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Assessment of somatosensory changes in Chinese temporomandibular disorders arthralgia patients by quantitative sensory testing

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Abstract

Background: Somatosensory changes in Chinese temporomandibular disorders (TMD) arthralgia patients have not been fully studied by the latest technologies.

Objective: This study aims at assessing somatosensory changes in Chinese TMD arthralgia patients quantitatively.

Methods: Standardised quantitative sensory testing (QST) was performed on the pain sites and contralateral sites of 40 patients diagnosed with TMD arthralgia according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) before and after medication; similar measures were taken in 40 age- and gender-matched healthy controls. Differences within and between groups were assessed through *Z*-scores, two-way ANOVA and loss/gain coding system.

Results: The pain sites of patients presented increased sensitivity to thermal stimuli and mechanical pain stimuli together with decreased sensitivity to mechanical tactile stimuli before medication ($P < .001$). Before treatment, 100% of patients had somatosensory abnormalities at the pain sites; the most frequent abnormalities were somatosensory gain to cold nociceptive, pinprick and pressure stimuli, and the most frequent loss/gain score was L0G3 (no somatosensory loss with a gain of thermal and mechanical somatosensory function; 70.0%). After treatment, although the clinical symptoms and signs of 40 patients disappeared, 80.0% of the patients' pain sites still showed multiple phenotype abnormalities. The most frequent loss/gain score was L0G2 (no somatosensory loss with a gain of mechanical somatosensory function; 35.0%).

Conclusions: Multiple phenotypes of facial somatosensory abnormalities were detected in Chinese TMD arthralgia patients before and after treatment, despite the disappearance of clinical signs and symptoms. Individual variations indicate a possible need for subgroup classification, individualised management and mechanism-based treatment.

KEYWORDS

medication, orofacial pain, quantitative sensory testing, sensory thresholds, somatosensory abnormalities, temporomandibular disorders

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1 | INTRODUCTION

Temporomandibular disorders (TMD) are a heterogeneous group of conditions characterised by pain in the temporomandibular joint and/or masticatory muscles and limited or painful jaw movement.[1] Epidemiological studies have indicated that TMD is common in the population and is related to a subject's impaired general health and quality of life.[2] Temporomandibular joint (TMJ) pain is becoming the chief complaint of most Chinese patients.[3] However, it is not sufficiently diagnosed or treated, which can develop into chronic pain without proper treatment and has significant impacts on the patient's jaw function and mental health.[4] The clinical diagnosis provides limited information about the pathophysiological mechanisms underlying pain experience that may guide the treatment. Thus far, the facial somatosensory changes underlying these diseases are still not fully understood. It is an open question whether the classification of pain syndromes, based solely on the aetiology, symptoms or signs, is the optimal method.[5] The individual pattern of somatosensory changes in the affected area likely reflects altered functions in sensory processing, and it seems to be preferable to classify pain conditions on patterns of somatosensory abnormalities and the likely underlying mechanisms.[6] It might be meaningful to stratify patients based on the somatosensory profile to approach mechanism-based classification and treatment.[7]

A subject's somatosensory function can be evaluated by quantitative sensory testing (QST). QST is a psychophysical test procedure used to quantify the functional state of the somatosensory system of a patient by means of calibrated, graded innocuous or noxious stimuli and subjective perception thresholds.[8,9] The German Research Network on Neuropathic Pain (DFNS) has developed a standardised QST protocol for evaluation and data analysis.[10] Compared with other traditional detection methods, QST can systematically and comprehensively detect the state and function of the nerve fibre pathway and has a high sensitivity, which can detect changes in the functional state of the sensory system before the occurrence of organic lesions. Several studies have described somatosensory function in myofascial TMD patients, with patients showing hypersensitivity to thermal, mechanical and electrical pain stimuli compared to healthy controls.[11-13] Relatively few studies have focused on arthrogenic TMD pain patients. Previous studies have primarily investigated the somatosensory changes in Caucasian TMD pain patients.[8] However, with the largest population in the world, the Chinese still remain understudied regarding the standardised QST protocols. China is made up of 56 distinctive ethnic groups which may indicate the potential presence of multiple somatosensory phenotypes. Research on somatosensory changes in temporomandibular arthralgia patients in China is just beginning, and until now, few comprehensive QST studies have been reported.[12,13]

The aim of this study was to assess somatosensory function in painful facial regions of Chinese TMD arthralgia patients according to the international Diagnostic Criteria for TMD (DC/TMD).[14] The full standardised QST protocol was carried out with the patients before and after medication (without clinical symptoms and signs).

2 | METHOD

2.1 | Participants

2.1.1 | TMD arthralgia patients

All Chinese individuals with a primary complaint of pain in the TMJ region were recruited from the Center for TMD and Orofacial Pain of Peking University School and Hospital of Stomatology, China, from 2014 to 2018. All patients were diagnosed with TMD arthralgia by the same TMD specialist who had received systematic training and calibration in the use of DC/TMD.[14] Pain came from the unilateral TMJ region; pain intensity at rest and during function was rated by the patient on a 0-10 cm visual analog scale (VAS; 0 = "no pain," 10 = "most pain imaginable"). No anatomical abnormalities of TMJ were found via cone beam computed tomography (CBCT). The exclusion criteria were as follows: fibromyalgia syndrome, headache or other chronic pain that might affect somatosensory function; systemic diseases, psychological diseases or previous radiotherapy or chemotherapy; intake of medicine affecting the central nervous system or any therapy aiming at releasing the pain in the TMJ region; and female menstrual period, pregnancy or lactation period. All patients were treated with meloxicam tablets (7.5 mg per day). Patients who did not feel pain in the TMJ area in combination with no familiar pain on jaw movement or palpation after treatment were included in this study. To avoid subjective and descriptive reports in assessments of the effectiveness of therapy, we used the Friction craniomandibular index (CMI) to evaluate the clinical therapeutic effect.[15] Friction's CMI is recommended as an objective criterion with good reliability and validity in clinical application.[15,16] Later studies have shown that the use of this index allowed for a safe evaluation of the signs and symptoms of temporomandibular disorders in the patients investigated.[17,18] To estimate the group size, a pilot study was conducted to measure all the QST parameters of 10 TMD patients. The mean value and standard deviation of each parameter were used to estimate the group size. For our power calculation, we assumed an equality of variance in the TMD and the reference groups. Considering the ethnic differences between Caucasian and Chinese populations, which might have an effect on the orofacial somatosensory data, we used the data from the reference group based on previous references as the normal data for the Chinese population.[13,19] We assumed that the QST results of TMD patients after treatment were equal to the normal data of the reference group. With $\alpha = .05$, two-tailed and a power of 80% ($\beta = .2$), we calculated the sample sizes of all parameters and the most one was 31 per group. Considering a compliance rate of 80%, we ultimately asked 40 patients and 40 healthy controls to participate in this study. Of the 290 Chinese patients, most were excluded because of multiple disorders, therapy affecting the central nervous system, chronic pain in a remote body part or incomplete clinical information. Finally, 40 patients (19 males and 21 females) aged 21 to 57 years old were recruited and completed the test. The psychosocial status of the TMD participants was evaluated using the SCL-90 with 9 domains.[20]

2.1.2 | Healthy participants

Healthy Chinese participants were recruited from the staff and students of Peking University School of Stomatology. The same TMD specialist evaluated all participants by using DC/TMD to exclude TMD patients. The exclusion criteria were as follows: reported chronic pain in the past 6 months or ongoing pain; systemic diseases, psychological diseases or previous radiotherapy or chemotherapy; intake of medicine affecting the central nervous system; and female menstrual period, pregnancy or lactation period. Finally, 40 healthy participants matched by age and gender were recruited and completed the whole test.

2.2 | QST protocol

The standardised QST protocol developed by DFNS and modified for the trigeminal region was used in this study.[8-10,12] All QST measures were performed in a quiet laboratory at 20-23°C. The QST protocol consisted of a total of 13 parameters: (a) thermal testing comprised 6 parameters for detection and pain thresholds for different thermal stimuli mediated by C and A-delta fibres: cold detection threshold (CDT); warm detection threshold (WDT); cold pain threshold (CPT); heat pain threshold (HPT); and number of paradoxical heat sensations (PHS) during the thermal sensory limen procedure (TSL) with alternating warm and cold stimuli. (b) Mechanical detection threshold (MDT) tests for A-beta fibre function. (c) Mechanical pain threshold (MPT) tests for A-delta fibre-mediated hyperalgesia or hypoalgesia to pinprick stimuli. (d) Stimulus-response functions: mechanical pain sensitivity (MPS) to pinprick stimuli assessment of A-delta fibre sensitivity to sharp stimuli and dynamic mechanical allodynia (DMA) assessment of A-beta fibre-mediated pain sensitivity to stroking light touch (CW, cotton wisp; QT, cotton-wool tip; BR, brush). (e) wind-up ratio (WUR) tests for the existence of the wind-up phenomenon. (f) Vibration detection threshold (VDT) tests for A-beta fibre function. (g) Pressure pain threshold (PPT) was the only test for deep tissue pain sensitivity, mainly mediated by C and A-delta fibres. In this study, the investigator was instructed and trained according to the latest guidelines.[9,10] All tests were performed following the sequence suggested by DFNS.

2.2.1 | Thermal thresholds

All thermal tests were performed using the Medoc Pathway (Ramat Yishai) with an Advanced Thermal Stimulator (30 × 30 mm). The baseline temperature was set at 32°C for all thermal tests, and the temperature alteration ratio was 1°C/s. The unit automatically stopped measurements when it reached a temperature of 0°C or 50°C and returned to the starting temperature of 32°C to avoid skin irritation. By pressing a stop button, a threshold value was determined in accordance with a continuously increasing or decreasing temperature of the thermode contact surface. The CDT, WDT, CPT and HPT were calculated from three consecutive individual values as an arithmetic value. For the TSL, the temperature first increased and then decreased, and the participants pressed the button when they perceived a change. The number of PHS was recorded.[9,13]

2.2.2 | Mechanical detection threshold

A set of standardised *von-Frey filaments* recommended by the DFNS was used to capture the MDT. To ensure accurate testing of the threshold, the filaments were always kept in the same manner until the filaments showed an "s-shape" bending. The contact time with the skin surface was approximately 2 seconds. To determine the tactile detection threshold, five repeated above- and below-threshold stimulus intensities were measured using a modified "level" method. The final threshold was the geometric mean of the five series.[9,13]

2.2.3 | Mechanical pain threshold

To determine the MPT, a set of custom-made needle stimulators was used. The stimulators consisted of blunt needles with a fixed intensity of 8, 16, 32, 64, 128, 256 and 512 mN, as well as a blunt, circular skin contact surface with a diameter of 0.25 mm. The individual needle stimulators were applied perpendicularly to the skin in five series of tests with ascending and descending stimulus intensities and a skin contact time of approximately 1-2 seconds. The method of "level," which was used to determine the MDT, was also used to determine the MPT.[9,13]

2.2.4 | Mechanical pain sensitivity and dynamic mechanical allodynia

To evaluate the MPS and DMA, a set consisting of the above-described needle stimulators, a cotton pad (~3 mN), a Q-Tip (~100 mN) and a soft brush (~200-400 mN) were used. A series of 10 measurements were made 3 times with the 10 stimulators (7 pinpricks and 3 tactile stimulators) applied in a different order as specified in the DFNS protocol. The test subjects were asked to rate the perception of the stimulus using a numerical rating scale from 0 to 100 (0 = no pain; 100 = worst pain imaginable). The extent of any DMA was determined using the same procedure. Overall, this procedure comprised 30 stimuli. All stimuli were applied with an interstimulus interval of 10 seconds. The MPS was calculated as the geometric mean of all the individual numerical values for the needle stimuli. DMA was calculated as the geometric mean of all the individual numerical values for the light touch stimuli.[9,13]

2.2.5 | Wind-up ratio for repetitive pinprick stimuli

To measure the WUR for repetitive pinprick stimuli, a needle stimulator with an intensity of 256 mN was used. For the more sensitive

skin of the face, 128 mN was used. The sensitivity of the skin to a single stimulus in the tested area was compared with the sensitivity to a series of stimuli (10 needle stimuli). The stimulation was carried out with a stimulus frequency of 1 Hz. The test subject rated the applied stimuli using the numerical rating scale (for a single stimulus and for the entire series of stimuli). The WUR test was repeated three times.[9,13]

2.2.6 | Vibration detection threshold

For the determination of the VDT, the *tuning fork* at a vibration frequency of 64 Hz using an 8/8 scale was used. It was bilaterally placed on the bony prominences: the zygomatic process, the lower edge of the mandible and the ulnar styloid process. The test subject indicated when the vibration of the tuning fork was no longer felt. The stimulus intensity was depicted from the scale of the tuning fork. This process was repeated three times, and the final threshold was the arithmetic mean.[9,13]

2.2.7 | Pressure pain threshold

The determination of the PPT was assessed using a *pressure algometer* (Medoc AlgoMed). It had a blunt rubber contact surface with which a pressure of 0-2000 kPa could be applied. The PPT was bilaterally measured on the lateral and posterior regions of the condylar process, and it was recorded as a kPa value, by which the perception of pressure turned for the first time into a painful sensation. The PPT was calculated as the arithmetic mean following three repeated measurements.[9,13]

2.3 | Testing sites and occasion

For TMD arthralgia patients, the testing sites for all parameters, with the exception of the VDT and PPT, were the painful TMJ region and the mirror region on the contralateral side. For the VDT, the testing sites were the zygomatic process, the lower edge of the mandible and the ulnar styloid process. For the PPT, the testing sites were the lateral and posterior regions of the bilateral condylar processes. The contralateral sites were tested first, and then, the painful sites were followed.

All the patients recruited for the study were examined twice according to the full standard QST protocol. The first time they came to see the doctor, while the second time was after medication treatment. In order to ensure to repeat the test on the same site after treatment, we asked the patient for approval to mark it with a grease pen (the colour could not be easily cleaned off) and to take care not to remove it when washing their face. As the second treatment was not long after the first treatment, the marker points of most patients could be easily located. Secondly, we recorded the relevant position of the midpoint of the leading edge of the external auditory canal by photography in case the marker was not clear after treatment.

For the healthy participants, the testing site for all parameters, with the exception of the VDT and PPT, was the corresponding right TMJ region. For the VDT, the testing sites were the right zygomatic process, the lower edge of the right mandible and the right ulnar styloid process. For the PPT, the testing sites were the lateral and posterior regions of the right condylar process.

2.4 | Data analysis and statistics

2.4.1 | *Z*-transformation of the QST data

There was no PHS or DMA in either group. For the remaining 11 parameters, the QST values were normally distributed in the log space and were logarithmically transformed before statistical analysis. Each variable of individual QST data was *Z*-transformed based on reference data: $Z = (X_{\text{single patient}} - \text{Mean}_{\text{reference}})/\text{SD}_{\text{reference}}$.[8,9] The data for the healthy participants were considered reference values. After *Z*-transformation, the distributions of all patients' QST data became normal.[8,13] *Z*-score values reflected the patient's sensitivity for each parameter. *Z*-scores above "0" indicated a gain of function, for which the patient was more sensitive to the tested stimuli compared to the controls (hyperaesthesia, hyperalgesia, allodynia). *Z*-scores below "0" indicated a loss of function, for which the patient was less sensitive to the tested stimuli compared to the controls (hypoesthesia, hypoalgesia). A *Z*-score of 0 ± 1.96 represented the range that included 95% of the healthy control subject data. Therefore, *Z*-score >1.96 or *Z*-score <–1.96 was considered an absolute abnormality for being outside the 95% confidence interval (CI) of the healthy control data.[8,9] In this study, we mainly focused on the absolute abnormalities of each patient.

2.4.2 | Somatosensory function loss and gain assessment

For a more detailed evaluation of the somatosensory function loss and gain conditions, we applied the loss and gain coding system.[13,21] It exhibited the abnormal condition of a patient's somatosensory function with a combination of the score of somatosensory loss of function (L0, L1, L2 or L3) and the score of somatosensory gain of function (G0, G1, G2 or G3). The number after the letter L or G revealed whether the abnormality was thermal only (1), mechanical only (2) or mixed (thermal and mechanical) (3). It was recorded as one of the following situations: L1, isolated loss of small fibre function (abnormal thermal detection thresholds [CDT, TSL or WDT] alone); L2, isolated loss of large fibre function (abnormal mechanical thresholds [MDT or VDT] alone); or L3, mixed loss of small and large fibre function.[13,21] For somatosensory gain, G1 or thermal hyperalgesia was recorded if abnormal thermal pain thresholds were found (abnormal CPT or HPT); G2, mechanical hyperalgesia was found if

abnormal mechanical thresholds were found (for MPT, MPS and PPT, or the DMA exceeded 0); and G3 represented mixed thermal and mechanical hyperalgesia. L0 revealed no abnormal loss of somatosensory function, while G0 revealed no abnormal gain of somatosensory function detected.

2.4.3 | Statistics

The *Z*-score data of the two groups showed equal variances in Levene's test ($P > .05$). The differences were compared using two-way analysis of variance (ANOVA) to evaluate the influence of site (pain site/non-pain site) and therapy (before/after medication) on each parameter of the QST data. The interactions and effect sizes were calculated, and ANOVAs were followed by *post hoc* comparisons using Bonferroni tests. The QST parameter values of TMD patients after treatment were compared with the healthy control group using the independent sample *t* test to see whether they had returned to normal range. All statistical calculations were performed using SPSS 20.0 software (IBM). $P < .05$ was considered statistically significant.

The distribution of the frequencies of loss and gain function according to the loss/gain coding system at the painful site between groups was evaluated with chi-square and Fisher's exact tests. Values of $P < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Participants

The clinical characteristics of the TMD arthralgia patients and healthy controls are shown in Table 1. There was no significant difference in age and gender between the patients and healthy controls. Other details are also shown in the table. Among the 40 patients, 4 patients (10%) were diagnosed arthralgia together with disc displacement with reduction according to the DC/TMD; 19 patients (47.5%) were diagnosed arthralgia together with myalgia; and 17 patients (42.5%) were diagnosed arthralgia with myalgia and disc displacement with reduction. The masticatory muscles involved for all patients diagnosed with myalgia in this study were mainly the lateral pterygoid muscles.

TABLE 1 Clinical characteristics of temporomandibular disorders (TMD) arthralgia patients and healthy control participants

	TMD arthralgia (n = 40)	Controls (n = 40)
Age (years)	32.9 ± 9.6	33.0 ± 9.5
Sex (male:female)	1:1.11	1:1.11
Pain duration (mo)	1.7 ± 0.3	/
Pain intensity (VAS)		
At rest	3.8 ± 0.1	/
During function	5.3 ± 0.1	/
Therapy time (days)	17.1 ± 2.1	/
Friction craniomandibular index		
Before medication	0.39 ± 0.12	/
After medication	0.02 ± 0.01	/
DC/TMD diagnoses (n [%])		
Arthralgia + Disc displacement with reduction	4 (10%)	/
Arthralgia + Myalgia	19 (47.5%)	/
Arthralgia + Myalgia +Disc displacement with reduction	17 (42.5%)	/

3.2 | Comparison of QST results

The QST absolute values, *Z*-score values of parameters and the results of the two-way ANOVA with the factor site (pain site/non-pain site) and therapy (before/after medication) are displayed in Table 2.

The *Z*-score values of most of the parameters except for WUR and VDT were significantly different before and after treatment ($P < .001$). Significant site differences were also found for the QST parameters mentioned above, with the pain site being more sensitive than the non-pain site, with the exception of MDT (the non-pain site was more sensitive than the pain site, $P < .001$).

There was also a significant therapy × site interaction for the QST parameters, with the exception of the WUR and VDT (Table 3). Before treatment, Chinese TMD arthralgia patients showed higher sensitivity in CDT (2.90 ± 1.31), WDT (2.35 ± 1.45), CPT (2.80 ± 0.34), HPT (2.33 ± 1.46), TSL (1.80 ± 1.53), MPT (3.21 ± 0.83), MPS (2.00 ± 0.80) and PPT (8.53 ± 2.78 and 9.51 ± 1.71) on the pain site than on the non-pain site ($P < .001$). The MDT (2.29 ± 1.11) showed the opposite result, that is the non-pain site was more sensitive than the pain site ($P < .001$). The independent sample t test indicated that all the QST parameters of both pain and non-pain sites of TMD patients after treatment showed no significant differences compared with the healthy controls ($P > .1$). The results of the parameters mentioned above showed no significant differences between the pain site and non-pain site ($P > .2$). Statistically significant differences could be detected in these items before and after treatment ($P < .001$).

3.3 | Somatosensory abnormalities of *Z*-scores in Chinese TMD arthralgia patients

The TMD arthralgia patients exhibited mixed somatosensory abnormalities before treatment. All 40 TMD arthralgia patients had parameters exceeding the 95% CI ($Z > 1.96$ or $Z < –1.96$) of the control group. The proportion of somatosensory abnormalities among the 40 patients is shown in Figure 1. Before treatment, the data showed that 100% of the patients had abnormal gain function for

TABLE 2 Mean and standard deviation (SD) of the quantitative sensory testing (QST) parameters before and after *Z*-transformation from pain site, non-pain site in the temporomandibular disorders (TMD) arthralgia group and unilateral site in the reference group and the somatosensory changes of *Z*-scores were assessed by a two-way ANOVA

	TMD Arthralgia Group							
	Before medication				After medication			
	Pain site		Non-pain site		Pain site		Non-pain site	
QST parameter	Absolute mean (SD)	*Z*-scores mean (SD)	Absolute mean (SD)	*Z*-scores mean (SD)	Absolute mean (SD)	*Z*-scores mean (SD)	Absolute mean (SD)	*Z*-scores mean (SD)
CDT	−0.67 (0.27)	2.90 (1.31)	−1.45 (0.53)	0.27 (1.18)	−1.47 (0.54)	0.21 (1.15)	−1.44 (0.54)	0.27 (1.16)
WDT	0.94 (0.51)	2.35 (1.45)	1.63 (0.62)	0.45 (1.07)	1.67 (0.71)	0.37 (1.06)	1.70 (0.71)	0.33 (1.10)
CPT	29.31 (0.85)	2.80 (0.34)	24.06 (2.50)	0.45 (1.21)	23.99 (3.06)	0.33 (2.08)	23.49 (3.29)	0.10 (1.85)
HPT	37.70 (2.32)	2.33 (1.46)	41.48 (2.88)	0.06 (1.64)	42.03 (3.17)	−0.24 (1.79)	41.70 (2.72)	−0.07 (1.54)
TSL	2.83 (0.93)	1.80 (1.53)	4.59 (1.51)	−0.19 (1.54)	4.61 (1.53)	−0.17 (1.64)	4.74 (1.45)	−0.35 (1.47)
MDT	1.86 (0.49)	−1.53 (0.43)	0.78 (0.35)	−0.09 (0.82)	0.82 (0.41)	−0.18 (0.77)	0.72 (0.38)	0.07 (0.93)
MPT	34.50 (10.39)	3.21 (0.83)	114.27 (39.00)	0.20 (1.05)	113.55 (41.03)	0.22 (1.06)	114.56 (39.79)	0.18 (1.01)
MPS	5.21 (2.20)	2.00 (0.80)	2.60 (1.67)	0.50 (1.29)	2.42 (1.56)	0.38 (1.29)	2.41 (1.51)	0.40 (1.21)
WUR	2.16 (0.48)	−0.10 (1.26)	2.11 (0.56)	−0.31 (1.54)	2.27 (0.48)	0.15 (1.49)	2.15 (0.65)	−0.28 (1.82)
VDT[a]	7.17 (0.30)	−0.15 (2.08)	7.25 (0.20)	0.42 (1.35)	7.08 (0.26)	−0.75 (1.77)	7.14 (0.22)	−0.29 (1.52)
VDT[b]	7.23 (0.15)	0.26 (0.95)	7.30 (0.19)	0.66 (1.19)	7.23 (0.16)	0.26 (0.98)	7.30 (0.20)	0.68 (1.20)
PPT[c]	86.28 (16.69)	8.53 (2.78)	158.68 (16.99)	−0.05 (1.47)	155.77 (20.96)	0.25 (1.86)	158.30 (19.25)	0.00 (1.66)
PPT[d]	65.83 (8.36)	9.51 (1.71)	132.11 (19.37)	0.37 (1.91)	132.67 (17.85)	0.30 (1.78)	137.18 (20.20)	−0.12 (1.93)

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

[a]Bold values are statistical significance.

[a]Zygomatic process,

[b]The lower edge of the mandible,

[c]The lateral region of the condylar process,

[d]The posterior region of the condylar process.

***$P < .001$, compared within group.

the CPT, MPT and PPT (thermal and mechanical hyperalgesia). For all nociceptive parameters, except for the WUR, only sensory gain was detected, with an abnormal rate from 40.0% to 65.0%; the WUR showed both sensory gain and sensory loss. For non-nociceptive parameters, the MDT showed only abnormal loss function, with an abnormal rate of 20.0%. The VDT showed both abnormal gain function and loss function; the other thermal parameters showed only abnormal gain function (20%-72.5%).

After treatment, only one non-nociceptive parameter (MDT) and one nociceptive parameter (MPT) showed no abnormal function at the pain site. The WUR showed loss function, with an abnormal rate of 10%; all of the other parameters showed both abnormal gain function and loss function from 2.5% to 35.0%.

3.4 | Somatosensory abnormalities in healthy participants

Due to natural variation, some somatosensory abnormalities were observed in the reference group (2.5%-10.0% for somatosensory loss and 2.5%-12.5% for somatosensory gain; Figure 1).

3.5 | Somatosensory abnormalities based on the loss/gain coding system

The distribution and frequency of participants according to the loss/gain assessment system are shown in Table 3. For the pain site, we found that before treatment, 100% of the patients had somatosensory abnormalities compared with 17.5% of the reference group ($P < .001$). L0G3 (no abnormal somatosensory loss with thermal and mechanical hyperalgesia) (70%) was the most frequent coding in the arthralgia group before medication, and L2G3 (mechanical abnormal somatosensory loss with thermal and mechanical hyperalgesia) (30%) was the second most frequent; both were significantly different from the reference group (both were 0.0%; $P < .001$).

After treatment, only 20.0% of patients had no somatosensory abnormalities at the pain site (reference group was 82.5%; $P < .001$). L0G2 was still observed in 35% of patients, which was significantly higher than the percentage in the reference group (12.5%) ($P < .001$). The cumulative proportion of somatosensory gain without any loss (L0G1, L0G2 and L0G3) (52.5%) was also significantly higher in patients compared with the reference group (15.0%) ($P < .001$), and

Reference Group		1	2	Interaction	Effect size		Interaction analysis (Site × Therapy)		
Unilateral site		Site	Therapy	1 × 2	Partial Eta-squared		Before medication-After medication mean (*P*)		Standard error
Absolute mean (SD)	*Z*-scores mean (SD)	*P*	*P*	*P*	Site	Therapy	Pain site	Non-pain site	
–1.54 (0.49)	0.00 (1.00)	<.001	<.001	<.001	0.227	0.243	2.687***	0.005 (0.985)	.269
1.88 (0.78)	0.00 (1.00)	<.001	<.001	<.001	0.149	0.168	1.975***	0.116 (0.659)	.264
23.12 (1.98)	0.00 (1.00)	<.001	<.001	<.001	0.156	0.18	2.475***	0.349 (0.308)	.341
41.53 (1.76)	0.00 (1.00)	<.001	<.001	<.001	0.098	0.153	2.569***	0.134 (0.710)	.36
4.24 (0.96)	0.00 (1.00)	<.001	<.001	<.001	0.112	0.109	1.978***	0.159 (0.646)	.346
0.76 (0.34)	0.00 (1.00)	<.001	<.001	<.001	0.237	0.202	–5.494***	–0.160 (0.351)	.137
122.80 (41.61)	0.00 (1.00)	<.001	<.001	<.001	0.379	0.37	2.990***	0.013 (0.954)	.222
1.84 (1.23)	0.00 (1.00)	<.001	<.001	<.001	0.093	0.122	1.619***	0.094 (0.720)	.26
2.18 (0.34)	0.00 (1.00)	.194	.562	.64	0.011	0.002	–	–	–
7.18 (0.15)	0.00 (1.00)	.058	.016	.834	0.023	0.037	–	–	–
7.19 (0.16)	0.00 (1.00)	**.017**	.945	.936	0.036	0.001	–	–	–
157.60 (11.49)	0.00 (1.00)	<.001	<.001	<.001	0.553	0.518	8.279***	–0.056 (0.900)	.449
134.91 (10.43)	0.00 (1.00)	<.001	<.001	<.001	0.635	0.642	9.208***	0.494 (0.231)	.410

the cumulative proportion of somatosensory loss without any gain (L1G0, L2G0 and L3G0) was 7.5%. The cumulative proportion of mixed loss and gain was higher in the TMD arthralgia group (20.0%) than in the reference group (2.5%) ($P < .05$).

3.6 | Psychosocial status of TMD patients

The SCL-90 scale indicated that 14 patients (35%) had psychological abnormalities compared with the reference data.[19] Somatisation (30%) was the most frequent one, while paranoid ideation, anger and hostility were the lowest (10%) (Table 4).

4 | DISCUSSION

The facial somatosensory changes of Chinese arthralgia patients before and after treatment were systematically studied using a standardised QST protocol for the first time. The mechanisms implicated in the pathophysiology of myofascial and arthrogenous TMD seem to be similar, and most studies with TMD have not assessed the somatosensory functions separately for each group, probably because of the small sample sizes.[11,22] Similarly in this study, it was not possible to assess the somatosensory functions in patients with "pure" TMJ pain, as most patients had comorbid diagnoses of myalgia or disc displacements (Table 1). First, the sample size was limited; second, for DC/TMD, most of those with arthralgia also fulfil the criteria for myalgia; finally, arthralgia and myalgia can easily become concurrent conditions probably due to local, regional and generalised sensitisation.[22,23] Lovrgen et al indicated that the association between a positive TMJ compression test and a DC/TMD arthralgia diagnosis was confounded by the presence of myalgia, while a negative TMJ compression test was strongly associated with the absence of a contralateral TMJ arthralgia diagnosis according to DC/TMD.[23]

German Research Network on Neuropathic Pain proposed comparing the QST results of individual patients with normal control parameters by means of *Z*-scores in data processing.[8-10] *Z*-score is an easily applicable standard presentation for comparisons of data from reference data. This approach accounts for the fact that the units of different QST test items are different, and possible data ranges differ vastly across variables. Moreover, a

TABLE 3 Loss and gain distribution on the pain site in temporomandibular disorder (TMD) patients and the healthy reference group

	Gain				
Loss	G0 (None)	G1 (Thermal)	G2 (Mechanical)	G3 (Both)	All
TMD patients (n = 40)					
Before medication					
L0 (None)	0 (0.0%)	0 (0.0%)	0 (0.0%)	28 (70.0%)	28 (70.0%)
L1 (Thermal)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
L2 (Mechanical)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (30.0%)	12(30.0%)
L3 (Both)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
All	0 (0.0%)	0 (0.0%)	0 (0.0%)	40 (100.0%)	40 (100.0%)
After medication					
L0 (None)	8 (20.0%)	5 (12.5%)	14 (35.0%)	2 (5.0%)	29 (72.5%)
L1 (Thermal)	0 (0.0%)	0 (0.0%)	3 (7.5%)	0 (0.0%)	3 (7.5%)
L2 (Mechanical)	2 (5.0%)	0 (0.0%)	3 (7.5%)	2 (5.0%)	7 (17.5%)
L3 (Both)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
All	11 (27.5%)	5 (12.5%)	20 (50.0%)	4 (10.0%)	40 (100.0%)
Reference group (n = 40)					
L0 (None)	33 (82.5%)	1 (2.5%)	5 (12.5%)	0 (0.0%)	39 (97.5%)
L1 (Thermal)	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	1 (2.5%)
L2 (Mechanical)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
L3 (Both)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
All	33 (82.5%)	1 (2.5%)	6 (15.0%)	0 (0.0%)	40 (100.0%)

Note: Loss/Gain coding system: L1 stands for hypoesthesia to thermal stimuli (abnormal loss of detection in cold or warm detection threshold, L2 stands for hypoesthesia to mechanical stimuli (abnormal loss of mechanical detection threshold or vibration detection threshold). G1 stands for hyperalgesia to thermal stimuli (abnormal gain of cold or heat pain threshold), G2 stands for hyperalgesia to mechanical stimuli (abnormal gain of function in mechanical pain threshold or sensitivity, dynamic mechanical allodynia, or pressure pain threshold). If both thermal and mechanical abnormalities were present, L3 or G3 were defined. 0 stands for normal values.

definition of hypo- and hyper-phenomena should be clearly described. The upregulation (gain, *Z* value greater than 0) or downregulation (loss, *Z* value less than 0) of somatosensory function can be easily clarified by the *Z*-score.[8,9] The main finding of this study was that multiple phenotypes of somatosensory abnormalities could be detected in Chinese TMD arthralgia patients by QST, even patients who exhibited no subjective symptoms and signs after treatment. Before treatment, patients showed both increased sensitivity for multiple nociceptive and non-nociceptive parameters and decreased somatosensory abnormalities in terms of a loss or gain of somatosensory function in the painful facial regions, compared with 17.5% of the reference group. The most frequent loss/gain coding scores was L0G3, and the second most frequent was L2G3. After treatment, 80.0% of patients still showed multiple phenotypes of abnormalities at the pain sites. Comparing the present study in the Chinese population and earlier studies in the Caucasian population, we may find that gain of mechanical function (mechanical hyperalgesia) is the most frequent abnormality for both Chinese and Caucasian TMD patients.[13,22,24,25]

4.1 | Group level facial somatosensory function assessment

Compared with the healthy control group, the TMD arthralgia group showed significantly increased sensitivity for nociceptive parameters (CPT, HPT, MPT, MPS and PPT) and thermal non-nociceptive parameters (CDT, WDT and TSL) on the pain sites before treatment. These results suggested that the function of the Aδ and C sensory nerve conduction pathways related to these test items was upregulated, and thermal hyperaesthesia, thermal hyperalgesia and mechanical hyperalgesia could be detected. These results were consistent with several studies based on Caucasian TMD patients.[22,25] At the group level, it seemed that the Chinese sample presented similar somatosensory changes as the Western samples of TMD patients by the same QST protocol, even though a previous study had indicated that ethic differences might exist in somatosensory functions between Chinese and Caucasian populations.[26] This upregulation might be related to a similar peripheral sensitisation process. In the pathological state of TMJ arthralgia, the nociceptors in the painful joint area and the corresponding Aδ

and C afferent fibres were in a state of continuous sensitisation, causing a pain response to physiological stimulation or an excessive pain response to noxious stimulation.[2,27] Possible mechanisms of peripheral sensitisation include inflammatory mediators that can directly activate nociceptors or lower the pain threshold, which leads to growth in the number of neurons that cause nociceptive stimulation and change the sensitivity; the electrophysiological properties of primary sensory neurons change; and the ion channels involved in nociception and conduction increase.[27,28] In this study, after anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAID), the corresponding thresholds in the TMD arthralgia group suggested effective regulation of peripheral sensitisation.

The MDT results in this study suggested that secondary tactile hypoesthesia coexisted with pain symptoms in the TMJ region of the TMD arthralgia patients. Kothari's study result, which focused on 34 Caucasians with arthralgia, is also consistent with the results of this study.[22] A high proportion of patients showed mechanical, tactile and vibrational hypoesthesia on the pain side. Pain-related tactile decline has been reported in many clinical and experimental studies, which was consistent with the results of this study.[13,25,26,29,30] This loss of tactile sensation might be associated with capsaicin-sensitive nociceptive neurons. Magerl et al performed a QST examination on the local injection area of capsaicin in healthy individuals. Hyperalgesia came together with tactile hypoesthesia in the local injection area. They believed that there might be a traffic branch between the mechanical sensory conduction pathway and the pain transmission pathway in the dorsal horn of the spinal cord. Selective and continuous activation of capsaicin-sensitive nociceptive neurons might cause the mechanical sensory conduction pathway to be interfered by signals from the pain pathway, which was expressed as mechanical sensory afferents that were suppressed and tactile sensation occurs.[29] Calford et al found that by selectively blocking the capsaicin-sensitive nociceptive neurons in the flying bat, it could rapidly induce the expansion of cortical receptor domains corresponding to mechanoreceptors. They believed that capsaicin-sensitive nociceptive neurons have a certain inhibitory effect on mechanical sensory afferents under normal conditions.[30] Based on the MDT results and the above research conclusions, we speculate that the above process may also exist in the trigeminal nerve conduction pathway in patients with TMD arthralgia. The capsaicin-sensitive nociceptive neurons in the painful joint area before treatment are in a continuous activation state, and the inhibitory effect is enhanced. The activation effect of capsaicin-sensitive nociceptive neurons in the original painful joint area is significantly attenuated after NSAID anti-inflammatory treatment, the corresponding mechanical sensory afferent inhibitory effect is also significantly attenuated, and MDT is significantly reduced, and tactile function is restored. This still needs further confirmation by related molecular biology research.

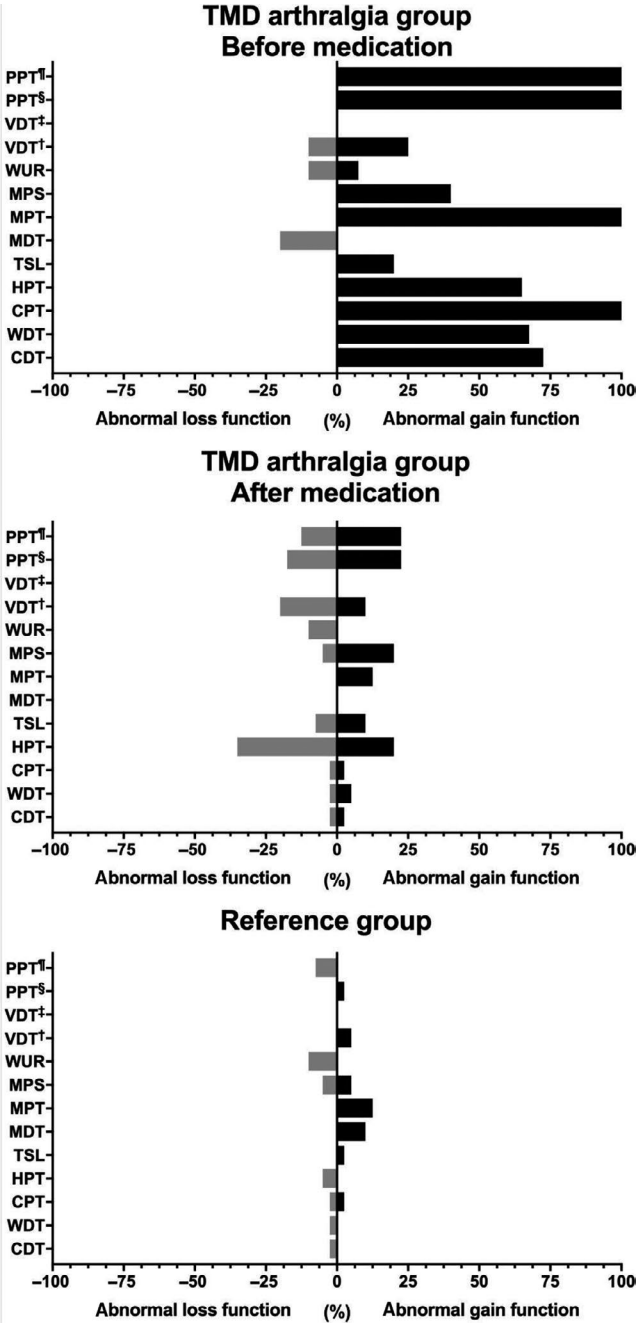

FIGURE 1 Absolute abnormalities for temporomandibular disorders (TMD) arthralgia patients in the painful area before and after medication and reference group. Values outside the 95% confidence intervals of healthy reference data are considered to be abnormalities. The *x*-axis shows the percentage of patients, with positive sensory signs plotted rightwards and negative sensory signs plotted leftwards. CDT, cold detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio. †zygomatic process, ‡the lower edge of the mandible, §the lateral region of the condylar process, ¶the posterior region of the condylar process

TABLE 4 Psychosocial status of Chinese TMD pain patients

Categories	n[a](%)	Patient (mean ± SD)	Reference data[b](mean ± SD)
Somatisation	12 (30%)	2.01 ± 0.71	1.37 ± 0.48
Obsessive compulsive	8 (20%)	2.05 ± 0.84	1.62 ± 0.58
Interpersonal sensitivity	6 (15%)	1.81 ± 0.74	1.65 ± 0.51
Depression	6 (15%)	1.92 ± 0.78	1.50 ± 0.59
Anxiety	10 (25%)	1.96 ± 0.77	1.39 ± 0.43
Anger and hostility	4 (10%)	1.80 ± 0.75	1.48 ± 0.56
Phobic anxiety	8 (20%)	1.56 ± 0.63	1.23 ± 0.41
Paranoid ideation	4 (10%)	1.61 ± 0.63	1.43 ± 0.57
Psychoticism	6 (15%)	1.60 ± 0.52	1.29 ± 0.42
Average	7.1 (17.8%)		

Note: The psychological status of patients was evaluated using the SCL-90 scale.

[a]n = the number of patients' scores outside the normal range of reference data (mean ± 1.96 SD).

[b]Reference data were based on the classical reference used for the data of the SCL-90 of a Chinese normal population: Jin H, Wu W, Zhang M. The preliminary results of SCL-90 analysis in a Chinese normal population. *Chin J Nervous Mental Dis* 1986;12:260-263.

4.2 | Individual facial somatosensory function assessment based on *Z*-scores

Studies have confirmed that even in patients with the same clinical diagnosis, somatosensory function changes are different and complex.[6-8] It is difficult to reflect the changes in sensory function of each individual pain patient simply by the study between the case group and the control group, resulting in the loss of partial information.[8,31] In this study, the types of somatosensory dysfunction in the 40 patients were mainly mechanical hyperalgesia and thermal hyperalgesia. Similar findings were demonstrated in myofascial TMD patients.[13,22,25] At the same time, we found that the upregulation or downregulation of the same test items varied from patient to patient. The up- or downregulation for different test items before and after treatment in the same patient was also different. These findings all suggest that TMD arthralgia may have different degrees and phenotypes of facial somatosensory changes, and the existing clinical diagnosis may not fully reflect the patient's disease characteristics.

4.3 | Somatosensory abnormalities based on the loss/gain system

The loss/gain system may display relevant combinations of sensory abnormalities. Similar to earlier studies, we also detected some somatosensory abnormalities in the healthy control group, but only 17.5% showed values outside the 95% CI.[8,13,21] This frequency is actually lower than expected based on simple probability calculations in healthy persons having at least 1 of 11 values outside the 95% CI ($1\text{-}0.95^{11} = 43.1\%$).[13,21] The study results showed that before treatment, a total of 100% of the TMD arthralgia patients exhibited somatosensory abnormalities at the most painful site. The most frequent somatosensory abnormalities in terms of gain of function in this study were mechanical hyperalgesia and thermal hyperalgesia. The most frequent somatosensory abnormalities in terms of loss of function were mechanical hypoesthesia, which was consistent with the results at the group level. Pfau's study indicated differences comparing TMD patients to the control participants, with the TMD group being more sensitive to painful stimuli but less sensitive to tactile stimulation than the control group.[25] Kothari's study showed a similar high percentage (83.3%) of somatosensory abnormalities and types of gain of function, while in terms of loss of function, the most frequent were non-painful thermal and mechanical submodalities.[22] MPS was also detected in 2.9% of TMD patients. It is difficult to directly compare the present study with other previous studies because the loss/gain system was not adopted. However, it seems that Chinese/East Asian TMD arthralgia patients presented different phenotypes of somatosensory function abnormalities of the large fibre function from Caucasian/Western TMD patients.

In addition, we found that although the clinical symptoms and signs of the 40 patients disappeared after medication, only 20.0% of the patients showed no somatosensory abnormalities at the pain site, and 12.5% of the patients still exhibited mechanical hyperalgesia. It should be regarded as abnormal even considering the existence of individual variance.[8] This suggests that determining whether the patients are recovering simply by clinical examination has certain limitations, as the disappearance of symptoms and signs may not mean that the patient's sensory function has returned to normal. Patients may still have individual items of somatosensory dysfunction. This dysfunction may not be discovered by routine clinical examination, which will have an impact on the quality of care and possibility of recurrence. The comprehensive understanding of the sensory function of patients before and after treatment through *Z*-scores has a certain significance for the patient's course tracking and efficacy evaluation.[6,31-33] Through the continuous detection of *Z*-scores, the

patient's sensory abnormality recovery process can be dynamically observed, and the treatment efficacy can also be evaluated.

4.4 | Individualised somatosensory function management of TMD arthralgia patients

At present, the relevant basic research on the mechanism of temporomandibular joint pain is more in-depth, and many signs of progress have been made in molecular biology.[1,5] However, research on changes in somatosensory function is lacking. The definition of pain indicates that pain is a sensory experience, and the production of pain means a change in the original sensory function status. Based on these widespread individual differences, different patients suffering from the same clinically diagnosed disorder may present with multiple phenotypes, which may be the critical influencing factor for unsatisfactory therapy.[6,7] A quantitative study of pain-related changes in somatosensory function throughout treatment progress has important implications for the development of subgroup classification, individualised management and targeted treatment effects.[7,31-33]

Individual responses to QST are related to a variety of biological and psychosocial mechanisms, which may have effect on the individual's somatosensory function.[34] Social factors, particularly interpersonal social factors, are associated with QST responses in healthy individuals and individuals with chronic low back pain.[35,36] Psychological factors such as anxiety, depression and some other factors are reported to be associated with QST responses in healthy and chronic musculoskeletal pain.[37-40] Psychological and psychosocial problems, such as somatisation and depression, have been reported to associate with TMD.[41-44] Some studies have shown that psychosocial factors may have effect on the response to conservative treatment of TMD and increase the risk for chronicity.[41,45] Jussi et al gave some indication of a possible negative effect on the depressive and non-specific physical symptoms (with pain items) on TMD treatment response.[46] Base on previous studies, the psychosocial status of our TMD patients and QST results, we conclude that the psychosocial factor might be a key cofactor to the individual response to treatment and recovery of somatosensory function. The heterogeneity of patients and the possible role of psychological factors should be taken into account in the clinical treatment and individualised pain management of TMD patients.[47]

From this study, we can see that the individual's response to the drug shows individual differences. The comprehensive understanding of the sensory function of patients before and after treatment through standardised assessments has a certain significance for the patient's course tracking and efficacy evaluation.[6,7,32] Through the continuous detection of somatosensory function, the patient's sensory abnormality recovery process can be dynamically observed, and the effective degree of the treatment can also be evaluated. In the clinical situation, it is necessary to develop a personalised treatment plan according to the actual facial sensory function changes of the patient to improve the clinical treatment effect.[13,32,33]

5 | LIMITATIONS

This study has certain limitations that restrict the promotion of the research results. The sample size of this study was small, and the part with no significant differences in the results may have been caused by insufficient research subjects. However, the results of the study provide a good basis for further research on the differences in facial somatosensory function of TMD arthralgia. In the future, we hope that we can expand the sample size through multicentre cooperation and conduct more in-depth analyses through factors such as gender, age and duration for further exploration.

6 | CONCLUSIONS

Multiple phenotypes of facial somatosensory abnormalities were detected in Chinese TMD arthralgia patients before and after treatment, despite the disappearance of clinical signs and symptoms. Individual sensory differences could be perceived in this study. Standardised QST and statistical procedures should be used for disease diagnosis and phenotyping Chinese TMD pain patients in the future. Treatment strategies can be improved if individualised quantitative markers can be developed to phenotype patients with TMD pain to realise personalised management.

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CONFLICTS OF INTEREST

The authors indicate no conflicts of interest with respect to the authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

Yang Wang is the first author and Qiufei Xie is the corresponding author. Yang Wang recruited all the participants, carried out this study, performed the statistical analysis and drafted the manuscript. Qiufei Xie participated in the design of the study, statistical analysis and revision of the draft. Yanping Zhao recruited the participants and revised the manuscript. Guangju Yang helped to revise the manuscript. All authors approved the final manuscript.

ETHICAL APPROVAL

The study was performed in accordance with the Helsinki Declaration and was approved by the local ethics committee (PKUSSIRB-2013012). All participants gave written informed consent.

PEER REVIEW

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