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Pain matters for central sensitization: sensory and psychological parameters in patients with fibromyalgia syndrome

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Abstract

Introduction: Patients suffering from fibromyalgia syndrome (FMS) are heterogenous. They often present with sensory abnormalities and comorbidities.

Objectives: We aimed to answer the following questions: (1) Is there a specific somatosensory profile in our patient cohort? (2) Can we detect subgroups characterized by a specific combination of sensory and psychological features? and (3) Do psychological parameters influence sensory signs?

Methods: In 87 patients with FMS quantitative sensory testing was performed on the hand and evaluated in combination with questionnaire results regarding pain, psychological comorbidities, sleep, and functionality.

Results: Patients presented different somatosensory patterns, but no specific subgroups regarding sensory signs and psychological features were detected. Hypersensitivity for noxious mechanical and thermal stimuli and hyposensitivity for nonnoxious mechanical stimuli were the most prominent features. Thirty-one percent of patients showed signs of central sensitization as indicated by abnormally increased pinprick hyperalgesia or dynamic mechanical allodynia. Central sensitization was associated with higher pain intensities ($P < 0.001$). Only a small influence of psychiatric comorbidities on mechanical pain sensitivity ($P = 0.044$) and vibration detection ($P = 0.028$) was found, which was partly associated with high pain intensities. A small subgroup of patients (11.4%) demonstrated thermal hyposensitivity (loss of small-fiber function).

Conclusion: Patients with FMS showed various somatosensory abnormalities. These were not significantly influenced by psychological comorbidities. Signs for central sensitization were detected in about one-third of patients and associated with higher pain intensities. This supports the notion of central sensitization being a major pathophysiological mechanism in FMS, whereas small-fiber loss may be less important.

Keywords: Fibromyalgia, Pain perception, Quantitative sensory testing, Comorbidities, Subgroups

1. Introduction

Fibromyalgia syndrome (FMS) is a prevalent pain condition, which is highly disabling for the afflicted patients.[53,65] Despite an increasing research interest, the underlying pathophysiology is poorly understood. Because the pain is widely distributed and patients complain about generalized hypersensitivity, including hypersensitivity to mechanical, thermal, and auditory stimuli,[20,21,25] central mechanisms have been proposed to be essential for the development and maintenance of this disorder.[12,64] Among others, this includes central sensitization[13,25] and central disinhibition.[31,33] Central sensitization is defined as increased responsiveness of nociceptive neurons in the

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central nervous system to either normal or subthreshold afferent input[13] (https://www.iasp-pain.org). Several studies have demonstrated enhanced noxious perception of repetitive nociceptive stimuli, ie, temporal or spatial summation.[47,55,58] Furthermore, a continuous input from sensitized peripheral nociceptors is believed to maintain central phenomena in general[3] and specifically for FMS.[56] Imaging studies have shown central aberrations in patients with FMS, eg, altered functional connectivity among pain-processing regions, supporting the idea of central mechanisms.[9] In addition, there has been evidence for small-fiber pathology as one underlying mechanism.[43,62] Individuals suffering from FMS often describe their pain with neuropathic descriptors such as prickling, burning, or pain attacks.[48] Previous FMS studies have found decreased detection thresholds for noxious thermal and mechanical stimuli[6,19,30,34,35,45] and elevated thresholds for nonnoxious stimuli such as light touch.[6] It has been proposed that reduced thresholds for heat and pressure were associated with distress.[30,41,46] Apart from somatosensory abnormalities, the patients often suffer from a variety of comorbidities such as anxiety, sleep disorders, or depression.[17,60] Given the heterogeneous clinical manifestation, it seems likely that FMS is not a discrete etiologic entity, but rather a conglomerate of many overlapping syndromes and symptoms.[12] Therefore many attempts have been made to identify subgroups of patients with specific phenotypes[23,48,54,61,69] focusing on pain intensity, psychosocial and cognitive criteria,[23,61] or the degree of impairment.[54] In this study, we focused on the relationship between psychological distress, sleep, and somatosensory signs. The aims of this study were to answer the following questions: (1) Is there a specific somatosensory profile in our patient cohort? (2) Is it possible to find specific subgroups that are characterized by a certain combination of sensory signs and accompanying restrictions of sleep, depression, or anxiety? and (3) Do accompanying factors such as sleep disorders, depression, or anxiety have an influence on the somatosensory signs?

2. Methods

2.1. Subjects

In total, 102 patients with FMS according to the 1990 American College of Rheumatology diagnostic criteria[67] were included. Because the revised American College of Rheumatology criteria were particularly created for clinical use in primary care, we refer to the 1990 American College of Rheumatology criteria, which are recommended to be used in research projects.[66] A strong overlap between both criteria has also been demonstrated recently.[10] Patients were recruited in collaboration with a rheumatologist specialised in fibromyalgia. Exclusion criteria were other neurological diseases, additional pain diagnoses (eg, orthopaedic or cancer pain), diabetes mellitus, or confounding psychiatric diagnosis (eg, psychosis or somatoform disorder). Patients with depressive symptoms were not a priori excluded because this is a frequent comorbidity[24] and should be specifically investigated within this study. After evaluation of the patients' history, examination of the tender points, and a neurological examination focusing on tendon reflexes and vibration sensation (tested on both sides on the medial malleolus) for investigation of possible polyneuropathy, 15 patients were excluded (**Fig. 1**).

The remaining 87 patients underwent quantitative sensory testing (QST), performed by an unbiased technical assistant, and completed different questionnaires to search for psychiatric comorbidities and sleep disorder and to capture the quality and quantity of the pain as well as the functional impairment. The study protocol was in line with the Declaration of Helsinki and approved by the Ethical Committee of the University of Schleswig-Holstein (AZ: A118/00). All participants gave written informed consent before and were free to terminate the study at any time.

2.2. Quantitative sensory testing

Quantitative sensory testing was performed according to the standardized protocol established by the German Research Network on Neuropathic Pain.[49] Assuming fibromyalgia as a widespread pain syndrome caused by a hyperexcitable state of the central nervous system, patients were examined on the dorsum of one hand of the more afflicted body site. The QST protocol comprises 13 thermal and mechanical parameters testing small- and large-afferent fiber function or their central pathways. In short, the protocol included investigation of mechanical detection threshold (MDT) and vibration detection threshold (VDT) representing the function of large myelinated fibers or central pathways, cold detection threshold and warm detection threshold (CDT and WDT), cold pain threshold and heat pain threshold (CPT and HPT), thermal sensory limen (TSL), presence of paradoxical heat sensation (PHS), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), and pressure pain threshold (PPT) representing small-fiber function or central pathways. In addition, wind-up ratio (WUR) and presence of dynamic mechanical allodynia (DMA) as further signs for central sensitization were assessed.

2.3. Assessment of clinical data

The following items were assessed: sex, age, weight, current medication, comorbidities, tender points, and disease duration. Pain was rated on an 11-point numerical rating scale (NRS) recording the average, minimal, and maximal pain intensity during the previous 4 weeks (0 = no pain; 10 = the worst pain imaginable).

In addition, the following validated questionnaires were used to assess possible comorbidities and sensory abnormalities: the Medical Outcomes Study Sleep Scale (MOS-SS), the Hospital Anxiety and Depression Scale (HADS) and Beck Depression Inventory-II (BDI-II), and the Fibromyalgia Impact Questionnaire (FIQ).

2.4. Hospital Anxiety and Depression Scale

The HADS is used to screen for the presence of anxiety (HADS-A) and depression (HADS-D) in patients with chronic diseases and has been satisfactorily validated in a German population.[28,32,52] Optimal cut-off levels for possible anxiety and depressive disorders are scores ≥8 for both subscales, resulting in sensitivities and specificities of approximately 0.80.[7] Subscale total scores range from 0 to 21, with 0 to 7 indicating noncases, 8 to 10 doubtful cases, and 11 to 21 definite cases. The global score reflects the overall psychological impairment.

2.5. Beck Depression Inventory-II

All patients who scored positive in the HADS-D (score ≥ 8) were further examined with the BDI-II to verify and grade the severity of the depression.[5] This self-administered questionnaire comprises 21 questions regarding depressive symptoms and cognition (ie, pessimism, hopelessness, loss of interest, and loss of energy). Each answer is scored on a 0 to 3 scale. Higher total scores indicate more severe depressive symptoms. The standardized

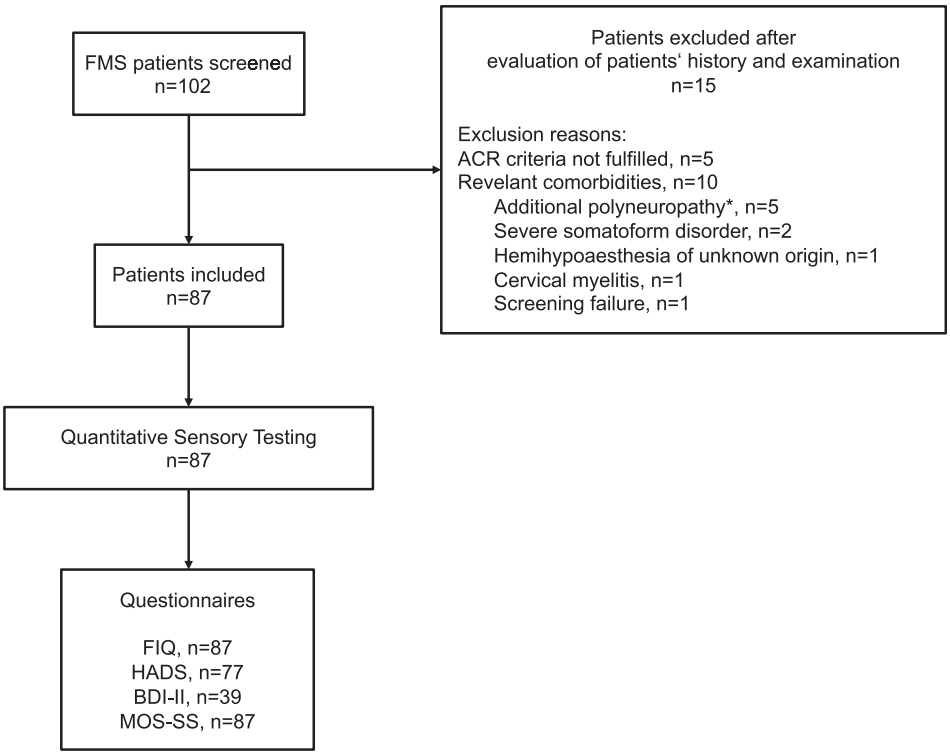

Figure 1. Recruitment of patients with fibromyalgia syndrome (FMS). *Polyneuropathies were excluded through examination of tendon reflexes and vibration sensation. BDI-II, Beck Depression Inventory-II; FIQ, Fibromyalgia Impact Questionnaire; HADS, Hospital Anxiety and Depression Scale; MOS-SS, Medical Outcomes Study Sleep Scale.

cut-offs are as follows: 0 to 13 minimal depression, 14 to 19 mild depression, 20 to 28 moderate depression, and 29 to 63 severe depression. The sensitivity of the BDI is rated with 84.6% and the specificity with 86.4%.

2.6. Medical Outcomes Study Sleep Scale

The MOS-SS evaluates the sleep impairment and quality.[26] It contains 12 items to assess 6 sleep dimensions referring to sleep disturbances, somnolence, sleep adequacy, snoring, awakening short of breath or with headache, and sleep quantity during the previous 4 weeks. Sleep quantity is the average sleep duration in hours per night with optimal sleep duration defined as 7 to 8 hours. The other dimensions are scored on a 0 to 100 scale with higher scores for sleep disturbance, somnolence, snoring, shortness of breath/headache, and lower scores for inadequacy reflecting worse sleep. There are no formal cut-off values, reference values of healthy subjects can be used.[27,42]

2.7. Fibromyalgia Impact Questionnaire

The FIQ comprised 10 items to assess implications of symptoms attributed to FMS in the daily activity over the past week.[8] The first item addresses physical functioning in 11 questions rated on a 4-point Likert scale. Items 2 and 3 determine the number of days in the last week on which the patients felt well or on the contrary were unable to perform their daily tasks. The last 7 questions about work difficulty, pain, fatigue, morning tiredness, stiffness, anxiety, and depression are rated on a 0 to 10 point visual analogue scale (0 = not affected at all; 10 = maximally affected). A higher FIQ score indicates a greater impact of the disease with a maximum score of 100.

2.8. Statistical analysis

For statistical analysis, IBM SPSS Statistics version 25 was used. Quantitative sensory testing parameters were compared with a reference database of healthy controls with the dorsum of the hand as reference site.[49] For calculation of z-values, data were normalized to the respective sex and age group of healthy controls (z = [individual value $\text{mean}_{\text{database}}$]/$\text{SD}_{\text{database}}$). The resulting z-scores are independent of the original measurement units and can be used to create somatosensory profiles. The 95% confidence interval of healthy controls is between −1.96 and +1.96. Z-values above "0" indicate gain of function (hyperfunction), ie, patients are more sensitive compared with controls (lower thresholds), whereas z-scores below "0" indicate loss of function (hypofunction), ie, lower sensitivity compared with controls (higher thresholds). Abnormal values were defined as z-values outside the 95% confidence interval of healthy controls (<−1.96 = abnormal loss; >+1.96 = abnormal gain).[40] Dynamic mechanical allodynia and PHS, absent under physiological conditions, were given with original values (DMA: 0–100 numeric rating scale; PHS: numbers of PHS, 0–3) and encoded as dichotomized variables (0 = normal; 1 = abnormal). Differences in z-values between healthy controls and patients were calculated using analysis of variance. Subgroup analyses for the presence or absence of central sensitization, comorbidities, pain intensity, pain duration as well as patients' age were performed. Central sensitization was defined as the presence of abnormally increased MPS and/or reduced MPT and/or presence of DMA. Comorbidities were defined as follows: a depressive disorder as HADS-D ≥ 8, an anxiety disorder as HADS-A ≥ 8, and sleep disorder as an MOS-SS sleep disturbance subscore ≥30%. For subgroups according to pain intensity, pain duration, and age, a median split was used, ie, NRS <6 or NRS

≥6 for pain intensity, < 11 years or ≥11 years for pain duration, and <52 years or ≥52 years for patients' age. Differences in z-values between patients' subgroups were assessed with analysis of variance, considering the NRS as a covariate in case of significant differences. Frequencies of abnormal z-values, ie, values outside the 95% confidence interval of healthy controls, were assessed using the χ^2 test or Fisher exact test for $n < 5$. Linear relationships of QST parameters and age, pain intensity, duration of symptoms, and questionnaire results were assessed by the Kendall tau-b correlation coefficient. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characterization

Patients' characteristics are shown in **Table 1**. As expected from epidemiological data,[2] most patients were middle-aged women. There was a substantial range in the pain duration (1–35 years). More than half of the patients reported that they had a local pain problem first and subsequently a pain generalization developed. Therefore, it was difficult for most patients to determine exactly when their pain started and it usually took several years until the patients received their diagnosis. The pain intensity (average, maximal, and minimal) was rated as very intense by many patients.

3.2. Questionnaire results

Self-reported data from questionnaires are shown in **Table 2**. Many patients scored positive for a comorbid anxiety disorder (definite 41.6%, doubtful cases 32.5%) or a depressive disorder (definite 27.3%, doubtful cases 23.4%). All patients who scored ≥8 in HADS-D were tested with the BDI-II, and the presence of a depressive disorder was indicated in all these patients. Sleep disorder was also a frequent problem: 98.8% of the patients were characterized by sleep somnolence (somnolence score >25%), 92.0% by sleep disturbance (disturbance score >30%), and 74.7% by sleep inadequacy (adequacy score <60%). We also evaluated the data regarding different combinations of comorbidities. As indicated in **Figure 2**, only 2.6% of patients did not suffer from any comorbidity at all, whereas most of the patients suffered from a combination of all 3 comorbidities (44.2%). Approximately 22.1% of the patients presented with one comorbidity and 31.2% with 2 comorbidities, whereby a combined sleep and anxiety disorder was most frequent (27.3%).

Table 1

Demographic data of patients.

	Fibromyalgia syndrome (n = 87)
Females	85 (95.5%)
Age (y)	50.4 ± 9.6 (19–68)
BMI (kg/m^2)	28.75 ± 6.72
Mean pain duration (y)	12.95 ± 9.03 (1–35)
Mean pain intensity	5.9 ± 1.9 (1–10)
Minimal pain intensity	3.7 ± 2.1 (0–10)
Maximal pain intensity	8.3 ± 1.7 (1–10)
Tender point count	16.8 ± 1.8 (11–18)
Patients on permanent pain medication	56 (65.1%)
Patients on antidepressants	53 (61.6%)

Mean values ± SD with mean range in brackets. Pain intensity was assessed using the numerical rating scale (NRS) with 0 = no pain and 10 = worst pain imaginable.
BMI, body mass index.

3.3. Quantitative sensory testing somatosensory profile

According to the LOGA-classification,[40] a substantial group of patients demonstrated loss of large-fiber function (45.9%, combined with loss of small-fiber function: 8%), whereas a smaller subgroup (11.4%) presented with decreased sensitivity to thermal detection (loss of small-fiber function). Part of these patients (35.5%) presented a combination of sensory loss and mechanical and/or thermal hypersensitivity, but 16.1% presented exclusively a hyposensitivity to nonnoxious mechanical stimuli, ie, large-fiber afferent loss or impaired central pathway function (**Table 3**).

3.4. Subgroup analysis

3.4.1. Central sensitization and pain intensity

In total, 27 patients (31.0%) showed signs of central sensitization defined as the presence of abnormally increased MPS and/or reduced MPT and/or presence of DMA. Significant differences between the patients with or without signs of central sensitization could be detected regarding average pain intensity ($P < 0.001$) and minimal pain intensity ($P < 0.001$), whereas patients with signs of central sensitization showed higher pain intensities (average pain intensity 6.96 vs 5.46; minimal pain intensity 4.88 vs 3.15). There was a positive correlation for average pain intensity with MPS ($\tau_b = 0.313$, $P = 0.0001$) and MPT ($\tau_b = 0.244$, $P = 0.003$). Regarding the presence of comorbidities there were no significant differences between both groups.

Subgrouping of patients based on pain intensity (NRS <6 vs NRS ≥6) in the respective QST profiles are shown in **Figure 3A**. Patients with higher pain intensities showed a higher sensitivity to mechanical pain, derived by higher values for MPT (0.98 vs 0.47, $P = 0.040$) and MPS (1.39 vs 0.52, $P = 0.003$). In addition, patients with an NRS ≥6 were characterized by an increased sensitivity to pressure pain (PPT, 2.66 vs 1.76, $P = 0.031$). In addition, patients with higher pain ratings presented more frequently an abnormally increased sensitivity to pressure and mechanical pain (PPT, 67% vs 42%, $P = 0.024$; MPS, 36% vs 11%, $P = 0.018$) (**Fig. 3B**).

3.4.2. Psychiatric comorbidities, age, and pain duration

The number of comorbidities had no significant influence on the QST profile (**Fig. 4**). When examining the QST parameters separately for the patients without substantial depressive symptoms (HADS-D < 8) vs patients with substantial depressive symptoms (HADS-D ≥ 8), no significant differences could be seen in z-values (**Fig. 5A**). However, depressed patients showed higher frequencies of abnormal MPS and VDT (MPS, 36% vs 16%, $P = 0.044$; VDT, 56% vs 32%, $P = 0.028$) (**Fig. 5B**). Considering the NRS as a covariate, MPS was significantly influenced by the NRS ($P = 0.007$) but not by depression ($P = 0.288$). In line with this, patients with an NRS ≥6 scored significantly more often positive for depression compared with patients with an NRS <6 (64% vs 34%, $P = 0.009$). In addition, the HADS-D correlated with average pain intensity ($\tau_b = 0.288$, $P = 0.001$). Furthermore, a mild positive correlation could be observed for BDI-II and PPT ($\tau_b = 0.153$, $P = 0.045$) and for FIQ and PPT ($\tau_b = 0.162$, $P = 0.036$). However, significant differences regarding PPT were only seen when

Table 2

Self-reported data of patients assessed with questionnaires (psychiatric comorbidities, sleep quality, and functionality).

	Fibromyalgia syndrome (n = 87)
Hospital Anxiety and Depression Scale (HADS)	
Anxiety subscale (HADS-A)*	
Total score	10.27 ± 4.33
Noncases; no anxiety (0–7)	20 (26.0%)
Doubtful cases; mild anxiety (8–10)	25 (32.5%)
Definite cases; moderate-to-severe anxiety ≥11	32 (41.6%)
Depression subscale (HADS-D)*	
Total score	8.01 ± 4.57
Noncases, no depression (0–7)	38 (49.4%)
Doubtful cases, mild depression (8–10)	18 (23.4%)
Definite cases; moderate-to-severe depression ≥11	21 (27.3%)
Beck Depression Inventory-II (BDI-II)†	
Total score	28.59 ± 11.72
Minimal depression (9–13)	2 (5.1%)
Mild depression (14–19)	10 (25.6%)
Moderate depression (20–28)	8 (20.5%)
Severe depression (29–63)	19 (48.7%)
Medical Outcome Study Sleep Scale (MOS-SS)	
Sleep disturbance	80 (92.0%)
Sleep somnolence	86 (98.8%)
Sleep inadequacy	65 (74.7%)
Sleep duration	6.14 ± 1.33
Fibromyalgia Impact Questionnaire (FIQ)	
Mean score	53.51 ± 17.72

Mean values ±SD.
* Missing data n = 10.
† BDI-II data are given for patients who scored positive in HADS-D (>8; n = 39).

comparing patients with severe depression (HADS-D ≥ 11) with patients with no or mild depression (HADS-D < 11). By contrast, no significant differences were observed when comparing patients without anxiety symptoms (HADS-A < 8) vs patients with anxiety symptoms (HADS-A ≥ 8). When focusing on sleep disorder no significant differences were seen in patients suffering from sleep disorder alone vs sleep disorder in combination with anxiety or a combination of all 3 comorbidities.

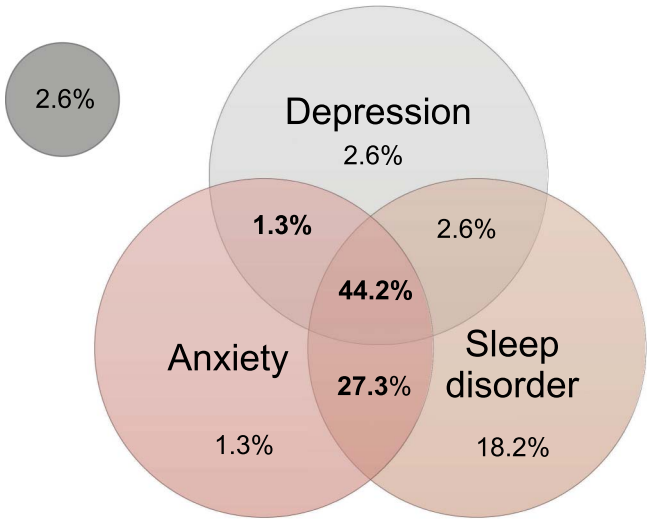

Figure 2. Frequency of comorbidities (depression, anxiety, and sleep disorder) in patients with fibromyalgia (n = 77). Absolute numbers: no comorbidities (separate dark gray bubble) n = 2, only depressive disorder n = 2, only anxiety disorder n = 1, only sleep disorder n = 14, anxiety and depressive disorder n = 1, depressive and sleep disorder n = 2, anxiety and sleep disorder n = 21, and all 3 comorbidities n = 34.

Other combinations of comorbidities were not examined because of low frequencies (**Fig. 1**). Subgrouping of patients based on age or pain duration revealed no differences in QST parameters.

4. Discussion

In this study, we examined the sensory profile of 87 patients with FMS in combination with an evaluation of pain, psychological comorbidities, sleep quality, and functionality.

The main findings were

(1) Subgroups were detected regarding somatosensory profiles, but not regarding a combination of sensory signs and questionnaire results. One large subgroup (31.0%) presented with signs of central sensitization in QST. Another substantial

Table 3

Different Combinations of gain and loss of detection in patients with FMS.

LOGA	Gain				Loss total
	G0	G1	G2	G3	
Loss					
L0	7 (8%)	6 (6.9%)	13 (14.9%)	11 (12.6%)	37 (42.4%)
L1	1 (1.1%)	0	0	2 (2.3%)	3 (3.4%)
L2	14 (16.1%)	1 (1.1%)	16 (18.4%)	9 (10.3%)	40 (45.9%)
L3	2 (2.3%)	1 (1.1%)	4 (4.6%)	0	7 (8%)
Gain total	24 (27.6%)	8 (9.2%)	33 (37.9%)	22 (25.2%)	

L0: no loss of detection (no loss of small-fiber or large-fiber function); L1: only thermal loss (isolated loss of small-fiber function defined as abnormal CDT or WDT values on the affected side in combination with normal MDT and VDT); L2: only mechanical loss (isolated loss of large-fiber function defined as abnormal MDT or VDT values on the affected side in combination with normal CDT and WDT); L3: mixed loss of detection (mixed fiber loss of function defined as both, loss of small- and large-fiber function); G0: no gain (no thermal or mechanical hyperalgesia); G1: only thermal hyperalgesia (defined as gain of function only for CPT or HPT); G2: only mechanical hyperalgesia (defined as gain of function only for MPT, MPS, DMA, or PPT); and G3: mixed hyperalgesia defined as presence of both thermal and mechanical hyperalgesia.
FMS, fibromyalgia syndrome.

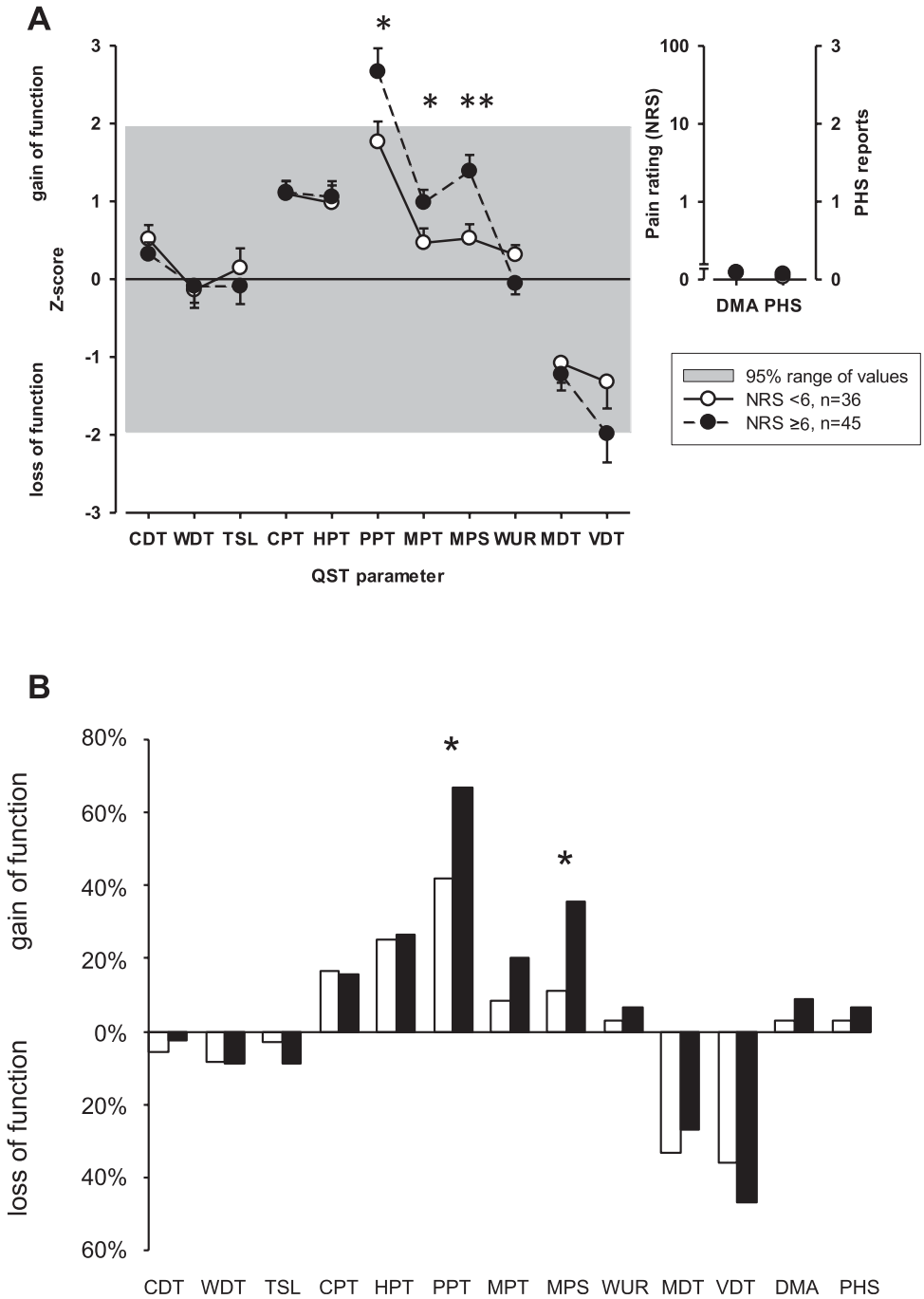

Figure 3. (A) QST profiles depending on pain intensity. QST profiles of patients with FMS suffering from high pain intensity (NRS ≥6, n = 45) compared with patients suffering from low pain intensity (NRS <6, n = 36); (B) Frequencies of abnormal QST parameters of patients depending on pain intensity. Frequencies of abnormal QST parameters of patients suffering from low pain intensity (white bars; NRS <6, n = 36) compared with patients suffering from high pain intensity (black bars; NRS ≥6, n = 45). *$P < 0.05$. CDT, cold detection threshold; CPT, cold pain threshold; 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; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

subgroup (45.9%) showed a decrease for nonnoxious mechanical stimuli, ie, large-fiber loss or impairment of central pathways, whereas a smaller subgroup (11.4%) presented with decreased sensitivity for thermal detection, ie, small-fiber loss or impairment of central pathways.

(2) Signs for central sensitization were associated with stronger pain intensities, but not with age or disease duration.

(3) The somatosensory abnormalities were not decisively influenced by the presence of additional comorbidities.

4.1. Subgroups regarding somatosensory profiles

One of the aims of our study was to detect specific subgroups with a certain combination of sensory signs and abnormalities regarding psychiatric comorbidities, sleep, and functionality. Interestingly, no significant differences regarding sensory parameters could be detected when looking at subgroups suffering from anxiety or sleep disorder. Patients with depression showed differences in VDT and MPS, which was associated with higher

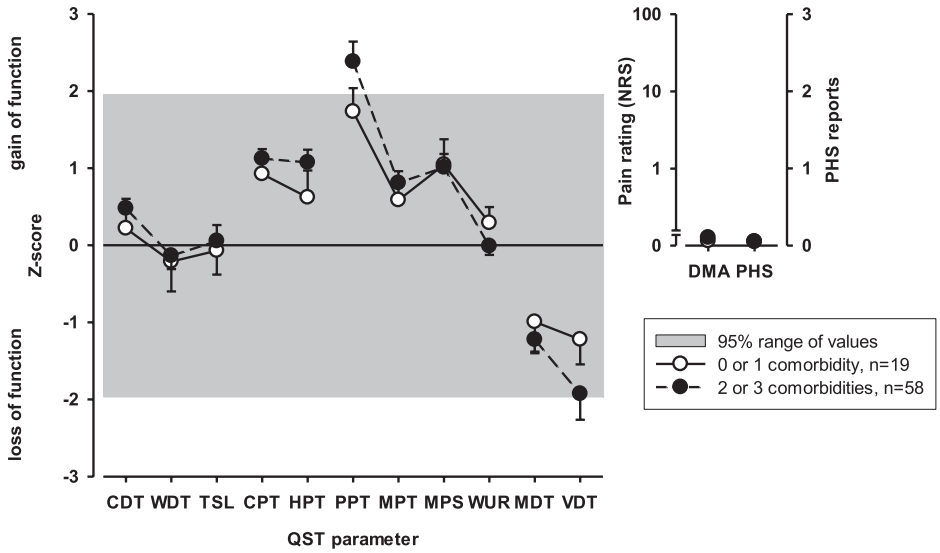

Figure 4. QST profiles of patients depending on the number of comorbidities. QST profiles of patients with FMS suffering from maximal one comorbidity (n = 19) compared with patients suffering from at least 2 comorbidities (n = 58); CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic 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; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

pain intensities. Furthermore, we could detect subgroups of patients regarding the somatosensory profiles alone.

4.2. Loss of large-fiber function

A substantial group of patients demonstrated loss of large-fiber function (isolated: 45.9%, combined with loss of small-fiber function: 8%). Part of these patients (35.5%) presented a combination of sensory loss and mechanical and/or thermal hypersensitivity, but 16.1% presented exclusively a hyposensitivity to nonnoxious mechanical stimuli. This result is surprising because patients with clinical signs for additional polyneuropathy were excluded after careful neurological examination, ie, assessment of tendon reflexes and vibration sensation. An increased VDT has been shown previously in a smaller cohort of 22 patients with FMS.[59]

A study by Gierthmühlen et al. showed similar results in patients with complex regional pain syndrome type 1 (CRPS-I), with 48% of patients presenting dysfunction of large-fiber afferent pathways.[22] Similar results have lately been found in another cohort of patients with CRPS-I.[44] Per definition no nerve lesion can be demonstrated in CRPS-I (similar as in patients with FMS), hence the presence of this finding still remains unclear. One explanation for the impairment of A-beta-fiber function could be a pain inhibition or masking phenomenon generated through continuous input from other fiber classes,[1,18,39] which has mostly been seen in experimental pain models. However, no correlation between VDT and/or mechanical detection threshold and average or worst pain intensities could be found in our patients. Another possible explanation could be attention deficits, which have been demonstrated in patients with FMS,[36,37] but this phenomenon should also be present in thermal detection thresholds.

4.3. Loss of small-fiber function

In contrast to previous work,[15,43,62] only a small subgroup of our patients showed signs of small-fiber loss, suggesting that small-fiber neuropathy may not be a major mechanism in fibromyalgia pathophysiology. Our results are in concordance with the results of Klauenberg et al., Hurtig et al., and Desmeules et al. who also found normal values for thermal detection thresholds in 35, 29, and 85 patients, respectively.[13,30,34] The subgroup of patients presenting with loss of small-fiber function did not differ regarding other evaluated parameters.

4.4. Central sensitization

Increased sensitivity to noxious mechanical stimuli is regarded as a sign for central sensitization phenomena,[68] which have been proposed as one major pathophysiological aspect in the maintenance of FMS symptomatology.[56,57,64]

A recently published study by Vecchio et al. showed an association between a reduction of intraepidermal nerve fiber density at the thigh and reduced laser-evoked habituation index in 81 patients with FMS.[63] The authors concluded that central sensitization may be the most relevant mechanism in FMS. We defined the following parameters as signs for central sensitization: decreased MPT and/or increased MPS and/or the presence of DMA. When including an abnormally decreased PPT in the definition of central sensitization, the total number of centrally sensitized patients would have increased to 55 patients (63.2%). Thus, 28 patients would have been defined as centrally sensitized alone because of abnormal PPT. Because hypersensitivity to blunt pressure (PPT) is omnipresent in FMS and associated with depressive symptoms, we deliberately excluded this parameter. According to this definition, a substantial part of patients (31.0%) showed central sensitization. Interestingly, signs of central sensitization did not correlate with the disease duration or patient's age. Instead, these parameters were associated with the average and minimal pain intensities.

Patients with fibromyalgia have previously shown increased brain responses compared with controls during painful mechanical stimulation,[38] giving us cause to speculate on the specific nature of an attentional bias and how this could present during QST. Indeed, QST could act as a functional operationalization of bias in attention and salience networks. Several meta-analyses[11]

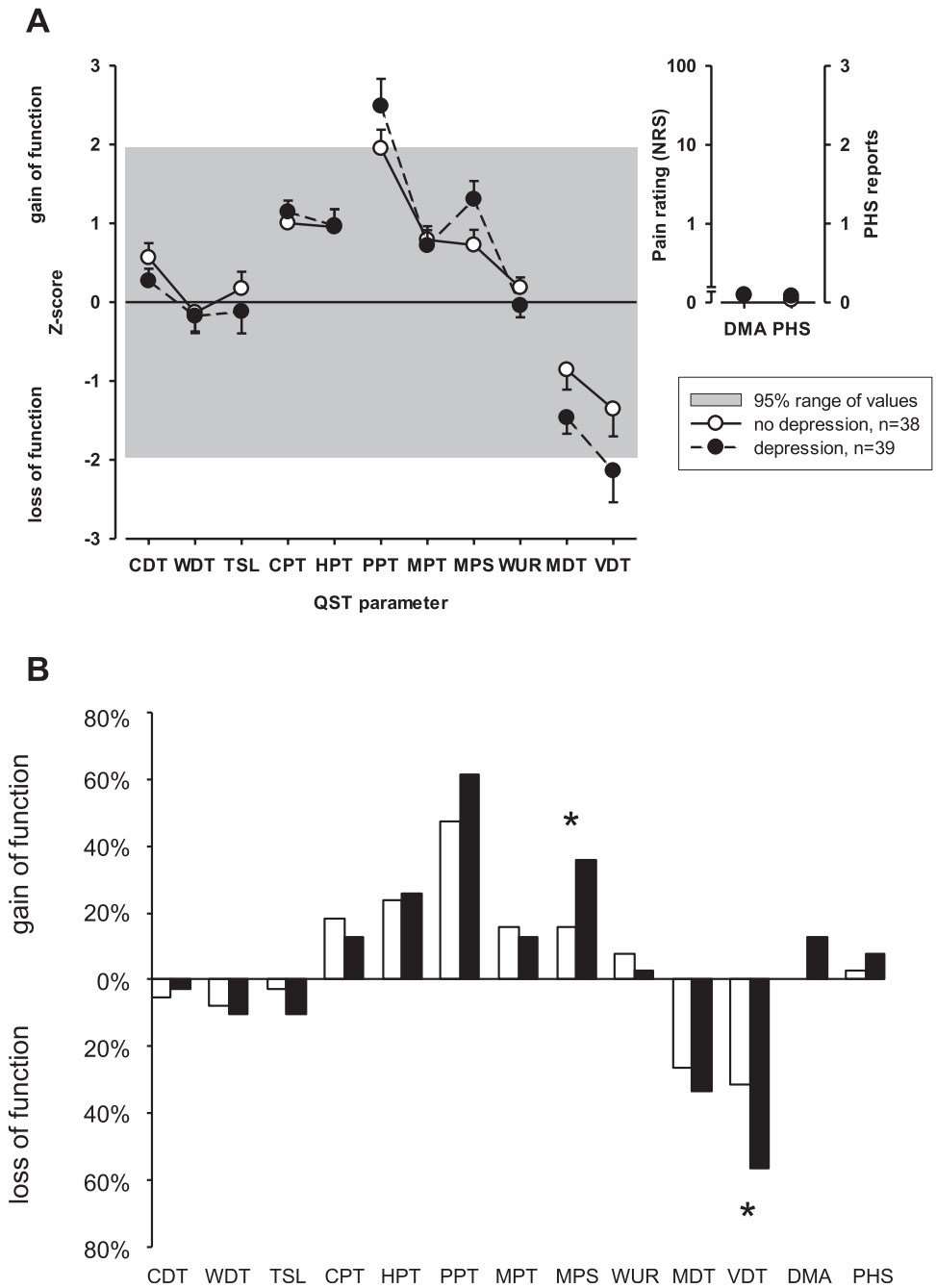

Figure 5. (A) QST profiles of patients depending on the presence of depression. QST profiles of patients with FMS suffering from no depression (HADS <8; n = 38) compared with patients suffering from mild or moderate-to-severe depression (HADS ≥8; n = 39). (B) Frequencies of abnormal QST parameters of patients depending on the presence of depression. Frequencies of abnormal QST parameters of patients suffering from no depression (white bars; HADS <8; n = 38) compared with patients suffering from mild or moderate-to-severe depression (black bars; HADS ≥8; n = 39); *$P < 0.05$. CDT, cold detection threshold; CPT, cold pain threshold; 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; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

have indicated the occurrence of selective changes in gray matter density in FMS and other chronic pain states that are correlated with differences in salience and attention networks in the prefrontal cortex. The role of brain networks modulating sensory experiences is detailed in the Embodied Predictive Interoception Coding model, which states that cognition can modulate a physical sensation through shifting the attentional focus and resampling the input, which then allows for changes in neuronal gain. Fluctuations in neuronal gain modulate the breadth of attention, and thus, the degree to which processing is focused on stimuli to which one is predisposed to attend.[4] This would entail that mechanical stimuli can reach salience on lower levels and to an exaggerated degree when detecting noxious stimuli, specifically in a group of patients with fibromyalgia, who have shown increased brain responses to such stimuli. Hence, the produced QST abnormalities could simply reflect the content of the abnormal previous recruitment by attention-dependent changes in synaptic gain.[14] To summarize, the observed differences could

reflect a FMS subgroup with a particular operant learning history tied to noxious mechanical stimuli, as well as a subgroup where anticipatory imprecision leads to generalization of stimuli. An inverse relationship between stimulus discrimination and generalization has been suggested in pain, arguing the less an organism is able to discriminate stimuli, the stronger is the generalization.[16,29]

4.5. Influence of psychiatric comorbidities on somatosensory parameters

As described before, decreased thresholds for thermal and mechanical stimuli (HPT, CPT, MPT, and PPT) are associated with more pronounced psychiatric distress.[41,59] No substantial differences could be found regarding sensory abnormalities when dividing our patients into subgroups according to psychiatric comorbidities. There was a mild correlation between BDI-II and PPT. Because an association could be seen between pain intensities and depression and PPT was significantly influenced by average pain intensity, the observed abnormalities seem to be partly driven by higher pain intensities. Patients with depression also presented more often with an abnormally increased MPS, which was presumably also mainly driven by pain intensity.

Neither an association of CPT and depression, as assumed by Klauenberg et al.,[34] nor an association of HPT and anxiety as shown by Tampin et al.[59] could be found in our patient cohort. We assume that this might be due to the heterogeneity of patients with FMS.

Regarding sleep disturbances, it has been described that subjects with one night of sleep deprivation show decreased thresholds for HPT, PPT, and CPT and an increase in MPS.[51] 18.2% of our patients presented with sleep disorder alone. In these patients, no difference in sensory perception could be detected in comparison with patients suffering from additional depression and/or anxiety.

4.6. Limitations of the study

The reported results may be biased by patients' medication, which might have an influence in terms of altered nociceptive processing under antidepressants or reaction times. Furthermore, as a psychophysical method, QST is influenced by the patients' ability and willingness to participate.[50] In addition, QST cannot differentiate between central and peripheral changes because it assesses the entire afferent pathway. An abnormal QST finding cannot prove neither small nor large-fiber pathology. As FMS is a generalized pain disorder, QST was only performed on one hand of the patients. Previous work demonstrated that sensory testing in FMS is comparable when one is testing the hand and the foot of patients.[34] Finally, because of the purely explorative approach, *P* values were not corrected for multiple testing, resulting in a less stringent statistical analysis.

5. Conclusion

Patients with FMS presented with various somatosensory abnormalities, whereby hypersensitivity to noxious mechanical and thermal stimuli and hyposensitivity to nonnoxious mechanical stimuli were the most prominent features. These abnormalities were not substantially influenced by additional psychological comorbidities. Signs for central sensitization were detected in a subgroup of almost one-third of our patients and influenced by high pain intensities, which supports the notion that central sensitization is an important pathophysiological mechanism in FMS, whereas loss of small-fiber function may be less important.

Disclosures

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