$) of the patients' painful faces were significantly lower than those of healthy controls. The WDT ($t = 2.343$, $P < 0.05$), CPT ($t = 2.143$, $P < 0.05$), TSL ($t = 2.544$, $P < 0.05$), MDT ($t = 5.119$, $P < 0.001$), and MPS ($t = 3.181$, $P < 0.01$) of the painful faces of patients were significantly higher than those of healthy controls. The MPS ($t = 2.456$, $P < 0.05$) of the contralateral face of patients was significantly higher than that of controls, suggesting possible central sensitization in patients with TN. No significant group differences were observed in the right hand.

Z scores of the QST data

The frequency of sensory abnormalities (*Z*-score > 1.96 or < − 1.96) was investigated (Fig. 2). There was a significantly higher frequency of loss of function (*Z*-score < − 1.96) for MDT (60%) on the painful face of patients than on the right side of controls ($P < 0.01$). On the contralateral side of patients, one-third showed loss of function (Z-score < − 1.96) in the MDT (33%, 4/12),

Table 3 Results of QST parameters for all participants (mean ± SD)

	Painful face	Contralateral face	Controls' face	Patients' hand	Controls' hand
CDT, Δ°C	− 1.61 ± 0.55	− 0.98 ± 0.4	− 0.95 ± 0.41	− 1.56 ± 0.79	− 1.42 ± 0.85
WDT, Δ°C	1.49 ± 0.59	1.31 ± 0.51	1.08 ± 0.52	3.17 ± 1.92	2.34 ± 1.1
TSL, °C	3.39 ± 1.17	3.23 ± 1.27	2.57 ± 0.84	5.97 ± 2.4	5.22 ± 2.43
CPT, °C	21.96 ± 4.14	18.85 ± 5.16	18.63 ± 5.58	15.92 ± 5.58	18.59 ± 4.59
HPT, °C	38.45 ± 2.92	39.7 ± 2.64	41.27 ± 3.49	43.29 ± 3.87	43.09 ± 3.87
MDT, mN	0.68 ± 0.54	0.32 ± 0.27	0.21 ± 0.12	1.75 ± 1.65	1.21 ± 1.1
MPT, mN	34.4 ± 17.94	46.59 ± 15.77	50.47 ± 26.07	86.3 ± 45.64	93.1 ± 42.23
MPS (− /100)	1.89 ± 1.05	1.65 ± 0.87	1.1 ± 0.71	0.63 ± 0.36	0.48 ± 0.24
WUR	3.07 ± 0.97	3.02 ± 1.17	2.73 ± 1.22	3.11 ± 1.12	2.52 ± 0.82
VDT (− /8 scale)	7.2 ± 0.38	7.27 ± 0.35	7.35 ± 0.24	7.55 ± 0.5	7.72 ± 0.2
PPTM, KPa	170.8 ± 57.58	163.5 ± 36.41	186.6 ± 58.32	–	–
PPTT, KPa	209.4 ± 61.93	211.6 ± 53.69	218.1 ± 60.99	–	–
PPTH, KPa	– –	–	–	325.7 ± 65.33	365 ± 78.92

Bold values indicate a significance level of 0.05

CDT: cold detection threshold, WDT: warm detection threshold, TSL: thermal sensory limen, CPT: cold pain threshold, HPT: heat pain threshold, MDT: mechanical detection threshold, MPT: mechanical pain threshold, MPS: mechanical pain sensitivity, WUR: wind-up ratio, VDT: vibration detection threshold, PPTM: pressure pain threshold (PPT) at the masseter, PPTT: PPT at the temporalis, PPTH: PPT at the right hand. The results of paradoxical heat sensation (PHS) and dynamic mechanical allodynia (DMA) were not listed since they were 0 for all participants. Values of CDT and WDT were changes of the temperature Δ°C (Δ = test value-32 °C). Negative Δ indicates that the test value was lower than the base temperature, and vice versa

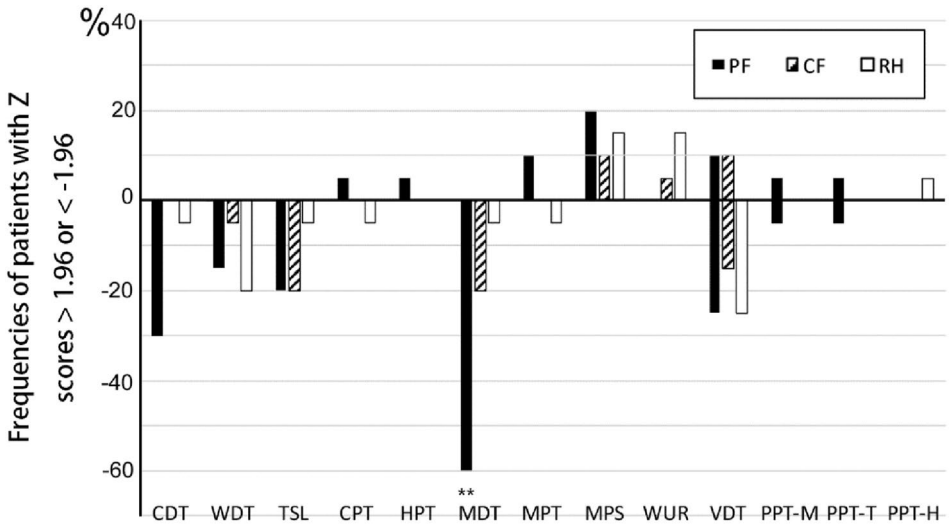

Fig. 2 Frequencies of abnormal *Z* scores from the quantitative sensory testing in trigeminal neuralgia patients. Bars with a positive direction show the frequency of *Z* scores > 1.96, indicating gain of function. Bars with a negative direction show the frequency of *Z* scores < − 1.96, indicating loss of function. Significantly higher frequency of abnormal *Z* scores than that of the controls; Fisher's exact test, $P < 0.01$. *CDT* cold detection threshold, *WDT* warm detection threshold, *TSL* thermal sensory limen, *CPT* cold pain threshold, *HPT* heat pain threshold, *MDT* mechanical detection threshold, *MPT* mechanical pain threshold, *MPS* mechanical pain sensitivity, *WUR* wind-up ratio, *VDT* vibration detection threshold, *PPTM* pressure pain threshold at the masseter, *PPTT* pressure pain threshold at the temporalis, *PPTH* pressure pain threshold at the right hand. *PF* the painful face of the patients. *CF* the contralateral face of the patients. *RH* the right hand of the patients

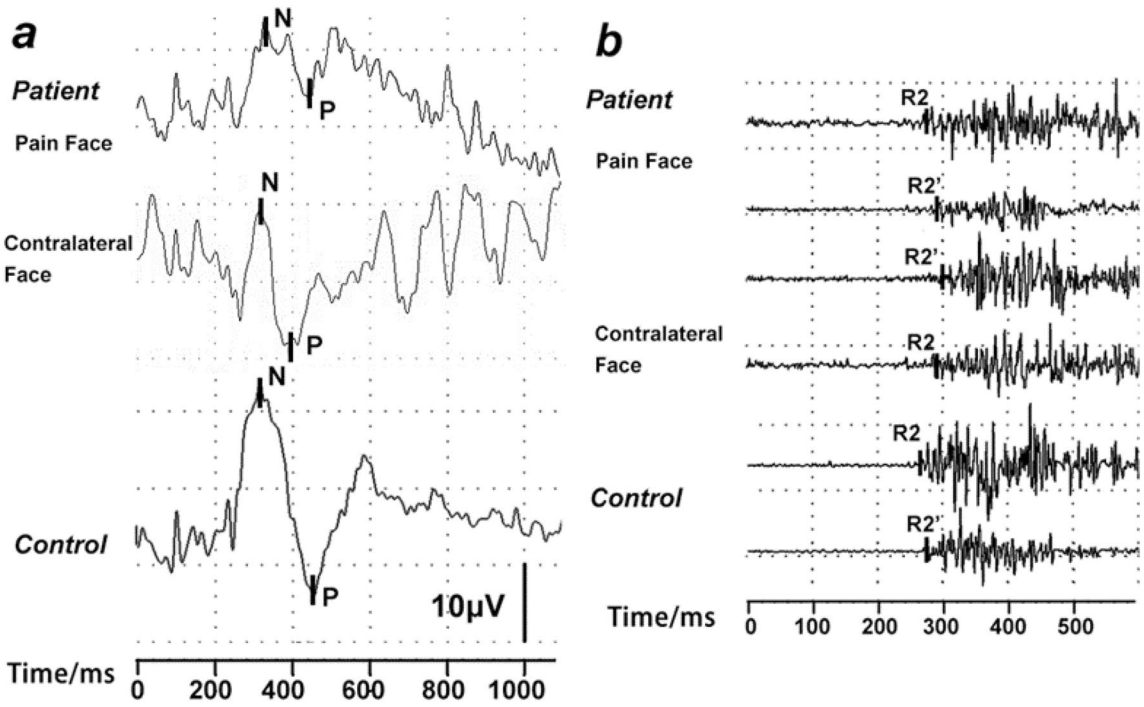

Fig. 3 Representative waves from the electrophysiological tests. **a** Contact heat-evoked potentials (CHEPs) from a healthy control participant and a patient, with stimulation applied on facial regions and recorded from the FCz electrode. A *N*–P wave could be recorded from the Cz electrode. Note that the N latency was delayed with a decreased *N–P* amplitude on the painful face in the patients compared with controls. **b** Blink reflex (BR) from a healthy control participant and a patient with applied stimulation on facial regions (reported from the bilateral lower bellies of orbicularis oculi). R2 was recorded from the same side as the heat stimulus, while R2' was recorded from the contralateral side

hinting at hypoesthesia. Other QST parameters were also detected with abnormal *Z*-scores (Fig. 2).

Electrophysiological tests

The N-P waves of CHEPs (Fig. 3a) and R2/R2' waves of BR (Fig. 3b) were evoked in both patients and controls (Table 4). The *N–P* waves of CHEPs in four patients and the R2/R2' waves of BR in five patients and four controls were unrecognizable and thus excluded from the analysis. There was no difference in the evoked rates of recognizable waves between the patients and controls (CHEPs: $P = 0.106$, BR: $P = 1.000$). The *N* latency was significantly longer on the painful side than on the contralateral face of patients ($t = 2.854$, $P < 0.05$) and the right face of controls ($t = 3.626$, $P < 0.001$). The *N–P* amplitude was significantly smaller on the painful side than on the contralateral face ($t = 3.378$, $P < 0.01$) and the right face of controls ($t = 4.783$, $P < 0.001$). There were no significant differences in P latency, R2 latency, or R2 latency among the comparisons of sites.

Sex differences

For most of the parameters, there was no sex differences, expect for MPT [Predicted mean (Least Square) female vs. male: 36.19 vs. 51.80 mN, $P = 0.0303$], MPS [Predicted mean (Least Square) female vs. male: 1.775 vs. 1.068 mN, $P = 0.0138$] and PPT [Predicted mean (Least Square) female vs. male: 163.9 vs. 201.3 kPa, $P = 0.0444$]. The sex difference suggested that females were more sensitive to mechanical pain stimuli than males were. The impact of disease × sex interaction was significant in CDT ($P = 0.0237$) and *N–P* amplitude ($P = 0.0455$). The detailed analysis found that female [Predicted mean (Least Square): CDT − 1.76 °C, N-P amplitude 7.47 μV] but not male TN patients [Predicted mean (Least Square): CDT − 1.39 °C, *N–P* amplitude 15.63 μV] had lower CDT and *N–P* amplitude than both females [Predicted mean (Least Square): CDT − 0.82 °C, *N–P* amplitude 27.7 μV] and male [Predicted mean (Least Square): CDT − 1.15 °C, *N–P* amplitude 22.85 μV] healthy controls, suggesting that female TN patients were less sensitive to cold sensory and potentially more central pain inhibition than male patients.

Table 4 Results and comparisons of electrophysiological parameters of the TN patients and controls

	Patients		Controls (γ)	α *vs* β	α *vs* γ	β *vs* γ
	Painful Face (α)	Contralateral Face (β)				
CHEPs	$n=16$	$n=16$	$n=20$			
N latency (ms)	376.6 ± 40.12	351.3 ± 37.27	331.0 ± 35.32	**$t^b=2.854$** **$P^b<0.05$**	**$t^c=3.626$** **$P^c<0.001$**	$t^c=1.673$ $P^c=0.1034$
P latency (ms)	456.8 ± 62.92	432.5 ± 56.47	437.5 ± 31.46	$t^b=1.931$ $P^b=0.0727$	$t^c=1.2$ $P^c=0.2385$	$t^c=0.3334$ $P^c=0.7409$
N-P amplitude (μV)	10.53 ± 8.65	18.84 ± 13.23	25.80 ± 10.15	**$t^b=3.378$** **$P^b<0.01$**	**$t^c=4.783$** **$P^c<0.001$**	$t^c=1.786$ $P^c=0.083$
BR	$n=15$	$n=15$	$n=16$			
R2 latency (ms)	273.0 ± 30.64	270.3 ± 36.15	269.7 ± 45.54	$t^b=0.4377$ $P^b=0.6683$	$t^c=0.2359$ $P^c=0.8151$	$t^c=0.039$ $P^c=0.9691$
R2' latency (ms)	273.8 ± 30.66	271.9 ± 36.58	271.9 ± 44.98	$t^b=0.3000$ $P^b=0.7686$	$t^c=0.1338$ $P^c=0.8945$	$t^c=0.0048$ $P^c=0.9962$

Results and comparisons of contact heat-evoked potentials (CHEPs) and blink reflex (BR) of the TN patients and controls. The *N* latency and *N–P* amplitude of the patients' painful faces were significantly delayed or decreased compared with those of the contralateral faces and those of the controls' faces. **N–P* waves of CHEPs in four patients and R2/R2' waves of BR in five patients and four controls were unrecognizable and thus excluded from the analysis

Bold values indicate a significance level of 0.05

[a]Fisher's exact test

[b]Paired *t* test

[c]Unpaired *t* test

Discussion

This study reported comprehensive abnormal QST results and electrophysiological data from Chinese patients with TN. The main findings include the following: (1) in the painful facial site of TN patients, thermal (via CPT and HPT) and mechanical (via MPT and MPS) hyperalgesia and thermal (via CDT and WDT) and mechanical (via MDT) hypoesthesia was detected, which suggested peripheral Aβ, Aδ, and C fiber dysfunction; (2) on the contralateral facial site of TN, mechanical hyperalgesia was demonstrated (via MPS), suggesting possible central sensitivity involvement; and (3) for electrophysiological tests, delayed N wave latency and decreased *N–P* amplitude of CHEPs were found on the painful facial site of TN, also indicating the peripheral dysfunction of the Aδ fiber pathway.

Peripheral nerve fiber dysfunction

On the painful face of patients with TN, decreased CDT and increased WDT, TSL, and MDT indicated thermal and mechanical hypoesthesia, while decreased HPT and MPT and increased CPT and MPS indicated thermal and mechanical hyperalgesia, reflecting peripheral *Aβ*/*Aδ*/*C* nerve fiber dysfunction. These results extend previous QST studies on TN [6–8, 18, 29], which also found hyperalgesia and hypoesthesia in the affected region.

Peripheral hypoesthesia indicated peripheral dysfunction of the large myelinated trigeminal fibers of the sites affected by TN, which is consistent with anatomical and pathological studies of demyelinated *Aβ* fibers in the compressed trigeminal nerve root [30]. Hyperalgesia may have been caused by the sensitization of *Aδ*/*C* fibers. In patients with TN, focal demyelinated *Aβ* fibers could form ephaptic contact and transmission with neighboring nociceptive myelinated Aδ and non-myelinated C fibers [31], where ectopic discharges and additional strikes could precipitate a TN pain attack [32, 33], which may sensitize these nociceptive fibers. Further, female participants showed increased mechanical hyperalgesia (as discovered by MPT, MPS, and PPT) than male participants, and female patients had lower CDT and N-P amplitudes than male patients. Similar results were previously observed in PPT and ischemia pain threshold [34, 35] and may be due to differences in sex hormones, endogenous opioid systems, and psychosocial mechanisms [36].

QST evidence for central sensitization

We found mechanical hyperalgesia (via MPS) on both sides of the patient's face, whereas TN pain attacks occurred on only one side. This widespread hyperalgesia in patients with TN indicates potential sensitization to the central nervous system. Sinay et al. found a decreased pain threshold in unaffected trigeminal branches [7], and Younis et al. reported decreased pain thresholds on the face and hand in patients

with TN [6], which are findings indicative of the central sensitization mechanism of TN. Functional brain imaging studies have also reported changes in the central nervous system of TN, such as the insular and anterior cingulate cortices [37, 38]. Hence, our study extends the laboratory evidence of central sensitization in patients with TN.

Other QST studies have barely reported evidence of central sensitization in TN patients, partially because MPS has not been examined, and few studies have reported data from non-affected regions. Therefore, we recommend that sensory examinations for TN should include comprehensive pain threshold parameters conducted in both painful and remote regions.

Hypoesthesia disclosed by Z scores

Z-scores can better disclose individual sensory abnormalities in neuropathic diseases. In the current study, the prominent finding from the *Z*-scores was a large proportion of patients with loss of function via MDT (60%, 12/20) on the painful face, suggesting a high frequency of peripheral hypoesthesia. This result indicates the unilateral dysfunction of Aβ fibers in patients with TN. Moreover, peripheral hypoesthesia via loss of function assessed by the MDT (33%, 4/12) was also present in the contralateral face of patients with TN, hinting at wide-spreading hypoesthesia, which may have been caused by the presynaptic inhibition of Aβ fibers at the spinal level [39] and is induced by pain-activated C fibers [19], also indicating central mechanism involvement.

Electrophysiological evidence for Aδ pathway dysfunction

The N-P wave of CHEPs was obtained at 51 °C, with the latencies and amplitudes of the controls consistent with previous data obtained in healthy individuals [22, 23]. A heat stimulus of 51 °C is considered to stimulate *Aδ* mechano-heat-sensitive nociceptors (AMH) [40], and lower temperatures of 41 °C can be used to stimulate C fibers in the non-orofacial region [22, 28]. However, efforts to apply 41 °C to the face failed to result in *N–P* waves in previous studies [22, 28], which may be due to the lower density of heat-sensitive receptors expressed by C fibers on the face. However, the actual distribution of these receptors in the orofacial region remains unclear. Electrophysiological methods that selectively assess unmyelinated C fibers in orofacial regions remain a challenge.

On the painful side of the TN patients' faces, the N latency of CHEPs was delayed, and the *N–P* amplitude decreased. Similar changes have been reported in laser-evoked potential studies [41]. Delayed *N* latency suggests lower nerve conduction velocity of small myelinated fibers, possibly derived from pathological changes upon nerve root compression [42]. The amplitude on the painful side was lower than that on the control's right face, indicating less pain perception, in contrast to the QST findings of peripheral hyperalgesia. However, the mechanisms underlying this contradiction remain unclear. Le et al. found a similar phenomenon, and they speculated that it may reflect the abnormal central pain inhibition mechanisms in TN, such as diffused noxious inhibition control (DNIC), which means that pre-existing pain could reduce the amplitude of evoked potentials at the central level [41].

Although the function of multiple types of nerve fibers was affected, we did not find an abnormal BR in TN patients, which is consistent with previous studies [9, 28]. In TN without primary causes other than nerve root compression, structural changes in the nervous system are considered to be slight or reversible [6, 40] and insufficient to disrupt the trigeminal reflex. In these patients, temporal-spatial summation at synapses is sufficient to provide robust brainstem reflexes and results in basically unaffected latencies [28].

Strengthens and limitations

Electrophysiological tests and QST are previously used to detect somatosensory and nerve pathway functions in some neuropathies and chronic pain conditions [6, 7, 12, 14]. Of these, there were three studies regarding TN [6–8], in which somatosensory functions were evaluated using less comprehensive QST parameters than in this study. In addition, this study used a comprehensive QST protocol consisting of 13 thermal and mechanical parameters, which led to a more comprehensive understanding of the somatosensory functions of patients and eggs. The WUR presents postsynaptic membrane plasticity in response to repeated stimuli. This study also combined neurophysiological parameters such as eggs. The CHEPs, which have not been reported in patients to our knowledge, provide a more comprehensive evaluation of the neurophysiological system of the TN. All these may be useful and applicable tools in clinical settings.

This study had several limitations. The recruited patients were relatively homogeneous, with moderate-to-severe pain and a less than one-year history of TN. More data need to be gathered for further analysis of the impact of pain intensity and disease duration on the results. In addition, the limited sample size also suggests careful consideration before popularizing our results to all patients with TN. For most parameters, the statistical power was greater than 0.6, partially suggesting the rationale for the current design. Nonetheless, parameters with less statistical power, such as WUR, VDT, PPT, and P/R2/R2' latency, indicated the requirement for further investigations with larger sample sizes. These limitations should be addressed in future research.

Conclusions

Patients with TN had peripheral hyperalgesia and hypoesthesia on the painful face, mediated by dysfunctional *Aβ*/*Aδ*/*C* fibers. Central sensitization has been suggested to be a pathological factor via widespread mechanical hyperalgesia in the contralateral face. Mechanical hypoesthesia revealed by *Z* scores suggested complex neuropathological mechanisms of *Aβ* nerve dysfunction in TN. *Aδ* pathway dysfunction was demonstrated by CHEPs in TN. This study indicated the comprehensive abnormal functions of the multi-fiber pathway associated with TN.

Author contributions YZL conducted the whole experiment, did the data analysis, drafted the manuscript; GJY provided technical support of QST and revised the manuscript; XLZ recruited the patients; YFK provided technical support of electrophysiological tests and revised the manuscript; QFX designed and supervised the whole experiment, critically revised the manuscript.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval This study is a part of populational study on sensory function changes in Chinese patients with orofacial pain and was approved by the Ethics Committee for Biomedical Sciences in Peking University School of Stomatology (PKUSSIRB-2013012). The whole research process was in agreement with the Declaration of Helsinki.

Informed consent Signed informed consent forms were obtained from all participants before entering the study.

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