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Somatosensory profiles in subgroups of patients with myogenic temporomandibular disorders and fibromyalgia syndrome

Doreen B. Pfau [a,*,1], Roman Rolke [b,1], Ralf Nickel [c], Rolf-Detlef Treede [a], Monika Daublaender [d]

[a] Department of Neurophysiology, Center of Biomedicine and Medical Technology Mannheim, Ruprecht-Karls-University Heidelberg, Mannheim, Germany
[b] Department of Neurology, University Medical Center, Johannes Gutenberg-University, Mainz, Germany
[c] Department of Psychosomatic Medicine and Psychotherapy, HSK Wiesbaden, Germany
[d] Policlinic of Oral Surgery, University Medical Center, Johannes Gutenberg-University Mainz, Mainz, Germany

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ABSTRACT

Some patients with myofascial pain from temporomandibular disorders (TMD) report pain in extra-trigeminal body regions. Our aim was to distinguish TMD as regional musculoskeletal pain syndrome ($n = 23$) from a widespread pain syndrome (FMS; $n = 18$) based on patients' tender point scores, pain drawings and quantitative sensory testing (QST) profiles. Referenced to 18 age- and gender-matched healthy subjects significant group differences for cold, pressure and pinprick pain thresholds, suprathreshold pinprick sensitivity and mechanical detection thresholds were found. Pain sensitivity in TMD patients ranged between those of FMS patients and healthy controls. The group of TMD patients was inhomogeneous with respect to their tender point count with an insensitive group ($n = 12$) resembling healthy controls and a sensitive TMD group ($n = 9$) resembling FMS patients. Nevertheless sensitive TMD patients did not fulfil diagnostic criteria for FMS in regard to widespread pain as shown by their pain drawings. TMD subgroups did not differ with respect to psychological parameters. The sensitive subgroup was more sensitive compared to healthy controls and to insensitive TMD patients in regard to their QST profile over all test areas as well as to their tenderness over orofacial muscles and trigeminal foramina. However, sensitive TMD patients had a short pain duration arguing against a transition from TMD to FMS over time. Data rather suggest an overlap in pathophysiology with FMS, e.g. a disturbance of central pain processing, in this subgroup of TMD patients. Those patients could be identified on the basis of their tender point count as an easy practicable screening tool.

1. Introduction

Pain in myogenic temporomandibular disorders (TMD) and fibromyalgia syndrome (FMS) are common chronic musculoskeletal pain conditions. Whereas TMD pain is considered to be a regional pain syndrome [12], FMS is characterized by widespread pain [53]. In temporomandibular disorders, 3 of 20 tender facial palpation sites are used as diagnostic criterion (Research Diagnostic Criteria/TMD; Dworkin and LeResche [12]) and trigger points as pathogenetic factor in myofascial pain in muscle tissues causing radiating pain are discussed. In contrast, fibromyalgia presents as a generalized pain disorder with widespread pain distribution (pain in at least two diagonally opposed quadrants plus axial skeletal pain; diagnostic criteria of the American College of Rheumatology (ACR) [53]). The other diagnostic criterion is an increased pain sensitivity over designated tender point areas ($\geqslant 11/18$; ACR reference) indicating a low pressure pain threshold in FMS patients [53,32]. A possible mechanism behind this pain disturbance is likely to be malfunction of central pain processing [33] rather than the presence of a primary muscle disease.

Despite apparent differences in pain distribution, similarities between these pain syndromes were noticed. Overlap of tender and trigger points was found in both patient groups [20], and

Abbreviations: CDT, cold detection threshold; CPT, cold pain threshold; DFNS, Deutscher Forschungsverbund Neuropathischer Schmerz = German Research Network on Neuropathic Pain; DMA, dynamic mechanical allodynia; FMS, fibromyalgia syndrome; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PHS, paradoxical heat sensation; PPT, pressure pain threshold; QST, quantitative sensory testing; SSRI, selective serotonin reuptakte inhibitors; TCA, tricyclical antidepressants; TMD, temporomandibular disorders (here meant as myogenic temporomandibular disorders); TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

* Corresponding author. Address: Department of Neurophysiology, Center of Biomedicine and Medical Technology Mannheim (CBTM), Medical Faculty Mannheim, University of Heidelberg, Ludolf-Krehl-Str. 13-17, D-68167 Mannheim, Germany. Tel.: +49 (0)621 383 9926; fax: +49 (0)621 383 9921.
E-mail address: doreen.pfau@medma.uni-heidelberg.de (D.B. Pfau).

[1] These authors contributed equally to this work.

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patients with TMD frequently describe pain in multiple body parts [39,48] which is inconsistent with the pathogenetic concept of myofascial trigger points and local disturbances of orofacial structures causing TMD pain. Accordingly, diffuse generalized pain disturbances were observed prior to onset and persistence of TMD symptoms [21,26], and increased evoked pain is also perceived in TMD patients in the contralateral body site [2,14] or in distant body regions [30,31,45]. Increased pain sensitivity during functional dental investigation was reported for both patient groups [7], stress and depression as signs of somatization were discussed as etiologic cofactors in TMD and FMS [1,6,7,26,34,41,49].

The purpose of our study was to determine similarities and differences between patients with temporomandibular disorders and fibromyalgia syndrome and to outline underlying neurobiological pain mechanisms in these patients.

In addition to clinical dental investigation and acquisition of a tender point score and trigger point count, we obtained a complete somatosensory profile using the standardized test protocol of quantitative sensory testing (QST) of the German Research Network on Neuropathic Pain (DFNS) [35,36]. It is a main hypothesis of this protocol that detected patterns of sensory plus and minus signs indirectly refer to underlying neurobiological mechanisms of altered pain sensitivity. Possible changes of central pain processing as sensitization of spinal nociceptive neurons or disturbances of descending noxious control systems may be uncovered [54]. The questions in detail were:

(1) Do patients with TMD and FMS share similar tender point scores and trigger point counts?
(2) Are sensory profiles similar or different?
(3) Is there evidence for spatial generalization of pain in TMD patients, marking a possible transition from TMD to FMS over time?

2. Materials and methods

2.1. Study population

Twenty-four patients with myogenic temporomandibular disorders (TMD) were investigated and diagnosed using axis I of the Research Diagnostic Criteria for TMD [12] by one investigator (MD). One man was excluded because he had received opioids on the examination day (see Fig. 1). The remaining twenty three patients (20 women, 3 men) had a mean age of 46.8 ± 13.1 years. Inclusion criteria were chronic uni- or bilateral myofascial pain (duration $\geqslant$6 months) in the face and exclusion of other face-related pain origins like neuropathic pain. This was ensured by a functional clinical investigation of the trigeminal and facial nerves. Five out of 23 TMD patients were receiving tricyclic antidepressants (TCA), one a selective serotonine-reuptake-inhibitor (SSRI) and one patient anticonvulsants (Gabapentin) on the examination day. One patient was receiving both TCA and SSRI. It was not required that patients had all their natural teeth nor a complete dental supporting area (canine to second premolar on each side of maxilla and mandible).

Additionally 18 patients with fibromyalgia syndrome (FMS) were sent with the diagnosis of FMS from Internist Rheumatologists to the Department of Psychosomatic Medicine and Psychotherapy of the Johannes Gutenberg-University Mainz, where they were examined again according to ACR criteria for FMS and included for study participation by a psychosomatic investigator (RN). Inclusion criteria were the classification criteria for fibromyalgia developed by the American College of Rheumatology (ACR; i.e. chronic widespread pain and 11 out of 18 possible tender points; widespread pain is defined as pain in axial plus upper and lower segment plus left- and right-sided pain) [53].

Four of those 18 patients with supposed FMS were excluded because their tender point score on the day of study investigation

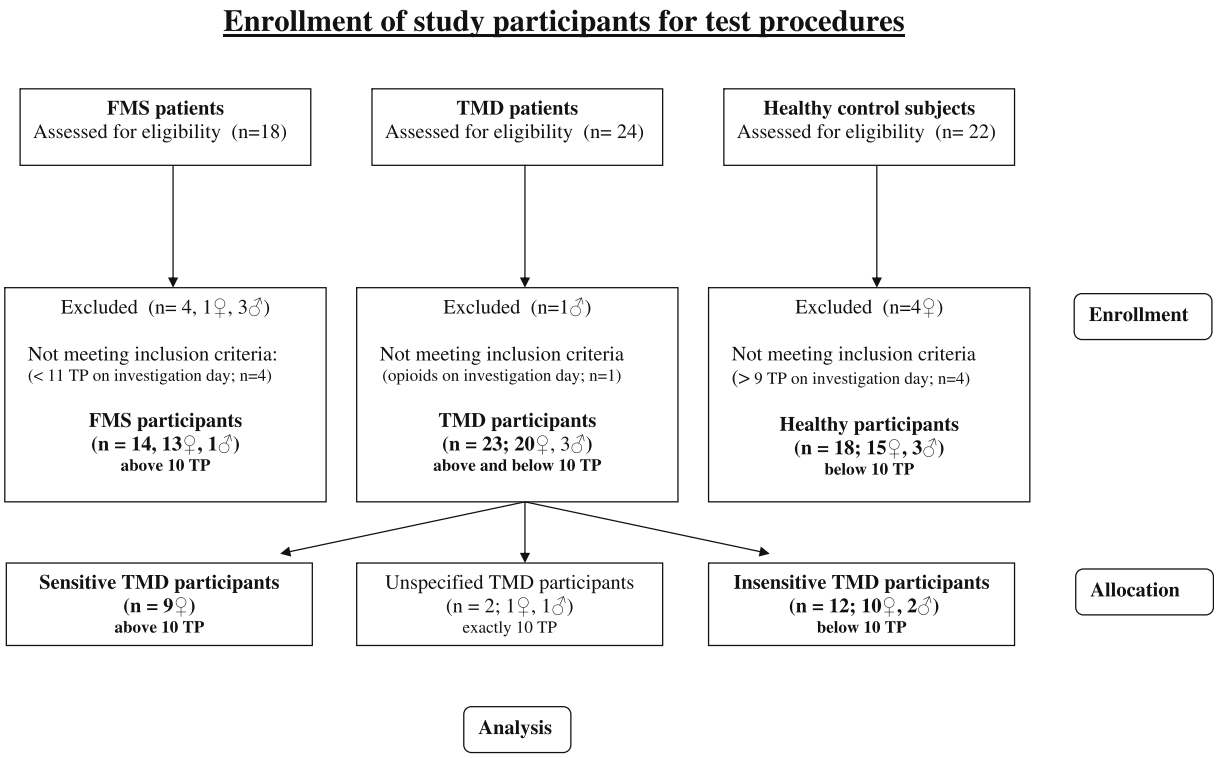

Fig. 1. Flow diagram of subject enrollment [4].

was below 11 even if they had fulfilled ACR criteria earlier (see Fig. 1). Such variability has been described before [8,47]. The remaining 14 patients with fibromyalgia syndrome (13 women, 1 man) had a mean age of 50.6 ± 5.1 years (mean ± SD). At the time of the study, 9 out of 14 patients were receiving selective serotonine-reuptake-inhibitors (SSRI), two tricyclical antidepressants and one a muscle relaxant. Two patients did not receive any analgesic medication on the examination day. All patients were allowed to continue taking their pain reducing medication prior to the investigation. Additionally, pain duration in months was assessed. Demographic data were compared using Mann Whitney U-test (SPSS 8.0; SPSS Inc., Illinois, USA).

For pain-free subjects we defined as inclusion criterion less than 10 tender points, as no diagnostic criterion for FMS should be fulfilled in our healthy controls. On the other hand a tender point score above 10 tender points as used as diagnostic criterion for FMS also occurs in 10% of pain-free women [47,52]. Since number of tender point score can fluctuate, we defined the number of 10 tender points as safety zone. Further exclusion criteria were migraine, tension type headache and pain of the temporomandibular joint during the last six months and reception of medication influencing pain perception (analgesics, antidepressants). According to these criteria, 22 healthy pain-free subjects (18 women, 4 men) underwent a tender point examination. Of those, subjects having less than 10 tender points out of 18 were included ($n = 18$; 15 women, 3 men; mean age 47.6 ± 14.5 years; see Fig. 1). Controls were not excluded if they showed signs of non-painful dysfunctions of temporomandibular system. The dental supporting area was completely preserved in all controls. Fifteen of them had their natural teeth or fixed dental prosthesis (PM1 to M1), one wore a dental plate and two controls had a partial dental plate.

2.2. Experimental characterization of patients and healthy controls

The following additional investigations were performed by an additional investigator (DP). All patients and healthy controls gave their written informed consent prior to study participation. The study was approved by the local Ethics Committee of Rhineland-Palatinate. All testing procedures were in accordance with the Declaration of Helsinki.

2.2.1. Investigation of tender points and pressure pain threshold sum score

A tender point score as one of the two criteria for diagnosis of FMS (American College of Rheumatology) was evaluated to investigate generalized pressure sensitivity and to assess presence of FMS in both patient groups and controls (for the presence of widespread pain as the other necessary criterion for diagnosis of FMS see Section 2.2.3.). That criterion was fulfilled if $\geqslant 11$ of 18 "positive" tender points on defined anatomical sites were present [53]. A tender point was counted as "positive" if the pressure pain threshold was lower than 393 kPa (corresponding to 4 kg/cm^2). For investigation, an electronic pressure algometer (Somedic, Sweden) with a probe area of 1cm^2 which was pressed on the skin with a ramp rate of 50 kPa/s was used to determine pressure pain threshold over the designated tender point areas. If evoked pain was not localized over the test area but was spreading along the myofascial structures, and threshold was lower than 393 kPa, this tested anatomic tender point area was counted as both, as trigger point and as tender point.

As the tender point score of patients with temporomandibular disorders was inhomogeneous, we divided them into a sensitive group ($\geqslant 11$ tender points; $n = 9$; 9 women; mean age ± SD 41.8 ± 15.4 years), showing at least 11 of 18 tender points like FMS patients, and an insensitive group, which was similar to healthy controls in regard to their tender point score ($\leqslant 9$ tender points; $n = 12$; 9 women, 2 men; mean age ± standard deviation 50.75 ± 11.3 years). Two TMD patients with an intermediate count of 10 tender points were not stratified to one of these groups and accordingly not included in the subgroup analysis.

For tender point analysis the described procedure for assessment of the tender point score was evaluated bilaterally and the number of trigger points was assessed. Data were presented as means ± standard deviation and as sum score over all tender points.

2.2.2. Quantitative sensory testing

Quantitative sensory testing (QST) was performed according to the protocol of the German Research Network on Neuropathic Pain (DFNS) [36]. The standardized QST battery consists of seven tests measuring 13 parameters. The tests can be grouped as follows:

- thermal detection thresholds for the perception of cold, warm and paradoxical heat sensations,
- thermal pain thresholds for cold and hot stimuli,
- mechanical detection thresholds for touch and vibration,
- mechanical pain sensitivity including thresholds for pinprick and blunt pressure, stimulus/response-functions for pinprick sensitivity and dynamic mechanical allodynia, and pain summation to repetitive pinprick stimuli (wind-up like pain).

QST was performed over cheek, trapezius and hand dorsum. Patients were investigated unilaterally over the more painful body side, controls were tested bilaterally.

2.2.2.1. Thermal detection and pain thresholds and the number of paradoxical heat sensations. Thermal testing was performed using the MSA thermo test device (SOMEDIC, Sweden). The baseline temperature was 32 °C and the contact area of the thermode was 12.5 cm^2. Cold detection threshold (CDT), warm detection threshold (WDT), paradoxical heat sensations by using the thermal sensory limen procedure (TSL), cold pain threshold (CPT) and heat pain threshold (HPT) were assessed using ramped stimuli 1 °C/s (for detailed description see [36]).

2.2.2.2. Mechanical detection threshold. Mechanical detection threshold (MDT) was assessed using a set of standardized von Frey filaments with rounded tips of 0.5 mm diameter (Optihair$_2$-Set Marstock Nervtest, Germany), which exert forces between 0.25 and 512 mN. Using the "method of limits", five threshold determinations were made, each with a series of ascending and descending stimulus intensities. The final threshold was the geometric mean of these five series.

2.2.2.3. Mechanical pain threshold. Pinprick stimulators (cylindrical tip, 0.25 mm diameter) with fixed stimulus intensities (8, 16, 32, 64, 128, 256 and 512 mN) were used to determine the mechanical pain threshold. Stimulators were applied in ascending order until the first percept of sharpness was detected. The threshold was calculated as the geometric mean of ascending and descending stimulus forces.

2.2.2.4. Stimulus/response-functions: mechanical pain sensitivity for pinprick stimuli and dynamic mechanical allodynia. Mechanical pain sensitivity (MPS) was assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain. Subjects were asked to give a pain rating for each stimulus on a '0–100' numerical rating scale ('0' indicating "no pain", and '100' indicating "most intense pain imaginable"). Dynamic mechanical allodynia (DMA) was assessed as part of the test above, using a set of three light tactile stimulators as moving innocuous stimuli: A cotton wisp exerting a force of ~3 mN, a cot-

ton wool tip fixed to an elastic strip exerting a force of ~100 mN, and a standardized brush (Somedic, Sweden) exerting forces of ~200–400 mN. The tactile stimuli were applied with a single stroke of approximately 2 cm in length over the skin.

2.2.2.5. Vibration detection threshold. The vibration detection threshold (VDT) represents the only disappearance threshold within the QST battery. This test was performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that was placed over a bony prominence (zygomatic process, scapula spine, ulnar styloid process) and left there until the subject could not detect vibration any more. Vibration detection threshold was determined with three stimulus repetitions.

2.2.2.6. Pressure pain threshold (PPT). The final test in the protocol was performed over muscle (masseter muscle, trapezius muscle, thenar eminence) using an electronic pressure algometer (Somedic, Sweden) with a probe area of 1 cm^2 (probe diameter of 1.1 cm) that exerts forces up to 20 kg/cm^2 corresponding to ≈2000 kPa. The pressure pain threshold was determined with three series of ascending stimulus intensities, each applied as a slowly increasing ramp of 50 kPa/s (≈0.5 kg/cm^2).

2.2.2.7. Z-transformation of QST data. To compare a single patient's QST data profile with the group mean of accurately age- and gender-matched healthy controls (data from left and right body side pooled) patients' data were Z-transformed for each single parameter by using the following expression:

$$\text{Z-score} = (\text{Mean}_{\text{single patient}} - \text{Mean}_{\text{controls}})/\text{SD}_{\text{controls}}$$

This procedure results in a QST profile where all parameters are presented as standard normal distributions (zero mean, unit variance). Z-values above "0" indicate a gain of function when the patient is more sensitive to the tested stimuli compared with controls (hyperalgesia, allodynia, hyperpathia), while Z-scores below "0" indicate a loss of function referring to a lower sensitivity of the patient (small and large fiber functions). A Z-score of zero represents a value corresponding to the group mean of the healthy control subjects.

2.2.2.8. Statistical analysis of QST data. The numbers of paradoxical heat sensations during the TSL procedure, cold pain thresholds, heat pain thresholds, and vibration detection thresholds were normally distributed. All other parameters were normally distributed in log-space and were transformed logarithmically before statistical analysis [35]. All statistical calculations were performed using 'Statistica' software for Windows (Statistica 8.0, StatSoft Inc., USA). Differences of Z-score QST data between patient groups/controls and tested body regions were compared using a two-way analysis of variance (ANOVA) with tested body areas as within-subjects factor and group (patients/controls) as between-subjects factor. Post hoc comparisons were calculated using LSD-post hoc tests (LSD; least significant difference). As dynamic mechanical allodynia (DMA) did not appear in healthy controls, we tested raw data with an unpaired t-test versus the expected value of zero.

2.2.3. Pain drawings

Due to the inhomogeneous appearance of patients with TMD concerning tender point score as one diagnostic criterion for FMS, we retrospectively attempted to analyze the spatial distribution of ongoing pain as parameter for "widespread pain" according to one of the two ACR diagnostic criteria for fibromyalgia [53]. Pain drawings were available in 17/23 patients with TMD (9/9 sensitive TMD patients; 8/12 insensitive TMD patients) and 9/14 FMS patients. Pain drawings of each group were scanned, superimposed and transformed into two-dimensional colour coded images. Body areas with high occurrence of pain were illustrated in dark red; body areas without pain appear white. A score of generalization according to the ACR criterion "widespread pain" was established to comprise data semi quantitatively. To evaluate overlap of TMD and FMS concerning pain distribution, the number of patients with "widespread pain" was determined. Patients with "face- and neck pain" were counted to assess the incidence of orofacial pain in FMS and TMD patients.

2.2.4. Psychological factors

As possible psychological and interacting factors we assessed levels of depression and anxiety, pain related interferences of daily work and catastrophizing as a frequently described coping strategy in patients with chronic pain associated with a negative course [18,23,25].

Anxiety and depression were assessed with the German version [22] of the Hospital Anxiety and Depression Scale [57]. The HADS-D is short and demonstrates good reliability in a German reference group. The scale contains seven items on "Anxiety" and seven on "Depression". Each question has four levels of possible responses, ranging from definitive agreement to definitive disagreement. It lends itself very well to implementation in patients with physical illness as it contains no questions whose responses could be determined by symptoms of a physical disease.

Pain related disabilities of daily work were assessed by using a validated German version [11] of the Pain Disability Index (PDI) [46]. This inventory asks if pain interferes with daily live activities concerning seven broad areas: family/home responsibilities, recreation, social activity, occupation, sexual behaviour, self-care and life-support activities. The PDI sum score ranges from 0 to 7.

Catastrophizing was determined by a subscale of the German version [29] of the Coping Strategies Questionnaire (CSQ) [37], one of the most widely used measures of pain coping strategies. The CSQ has eight subscales: diverting attention, reinterpreting pain sensations, coping self-statements, ignoring pain sensations, praying or hoping, catastrophizing, increasing activity level and increasing pain behaviors. The SF-36 is a frequently used instrument measuring global health-related quality of life on eight scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The resulting individual values were compared to means and standard deviations (SD) of age- and gender-matched reference groups out of the German normal population. The results of the SF-36 were computed as Z-values [5,51]. Psychological factors were compared using an oneway ANOVA and a Scheffé post hoc test. A linear trend in the order healthy controls – insensitive TMD patients – sensitive TMD patients and FMS patients was tested. Additionally pain duration of patient groups was assessed in months and compared using a non-parametric test (Mann–Whitney *U*-Test).

2.2.5. Dental examination

For intraoral dental examination the dentition and static contacts were noted as well as signs of oral habits using an abbreviated investigation protocol, respecting restricted duration of patient's total investigation. We acquired the number of missing teeth, of missing teeth replaced by removable dentures or bridges, and the numbers of crowned or filled teeth. Distances of overbite, overjet and interocclusal distances were gauged.

For extraoral examination the functions of muscles, nerves and the movements of the temporomandibular joint were tested. We investigated the function of the facial nerve and the sensitivity to pressure over trigeminal foramina. Signs of underlying myogenic orofacial hyperactivity were documented after checking the mimic

muscles, masticatory and neck muscles. Temporal muscle, masseter muscle, sternocleidomastoid muscle, muscles of the cervical spine, trapezius muscle and suprahyoidal muscles were palpated with the finger tips of the index and the third finger, using the non-dominant hand of the investigator to fix the head e.g. the mandible. For extraoral muscle palpation we used an approximate pressure of 1 kg, for intraoral muscle and joint palpation an approximate pressure of 0.5 kg. Reference region for pressure sensitivity over muscles was thenar eminence. We checked if a single active mandibular movement (forward movements, laterotrusion and mouth opening) or an assisted backward movement was painful. Pain during muscular overexpansion of temporal muscle, medial and lateral pterygoid muscle and masseter muscle were investigated.

Data of pain during functional dental investigation were evaluated as absolute data indicating number of participants and in percent of participants showing pain during investigation. Data were compared by a Yates' corrected chi-square test. Parameters of dentition are assessed as mean ± SD and compared by *t*-test.

3. Results

3.1. QST procedures show significant differences comparing patients and controls across the tested body regions

ANOVA of QST data demonstrates differences comparing TMD and FMS patient groups and controls for CPT (cold pain threshold), PPT (pressure pain threshold), MPT (mechanical pain threshold), MPS (mechanical pain sensitivity) and MDT (mechanical detection threshold) (Table 1, Fig. 2) with patients more sensitive to painful stimuli, but less sensitive to tactile stimulation. Additionally, ANOVA revealed differences across tested body regions (cheek, trapezius and hand dorsum) for the parameters CPT, PPT and MDT. The significant group by region interaction term for CPT indicates that cold hyperalgesia was localized to the trapezius muscle region and not generalized to the entire body in both patient groups, the interaction term for PPT indicates differences between the patient groups over hand dorsum and trapezius (Fig. 2, for detailed raw data see Online Supplemental Table 3).

Both patient groups showed cold hyperalgesia localized over trapezius muscle ($p < 0.01$; Fig. 2) while no changes were found over hand dorsum and cheek compared to healthy controls. Generalized increased pressure sensitivity was demonstrated by patients with FMS over hand, trapezius (both $p < 0.001$) and cheek ($p < 0.05$) compared to controls, over hand and trapezius compared to TMD patients ($p < 0.01$). This finding agrees with the well known generalized pressure hyperalgesia in patients with fibromyalgia syndrome corresponding to the tender point investigation. TMD patients did not show pressure hyperalgesia over any test area (Fig. 2). Pinprick hyperalgesia was present in TMD over hand and trapezius ($p < 0.05$), while this finding over cheek was only present by trend. FMS patients showed pinprick hyperalgesia over trapezius muscle ($p < 0.05$). In spite of significant ANOVA main effects, no post hoc differences between patients and healthy controls were found in regard to the mechanical pain sensitivity (MPS) of TMD and FMS patients. Furthermore, FMS patients demonstrated increased mechanical detection thresholds over trapezius ($p < 0.05$) and cheek ($p < 0.01$) compared to healthy controls, while TMD patients did not differ from control group.

3.2. Tender and trigger points in patients with TMD and FMS

Healthy controls and patients with TMD had a lower mean tender point score (5.3 ± 0.6 and 8.9 ± 1.1) than patients with FMS (16.1 ± 0.5) over the designated tender point areas (mean ± SEM; $p < 0.001$ FMS vs. HC and TMD; $p < 0.01$ HC vs. TMD; unpaired *t*-test). The mean pressure initiating pain summed over the 18 standard test regions for the presence of tender points was 9404 ± 593 kPa in controls, 7772 ± 511 kPa in patients with TMD and 4321 ± 330 kPa in patients with FMS (mean ± SEM; $p < 0.001$ FMS vs. HC and TMD; $p < 0.05$ HC vs. TMD; unpaired *t*-test). This trend was affirmed by the count of trigger points; while healthy controls showed on average (mean ± SEM) 0.06 ± 0.055 trigger points, patients with TMD had 0.74 ± 0.20 trigger points. Patients with FMS had the highest trigger point count with 3 ± 0.96 trigger points in tender point areas. Trigger point scores of TMD and FMS patients differed significantly from those of healthy controls (both $p < 0.01$), those between TMD and FMS also differed significantly ($p < 0.05$; unpaired *t*-test). Co-localization of tender points and trigger points was found in 64% of FMS patients and similarly in 44% of patients with TMD. One healthy control subject showed one trigger point.

In regard to a diagnostic criterion of the American College of Rheumatology for fibromyalgia syndrome, 9 TMD patients showed more than 10 positive tender points (sensitive TMD patients) as did FMS patients, and 12 TMD patients had less than 10 positive tender points (insensitive TMD patients) as did the included healthy control subjects. Two out of 23 TMD patients with exactly 10 tender points were excluded from subgroup analysis.

The subgroup of insensitive TMD patients ($n = 12$) had a significantly higher pressure pain threshold of 9744 ± 447 kPa and a tender point score of 4.5 ± 0.7 (mean ± SEM; both parameters $p < 0.001$) compared to sensitive patients with temporomandibular disorders ($n = 9$). Those patients showed a pressure pain threshold

Table 1
ANOVA comparing Z-score sensory profiles of healthy controls and patients with fibromyalgia and myogenic temporomandibular disorders over cheek, trapezius and hand

QST parameter	Patient groups/controls		Body region		Interaction group by region	
	F-value	*p*-value	*F*-value	*p*-value	*F*-value	*p*-value
CDT	0.8	n.s.	2.5	n.s.	1.8	n.s.
WDT	0.2	n.s.	1.7	n.s.	1.8	n.s.
TSL	0.8	n.s.	1.2	n.s.	0.7	n.s.
CPT	6.1	<0.01	9.1	<0.001	3.0	<0.05
HPT	2.5	n.s.	2.2	n.s.	1.0	n.s.
PPT	26.4	<0.001	5.2	<0.01	4.5	<0.01
MPT	9.7	<0.001	2.6	n.s.	1.1	n.s.
MPS	4.9	<0.05	1.9	n.s.	1.6	n.s.
WUR	2.2	n.s.	0.0	n.s.	0.2	n.s.
MDT	6.8	<0.01	5.9	<0.01	2.0	n.s.
VDT	1.1	n.s.	2.0	n.s.	0.7	n.s.
DMA	4.7	<0.05	0.6	n.s.	1.1	n.s.

There was no significant occurrence of PHS in our healthy controls and the patient groups.
n.s. = not significant ($p \geqslant 0.05$).

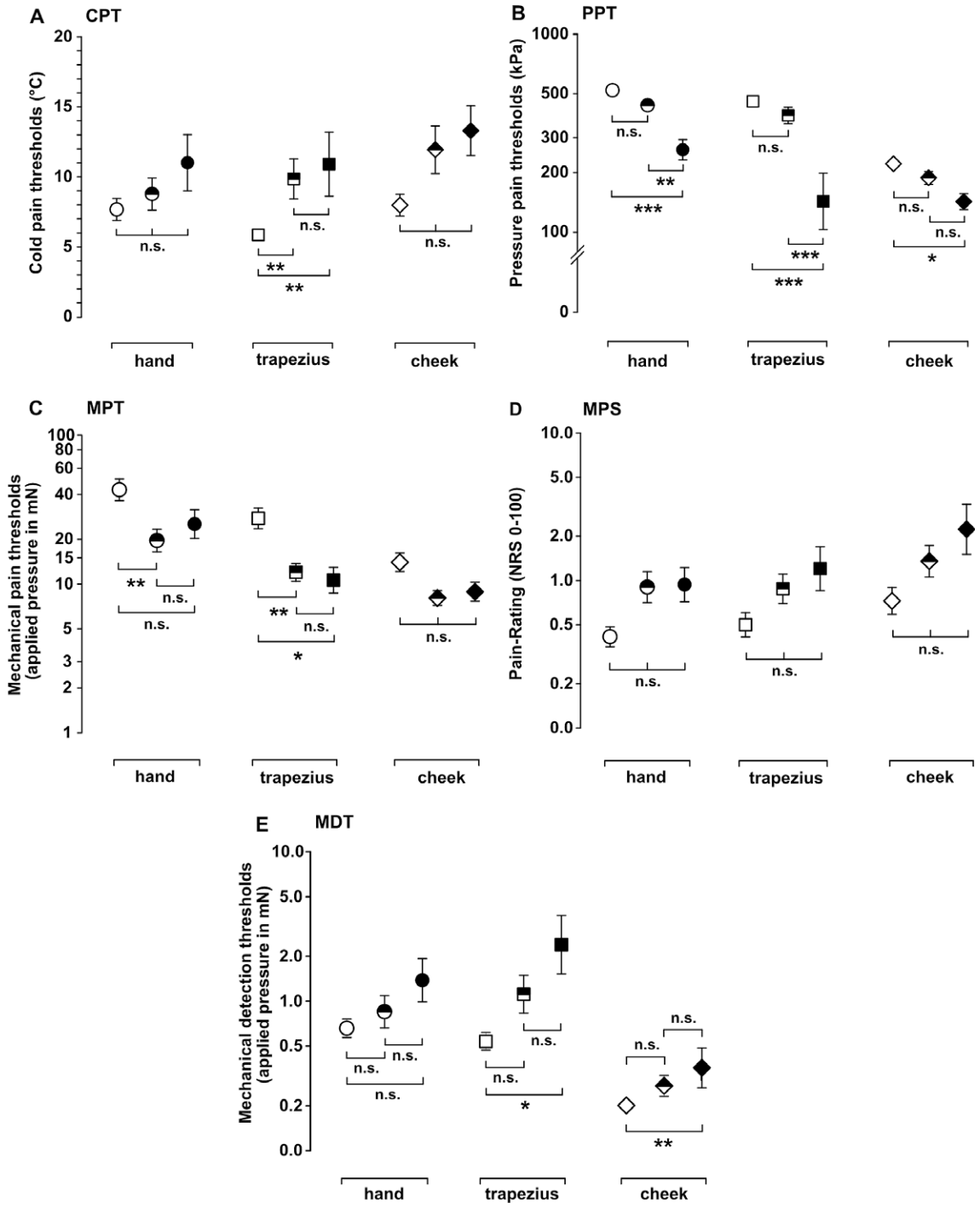

Fig. 2. Cold pain thresholds (CPT), pressure pain thresholds (PPT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS) and mechanical detection threshold (MDT) of FMS (filled symbols) and TMD (semifilled symbols) patients compared to healthy control subjects (open symbols). ANOVA (see Online Supplemental Table 1); LSD-post hoc-tests; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; mean thresholds ± SEM.

of 5387 ± 263 kPa and a tender point score of 14.6 ± 0.9 over all test areas. Trigger points between subgroups did not differ significantly (mean ± SEM: insensitive TMD patients: 0.83 ± 0.32 trigger points, sensitive TMD patients: 0.67 ± 0.29 trigger points).

3.3. Pain drawings

The face as painful body area was depicted in all TMD patients in pain drawings, neck pain occurred in four insensitive (67%) and four sensitive (44%) patients with TMD (Fig. 3a–c). In general, insensitive TMD patients showed a pain distribution restricted to face, head and neck. In sensitive TMD patients, pain was not restricted to the orofacial region, but never included the hand. All of our FMS patients showed generalized pain including face and neck pain in eight subjects (89%), of whom four subjects presented signs and symptoms of TMD (44%) during clinical examination. The number of subjects with widespread pain in patients with FMS (100%) differed significantly from that in insensitive (17%; $p < 0.001$) and sensitive (22%, $p < 0.01$) patients with TMD, indicating lack of incidence of fibromyalgia in most patients with TMD.

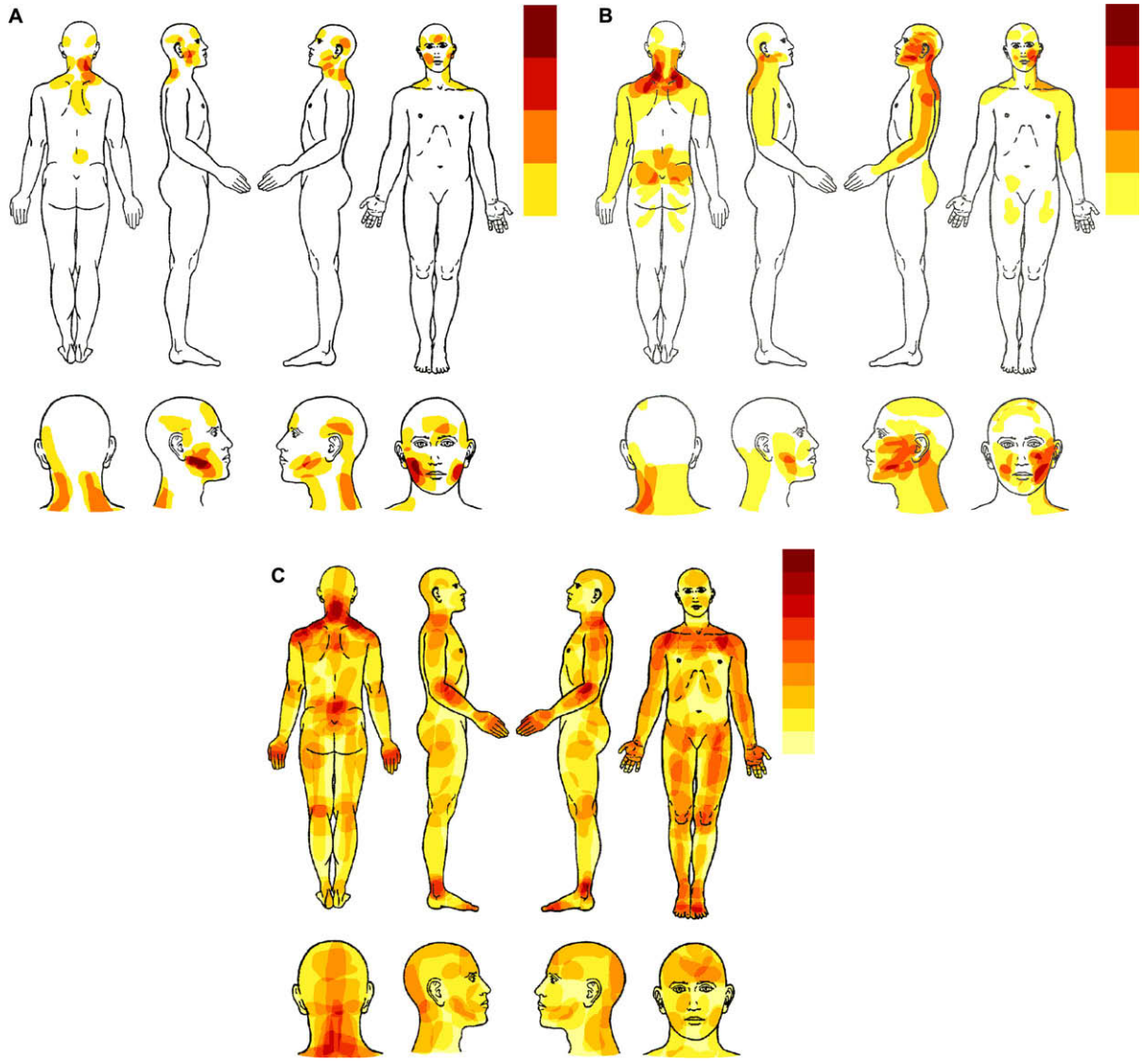

Fig. 3. Superposition of pain drawings of (A) insensitive TMD patients (n = 9 out of 12), (B) sensitive TMD patients (n = 9 out of 9) and (C) FMS patients (n = 9 out of 14). The white part of the relativized spectrum marks areas without pain in any patients, the dark red part marks pain areas in the maximal number of patients with overlapping pain areas (TMD insensitive: n = 4; TMD sensitive: n = 5; FMS: n = 9).

3.4. Sensory profiling of insensitive and sensitive patients with temporomandibular disorders and fibromyalgia

Z-score QST profiles showed that insensitive TMD patients resembled healthy controls especially over the hand dorsum, with few localized somatosensory changes over cheek and trapezius (Fig. 4, left column). As minus symptoms, a mechanical hypoesthesia was present over the cheek ($p < 0.001$) and a cold hypoesthesia was found over the trapezius ($p < 0.05$, Fig. 4). As plus sign a pinprick hyperalgesia was detected over trapezius ($p < 0.05$) and a dynamic mechanical allodynia was found in one out of 12 patients over the cheek.

In contrast, compared to controls and insensitive TMD patients, sensitive TMD patients showed a generalized pressure hyperalgesia ($p < 0.05$ over all test areas, see Online Supplemental Table 5a–b), cold pain hyperalgesia over trapezius and cheek ($p < 0.05$) and heat pain hyperalgesia ($p < 0.05$) over all test areas (Online Supplemental Table 5a–b). Compared to controls, mechanical pain threshold was decreased, mechanical pain sensitivity was increased over the hand ($p < 0.05$). So both, sensitive patients with TMD and patients with FMS (Fig. 2) showed signs of sensory gain and hardly differed (Fig. 4, superimposed sensory profiles in the right column).

3.4.1. Incidence of pathological QST-values within the patient's groups

Additionally to the preceding reports of group comparisons between healthy controls and patient groups, numbers of individual patients with pathological values outside the normative range (±1.96 standard deviation) are shown in Online Supplemental Table 3b and are grouped here, if more than a third of the patient's group presented pathological individual Z-score values:

Sensitive TMD patients showed a cold hypoesthesia over the trapezius. A cold hyperalgesia was presented by sensitive TMD patients over all test areas, by FMS patients over cheek and trapezius. Over all test areas, sensitive TMD patients showed a heat hyperalgesia, FMS patients a pressure hyperalgesia. Sensitive TMD patients presented a pinprick hyperalgesia over the hand. Insensitive TMD and FMS patients showed a tactile hypoesthesia over the cheek, sensitive TMD and FMS patients over the trapezius.

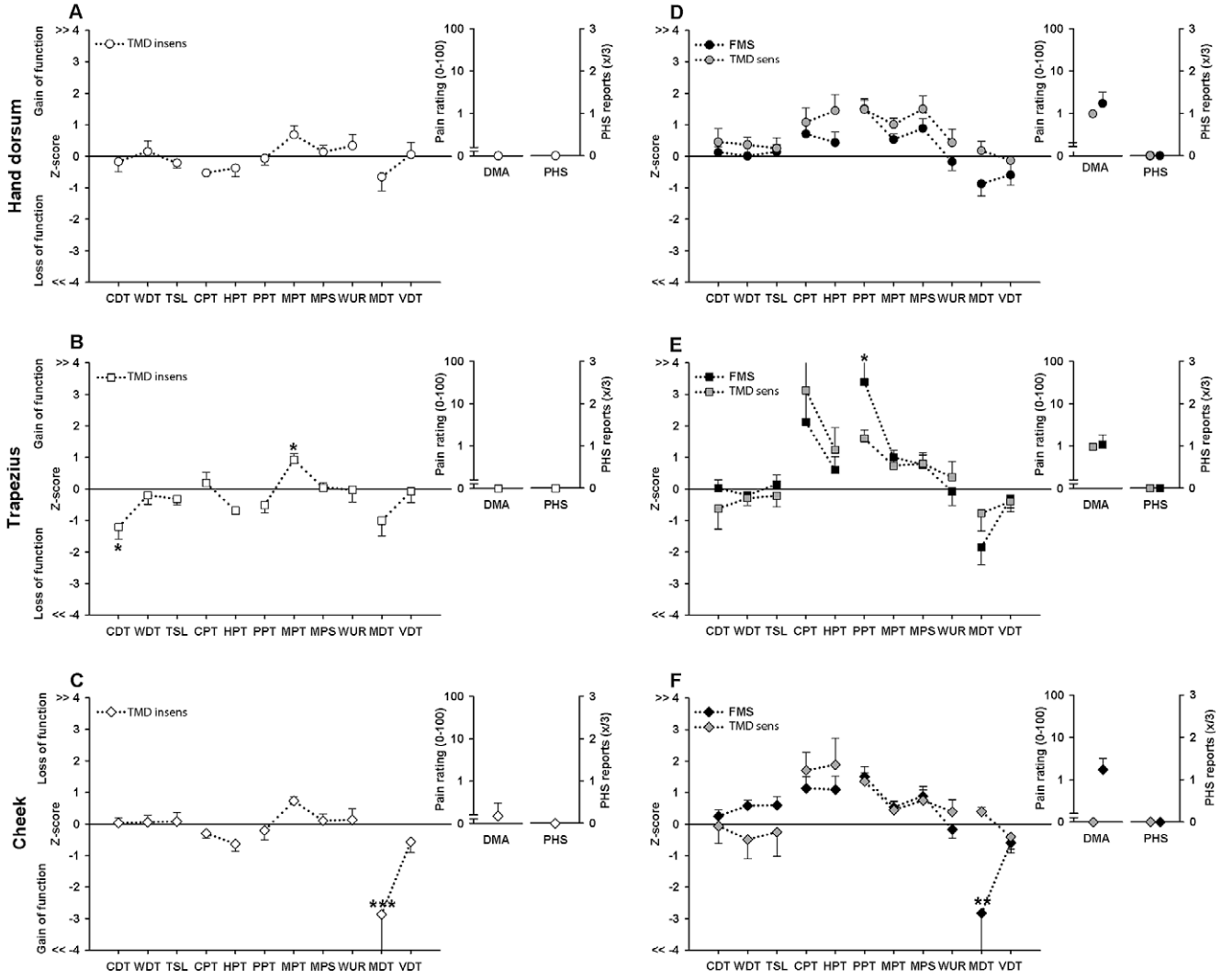

Fig. 4. Sensory profiling. The Z-score sensory profiles are shown for all tested QST parameters over cheek, trapezius and hand, healthy control subjects are represented by a Z-score of "zero". The first column shows the Z-score QST profiles of insensitive TMD patients ($n = 12$; first column) compared with healthy control subjects. For the number of individual values outside the normative range (between + and −1.96 standard deviation) see Section 3.4.1 in the text and Online Supplemental Table 3b. The second column shows the superimposed Z-score QST profiles of sensitive TMD ($n = 9$) and FMS patients ($n = 14$), comparing sensitive TMD patients vs. FMS patients. ANOVA (Online Supplemental Table 4); LSD-post hoc test: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Error bars mark SEM. For post hoc comparisons of sensitive vs. insensitive TMD patients, controls vs. sensitive TMD patients and of FMS vs. insensitive TMD patients see Online Supplemental Table 5a–c).

Altogether, most individual values of our patients were typically still within the normal range of healthy controls. Nevertheless, according to significant statistical comparison of patient groups versus control subjects (see Fig. 2 for FMS patients, Fig. 4, second column for insensitive TMD patients and Online Supplemental Table 5b for sensitive TMD patients), most significant parameters (13/20) are based on a substantial number ($\geqslant$ a third) of patients with pathological individual values. Some significant parameters (7/20) are based on a large number of patients with high or low Z-score values within the normal range.

3.5. Pain duration

Although sensitive TMD patients and patients with FMS resembled each other in many parameters pain duration was significantly longer in FMS patients than in sensitive TMD patients ($p < 0.01$, Mann–Whitney-Test, SPSS; see Fig. 5). There was no significant difference in pain duration between the two subgroups of TMD ($p = 0.12$).

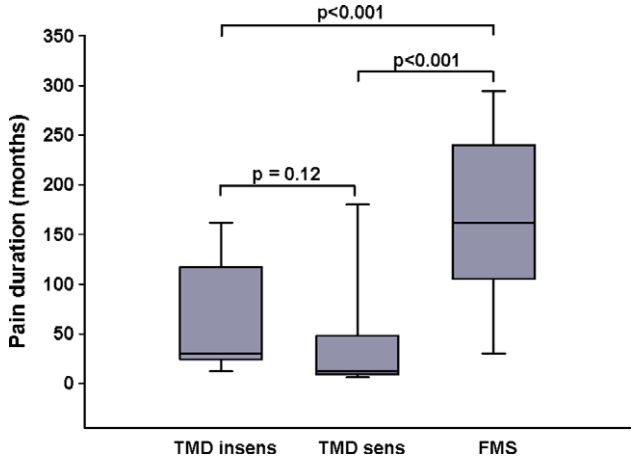

Fig. 5. Pain duration in insensitive (TMD insens) and sensitive (TMD sens) TMD patients and FMS patients (FMS). Error bars mark SD.

3.6. Psychological factors associated with widespread pain

Significant group differences were found in pain evaluating questionnaires PDI, SF-36, and possible pain predicting parameters as were anxiety and depression (HADS) and catastrophizing (CSQ 6). A linear trend could be shown for these parameters following the rule FMS → sensitive TMD → insensitive TMD → healthy controls. According to this finding FMS patients differed significantly from healthy controls in all these parameters while TMD patients ranked in-between without showing significant differences between sensitive and insensitive TMD patients and FMS patients (Fig. 6 and Online Supplemental Table 6.

3.7. Dental examination

Sensitive patients with TMD and patients with FMS demonstrated an increased pressure sensitivity over trigeminal foramina ($p < 0.05$; see Table 2). Corresponding to the generalized pressure sensitivity demonstrated in QST, FMS patients showed an increased pressure pain sensitivity during palpation of facial muscles (temporal and masseter muscles $p < 0.05$; Table 2). Suprahyoid and neck muscles (sternocleidomastoid and musculature of the cervical spine; all $p < 0.01$; see Online supplemental Table 1) were also more sensitive. Pressure hyperalgesia was additionally found over thenar muscle ($p < 0.05$). Sensitive ($p < 0.01$) more than insensitive ($p < 0.05$) patients with TMD showed increased pressure sensitivity over temporal and masseter muscles but not over thenar muscle indicating lack of widespread pain in general compared to patients with FMS. Additionally sensitive TMD patients showed a higher pressure sensitivity over suprahyoid muscles ($p < 0.01$) and sternocleidomastoid muscle ($p < 0.05$; Online supplemental Table 1). Sensitivity in patient groups over trapezius muscle could not be ascertained because even healthy controls demonstrated muscular pain during palpation in this area (Table 2). However, comparing patient groups, significantly more sensitive than insensitive TMD patients showed muscle pain over the trapezius muscle ($p < 0.05$, Table 2). Mouth opening was painful in significantly more patients with FMS ($p < 0.05$) and sensitive patients with TMD ($p > 0.01$) than in healthy controls. FMS patients ($p < 0.01$) and insensitive TMD patients ($p < 0.05$) showed a smaller gap between occluding surfaces of opposing teeth in resting position (Table 2).

4. Discussion

In this study, a group of TMD patients was split with respect to patients' tender point score (one of the ACR criteria for FMS) into an insensitive subgroup resembling healthy control subjects and into a sensitive subgroup resembling FMS patients. The sensitive TMD subgroup showed more expanded pain areas on superimposed pain drawings and generalized changes in pain perception over cheek, trapezius and hand dorsum in contrast to insensitive TMD patients with more localized changes without fulfilling FMS diagnostic criteria in most subjects. Even if we found those extensive differences in ongoing and evoked pain perception, no differences in regard to psychological parameters such as pain influenced behaviour (PDI and SF-36) and possible pain predicting variables as anxiety, depression and catastrophizing between both TMD subgroups could be identified. Even pain duration and trigger point score did not differ between both TMD subgroups.

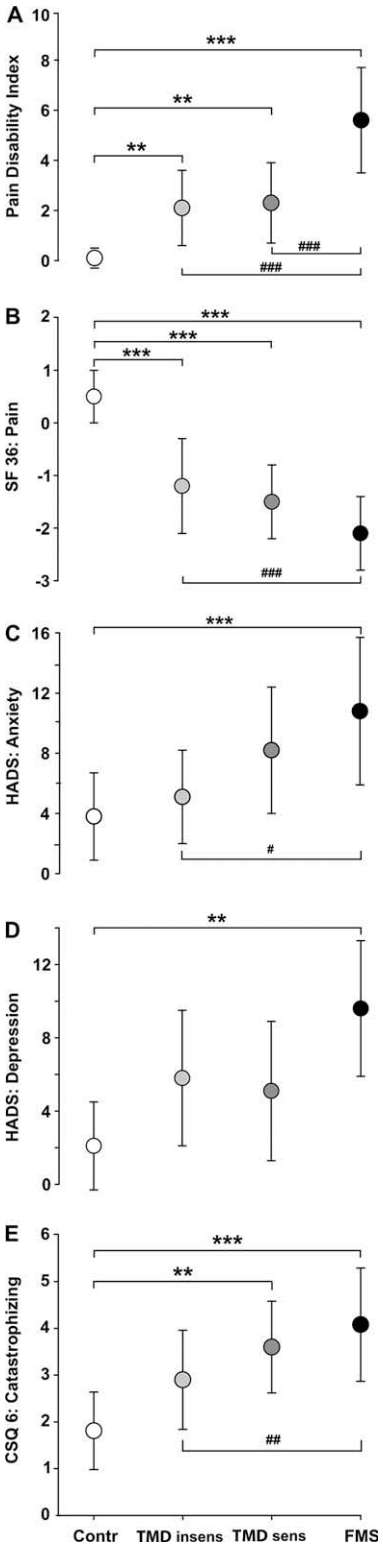

Fig. 6. Psychological parameters in healthy control subjects (Contr.; $n = 18$), insensitive (TMD insens; $n = 12$) and sensitive (TMD sens; $n = 9$) TMD patients and FMS patients ($n = 14$). ANOVA; Scheffé post hoc test: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ compared to healthy controls; #p < 0.05; ##p < 0.01; ###p < 0.001 compared to FMS. Error bars mark SEM. All parameters showed significant linearity.

4.1. Subgroups of patients with temporomandibular disorder

Some studies investigating pain sensitivity of TMD patients in extra-trigeminal regions reported increased experimentally evoked pain in non-facial areas [30,40,45], while others failed to detect this phenomenon [6]. It was suggested that generalized up-regulation of CNS responsiveness to aversive stimulation may constitute a pathophysiologic mechanism contributing to myofascial pain in TMD patients [30,31,40]. Furthermore, a disturbance of

Table 2
Clinical investigation.

	Control	TMD insens	TMD sens	FMS
Sensitivity of trigeminal foramina				
Pain during palpation of ophthalmic foramen	0 (0%)	2 (17%)	5 (56%)**	7 (50%)*
Pain during palpation of maxillary foramen	2 (12%)	4 (33%)	7 (78%)**	11 (79%)***
Pain during palpation of mental foramen	2 (12%)	4 (33%)	5 (56%)*	10 (71%)**
Muscle sensitivity				
Pain during palpation of temporal muscle	0 (0%)	4 (33%)*	5 (56%)**	7 (50%)*
Pain during palpation of masseter muscle	4 (22%)	8 (67%)*	9 (100%)***	10 (71%)*
Pain during palpation of trapezius muscle	13 (72%)	6 (50%)	9 (100%)#	14 (100%)
Painful palpation of thenar muscle	3 (18%)	2 (17%)	2 (22%)	9 (64%)*
Sensitivity during mouth opening	0 (0%)	3 (25%)	5 (56%)**	5 (36%)*
Gap between occluding surfaces of opposing teeth in resting position (mm)+	2.1 ± 0.8	1.4 ± 0.6*	1.6 ± 0.6	1.1 ± 0.5**

Control = Control subjects, $n = 18$; TMD insens = Insensitive patients with myogenic temporomandibular disorders, $n = 12$; TMD sens = Sensitive patients with myogenic temporomandibuar disorders, $n = 9$; FMS = Patients with fibromyalgia syndrome, $n = 14$. Data specified in number of patients and per cent.
* $p < 0.05$ compared to healthy controls.
** $p < 0.01$ compared to healthy controls.
*** $p < 0.001$ compared to healthy controls.
# $p < 0.05$ comparing sensitive vs. insensitive TMD patients, Yates'corrected chi-square test, Statistica.
+ Data specified in means (mm) ± standard deviation; student's *t*-test, Excel.

the endogenous opioid system in TMD patients with myalgia was suggested, based on an observed deficit in pain inhibition by painful ischemic stimulation [24]. Fillingim et al. reported on subgroups of pain-sensitive and pain-tolerant TMD patients based on an ischemic pain task [15]. This sensitive subgroup on ischemic pain also had a significantly lower heat pain tolerance than the insensitive subgroup and control subjects.

In the present study, TMD subgroups were distinguished by tender points, a simple clinical sign that is part of FMS diagnosis. Sensitive TMD patients showed in addition to their high tender point score ($\geqslant 11$ tender points) increased pain sensitivity for the same stimuli as fibromyalgia patients, namely cold and pinprick hyperalgesia, hyperalgesia to blunt pressure and the occurrence of dynamical mechanical allodynia without fulfilling the second FMS diagnostic criterion "widespread pain" in 78% as shown by drawings of patients' ongoing pain. This could indicate TMD as precursor of FMS in a continuous spectrum sharing the same underlying pathology [16], but we did not find a continuum in pain duration in regard to insensitive, sensitive TMD patients and FMS patients.

Lower thresholds to cold pain [3,10,27] and pressure pain [27,28] have been reported before for FMS and can point to a central nociceptive sensitization [54] or a disinhibition. Analogous to the findings in FMS, the occurrence of pinprick hyperalgesia and a dynamic mechanical allodynia in sensitive TMD patients suggest a central sensitization [30,31,35,50,56].

Correspondingly, QST pain parameters of insensitive TMD patients did not differ from healthy control subjects except for a pinprick hyperalgesia over the trapezius muscle and an allodynia in some patients just over the cheek.

Hypoesthesia over the face could be caused by a localized pain complaint due to a direct activation of muscle nociceptors in insensitive patients with TMD [42] as also observed over the auriculo-temporal nerve in myogenic TMD patients during electrical stimulation [13]. A tactile hypoesthesia marks not necessarily a structural damage to tactile pathways but could occur due to central plasticity induced by activation of the nociceptive system [17]. A tactile hypoesthesia is often observed together with neurogenic hyperalgesia what could explain the hypoesthesia here in FMS patients.

4.2. Incidence of tender points and trigger points

Whereas trigger points characterize myofascial pain and did not differ between TMD subgroups, investigation of tender points is usually performed in diagnosing FMS. Thus both diagnostic parameters are rarely tested in the same patients for clinical examination, and therefore their coexistence was rarely described previously [7,20,55]. In the present study we found a coexistence of tender and trigger points in 64% of FMS patients and 44% of TMD patients. This finding is almost identical to the findings of Granges and Littlejohn [20]. Furthermore tender point investigation in our study served as a possible way to distinguish patients with a generalized from those with a localized pain disturbance. Therefore most TMD patients did not fulfil diagnostic criteria for FMS; insensitive TMD patients failed a priori by reason of a low tender point count, most sensitive patients failed by reason of not having widespread pain. This finding points to shared mechanisms rather than comorbidity [9] in that TMD subgroup and FMS patients.

4.3. Pressure pain thresholds

In sensitive TMD patients pressure pain thresholds were lower compared to healthy subjects over trigeminal and extra-trigeminal test areas confirming previous reports [45]. Even though orofacial muscles in both TMD subgroups showed increased pressure sensitivity during clinical investigation, insensitive TMD patients failed to show increased pressure pain sensitivity during QST over standard testing areas. These results are inconsistent with other measurements of pressure pain thresholds over affected muscles in patients with TMD [14] and could be caused by standardization of test procedures in our study. Firstly, QST was performed over superficial part of masseter muscle as pre-specified part in all patients while muscular pain in TMD can originate from 10 diagnostic pressure points over chewing muscles per side [12]. Secondly, muscular pain occurring as taut band, myogelosis or trigger point can probably not be assessed correctly without an exact individual adjustment to patients' pain location. So standardization of test area could have been disadvantageous in this special question. In sensitive patients with TMD this effect was not observed – probably due to a generalized increased sensitivity to evoked pain.

4.4. Psychological and interacting factors associated with widespread pain

As in earlier studies shown [19,38], higher levels of anxiety, depression and catastrophizing were found in our FMS patients. In addition they reported the longest pain duration and the highest impairment in daily life compared to sensitive and insensitive TMD

patients and healthy controls. With regard to all variables investigated, TMD patients ranked in-between FMS patients and healthy controls. However sensitive TMD patients did not differ significantly from insensitive TMD patients arguing against a transition from TMD to FMS over time. Previous studies have already shown that even in healthy controls without chronic pain catastrophizing is associated with higher pain ratings [43]. The results of our study support the interpretation that psychosocial parameters may be, to a large extent, independent predictors for the development of chronic pain conditions and their generalization, and may further indicate that catastrophizing is not simply a symptom of anxiety or depression as discussed previously [44].

4.5. Limitations of the study

Due to the cross-sectional design we cannot clearly attribute anxiety, depression and catastrophizing as a reaction to the chronic pain conditions or the duration of pain. Furthermore the cross-sectional design only examines point prevalence of tender point scores in participants. That might be problematical as widespread and regional pain complaints have a variable time course and a high tender point score marks general distress as also correlating with sleep disturbances [8]. This variability includes tender point counts of 10 or more in 10% of the average non-painful female population [47,52], possibly explaining why four female pain-free controls had more than 9 tender points on examination day and were excluded from the study.

4.6. Clinical implications

In the present cross-sectional study we report a possible way to identify a subgroup of TMD patients with generalized increased evoked pain sensitivity and to differentiate it from TMD patients with a more localized pain complaint, using tender point investigation according to the diagnostic criteria for FMS. This sensitive subgroup exhibited additionally to the increased tender point score the same somatosensory changes that occurred in a group of FMS patients without fulfilling the second FMS diagnostic criterion "widespread pain". This result indicates that shared underlying pain mechanisms may be present in this sensitive subgroup of TMD patients and FMS rather than comorbidity. Distress, fatigue or depression [8] may be the shared pathology. It remains to be tested, how stable the distinction of sensitive and insensitive TMD patients is, and whether fluctuation of this phenotype might indicate fluctuation in underlying pathology. For further studies of mechanisms behind the tender point concept, it may be useful to study TMD instead of FMS. As TMD patients can easily be divided into groups concerning to their general pain perception by measurement of tenderness over tender points, different treatment approaches should be considered. While TMD as localized pain complaint probably can be treated successfully by oral splints and physiotherapy, central pain influencing drugs and an interdisciplinary therapy concept should be considered in TMD patients with a generally increased pain sensitivity at an early time, separated by additional tender point investigation. Those therapy options for TMD patients with a high tender point score need to be tested in prospective trials with stratification.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2009.08.010.

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