Quantitative Sensory Testing Profiles in Chronic Back Pain Are Distinct From Those in Fibromyalgia

Klaus Blumenstiel, MD,† Andreas Gerhardt, MA,* Roman Rolke, MD,‡§ Christiane Bieber, MD,* Jonas Tesarz, MD,* Hans-Christoph Friederich, MD,* Wolfgang Eich, MD, PhD,* and Rolf-Detlef Treede, MD, PhD‖*

Objectives: Alterations in the central nervous system leading to higher pain sensitivity have been shown in both chronic back pain (CBP) and fibromyalgia syndrome (FMS). The aim of this study was to disclose commonalities and differences in the pathophysiology of FMS and CBP.

Methods: We used the quantitative sensory testing protocol of the German Research Network on Neuropathic Pain to obtain comprehensive profiles of somatosensory functions. The protocol comprised thermal and mechanical detection and pain thresholds, vibration thresholds, and pain sensitivity to sharp and blunt mechanical stimuli. We studied 21 FMS patients (mean pain duration: 13.4 y), 23 CBP subjects (mean pain duration: 15.9 y), and 20 healthy controls (HCs). Each participant received the test battery on the back and on the dorsal hand (pain-free control site).

Results: On the back, FMS patients showed increased thermal and mechanical pain sensitivity compared with HCs and CBP participants. On the hand dorsum, FMS patients showed higher mechanical pain sensitivity compared with CBP participants and HCs and higher cold pain sensitivity compared with HCs. CBP participants showed increased pressure pain sensitivity and lower vibration sensitivity on the back, but no significant differences on the hand dorsum compared with HCs.

Discussion: FMS patients showed increased sensitivity for different pain modalities at all measured body areas, suggesting central disinhibition as a potential mechanism. CBP participants in contrast, showed localized alterations within the affected segment possibly due to peripheral sensitization.

Key Words: fibromyalgia syndrome (FMS), chronic back pain (CBP), quantitative sensory testing (QST)

(*Clin J Pain* 2011;27:682–690)

Received for publication May 19, 2010; revised January 25, 2011; accepted February 25, 2011.

From the *Department of General Internal Medicine and Psychosomatics, Medical Hospital, Ruprecht Karls University Heidelberg, Heidelberg; †Department of Psychosomatic Medicine and Psychotherapy, Fürst-Stirum-Hospital, Bruchsal; ‡Department of Neurology, University Medical Center of the Johannes Gutenberg-University, Mainz; §Department of Palliative Care, University of Bonn, Bonn; and ‖Division of Neurophysiology, Center for Biomedicine and Medical Technology Mannheim (CBTM), Ruprecht Karls University Heidelberg, Mannheim, Germany.

Supported by grants of the Federal Ministry of Education and Research (BMBF, grant No. 01EM0112; No. 01EM0506; No. 01EM0901). There are no conflicts of interest related to the manuscript on the part of the authors. Klaus Blumenstiel, MD and Andreas Gerhardt, MA, contributed equally to the study.

Reprints: Andreas Gerhardt, MA, Medical University Hospital Heidelberg, Internal Medicine II, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany (e-mail: andreas.gerhardt@med.uni-heidelberg.de).

Fibromyalgia syndrome (FMS) and chronic back pain (CBP) are common, an increasing cause of consultations in primary care, and of enormous socioeconomic relevance.[1,2] Therapeutic interventions are often unspecific and of minor success,[3,4] probably because of the fact that their etiologies and pathogeneses are still widely unknown.

Despite much research, the pathogenesis of FMS is still a matter of debate. One of the most promising approaches addresses the role of the (central) nervous system (CNS). A series of techniques have been applied to detect abnormalities in the CNS, such as functional neuroimaging, electrophysiological techniques, laser-evoked potentials, investigation of spinal fluid, and, in particular, quantitative sensory testing (QST).[5] QST is a method that is used to assess the somatosensory function. A comprehensive QST protocol allows to determine pain and detection thresholds and to distinguish local versus generalized and peripheral versus central nervous mechanisms. To date, QST studies in FMS have shown decreased mechanical/pressure and thermal pain thresholds,[6–9] temporal summation of pain ("wind-up") reflecting an increased excitability of spinal cord neurons,[10] and signs of central hypersensitivity.[11] Other studies suggest a reduced habituation to pain[12] and central sensitization[13,14] as mechanisms involved.

QST aberrations including signs for abnormal central nervous pathways have also been found in nonspecific CBP, the most common type of all CBPs.[15] Studies reported low pain thresholds and pain tolerance values.[16] A study by Giesecke et al[17] revealed hyperalgesia in FMS and CBP patients in comparison with healthy controls (HCs) when experimental pain was applied to a neutral site (thumbnail). Moreover, patients with FMS and CBP showed similar activation in pain-related cortical areas in functional magnetic resonance imaging, which was different from that in HCs. Baraniuk et al[18] studied opioid neurotransmitters in the cerebrospinal fluid and found that Met-enkephalin-Arg6-Phe7 was greater in both FMS and CBP patients than in HCs. In addition, FMS patients often report that their disease started with simple back pain[19,20] and thus CBP may be a pre-stage to FMS.[21]

It is the main hypothesis of a mechanism-based diagnosis in chronic pain syndromes that defined symptoms and signs reflect possible underlying neurobiological pain mechanisms.[22,23] Although in the case of a central disinhibition all types of thermal and mechanical pain thresholds may be generally decreased with an increased response to suprathreshold stimuli, thermal and mechanical detection and pain thresholds are increased in the presence of deafferentiation due to axonal damage. Moreover, localized pin-prick hyperalgesia and/or dynamic mechanical

allodynia may point to a central sensitization of the nociceptive system, whereas localized heat and pressure hyperalgesia are cardinal signs of a peripheral sensitization. Hence, we addressed the following questions in the present study:

(1) Are there distinct sensory profiles in FMS and CBP?
(2) If so, do clinical signs conclusively reflect possible underlying neurobiology?
(3) Do FMS and CBP share the same neurobiological mechanisms as indirectly reflected by QST?

MATERIALS AND METHODS

Participants

In the present study, 21 patients with a diagnosis of FMS, 23 participants with CBP, and 20 HCs were included. Inclusion criteria were female sex and being free of diseases affecting sensory processes (for sociodemographic data, see Table 1). Study participants were screened (physical examination, blood tests, past medical history, and, if indicated, further technical investigations such as x-ray or magnetic resonance imaging) to rule out diseases affecting sensory processes. Patients were also excluded if they reported pain at the hand dorsum, as this area was destined to be the control site.

FMS patients who fulfilled the diagnostic American College of Rheumatology criteria[24] were recruited from an outpatient clinic of the Medical University Hospital of Heidelberg. The CBP sample was drawn from participants who had a sample in an epidemiological study on CBP (Generalization of Pain: A Prospective Population-based Survey with Clinical Examination as part of the German Back Pain Research Network, supported by the Federal Ministry of Education and Research). A representative sample of 4000 inhabitants in the south-west of Germany was approached by mail and they were asked whether they had CBP. CBP was defined as the presence of back pain for at least 45 days within the last 3 months. A total of 2408 individuals responded to the mail survey. Of them, 427 fulfilled the criteria of CBP and were invited to a clinical investigation. Finally, 303 individuals participated in the study. Participants were questioned about the existence of comorbidity (explicitly neuropathy, diabetes, relevant alcohol consumption, infections, inflammatory diseases, disc hernia, past severe injuries) and they received a physical examination (general, rheumatological, neurological). In case of signs for serious pathological findings (eg, ischialgia or severe injuries such as whiplash), participants were excluded, and a further investigation was advised. Of the 303 participating individuals, 20 repored specific back pain (5 had Bechterew disease, 3 rheumatoid arthritis affecting the spine, 1 polymyalgia rheumatica, 3 tumor/metastases, 1 fracture of the vertebral body, 1 spondylolysis, and 6 disc hernia). The remaining 283 participants represented a nonhomogeneous group of nonspecific CBP according to the distribution in the general population. Of them, 23 female participants with nonspecific back pain were included in the present QST investigation consecutively. Participants were advised not to take pain medication 24 hours before investigation. HCs were recruited per advertisement. All participants were white.

The present study has been approved by the Ethics Research Committee of the Faculty of Medicine, University of Heidelberg. Participants gave written informed consent. They received an allowance of 10 Euros (about 12 dollars). The study was carried out in compliance with the Declaration of Helsinki.

Disability

Disability levels were measured using the FFbH (Hannover Functional Ability Questionnaire for measuring pain-related disability). It consists of 12 self-administered items that especially focus on daily activities restricted by musculoskeletal disorders (eg, "Can you wash your hair in a washbasin"). The response format is in 3 stages ("yes," "yes with trouble," "no or with the help of another person"). The answers were transformed to a functional ability score ranging from 0% to 100% (80% to 100% = no functional disability, about 70% = moderate disability, < 60 = relevant disability). Data from different studies indicate that the FFbH meets relevant psychometric criteria and is sensitive to change.[25]

QST Protocol

The somatosensory function was assessed using the comprehensive QST protocol that was developed as part of the German Research Network on Neuropathic Pain (DFNS).[26] It covers all relevant aspects of the somatosensory system, including large and small fiber function, and signs of central sensitization (dynamic tactile allodynia, punctate mechanical hyperalgesia). In this manner, detailed profiles of somatosensory function for the tested body areas are obtained.

Test sites were over paraspinal muscles and on the dorsum of the hand. Patients with FMS and CBP were tested on the most painful area in the back and on the hand dorsum of the same side of the body as a pain-free control site. The most painful area was determined on the basis of the patient's report during the office visit about present ongoing pain. Nine FMS patients were tested on the left, whereas 12 were tested on the right side of the body. Among CBP patients, 9 were tested on the left and 14 on the right side of the body, which was not significantly different from the FMS group ($\chi^2 > 0.05$). In CBP, all paraspinal test sites were in lumbar segments. For FMS, 16 test sites were in cervical and 5 were in lumbar segments. We had previously found that pressure pain thresholds (PPTs) are quite uniform across different muscles.[27] Pain-free controls were tested on the hand dorsum and in cervical segments (over the trapezius muscle) of both sides of the body. All tests were first conducted over an area that was not tested later during the QST session.

Thermal Detection and Thermal Pain Thresholds

The tests for thermal detection, thermal pain thresholds, and paradoxical heat sensations (PHS) were conducted using a TSA 2001-II (MEDOC, Israel) thermal sensory testing device.[28] All thresholds were obtained with ramped stimuli (1°C/s, 32°C baseline, 0°C and 50°C cutoffs, 8 cm^2 thermode), which were terminated when participants pressed a button. The mean of 3 consecutive measurements was calculated. Thermal sensory limen, a test with alternating warming and cooling ramps, was used only as a provocative test to induce PHS.

Mechanical Detection Threshold

Mechanical detection threshold (MDT) was measured with a standardized set of modified von Frey filaments

TABLE 1. Sociodemographic Variables

	Fibromyalgia	Chronic Back Pain	Pain-free Healthy Controls
N	21	23	20
Age, mean (SD)	50.6 (9.5)	43.4 (8.6)	38.3 (7.6)
Marital status, N (%)			
Unmarried	9 (45)	3 (13)	12 (58)
Married	9 (45)	14 (61)	5 (24)
Divorced/separated	2 (15)	6 (26)	1 (5)
Widowed	0	0	2 (9)
Not specified	0	0	2 (9)
Education, N (%)			
< 10 y of education	13 (64)	9 (39)	1 (5)
≥ 10 y of education	6 (29)	14 (61)	19 (95)
Not specified	2 (9)	0	0
Occupational situation, N (%)			
Full-time working	5 (24)	8 (35)	10 (50)
Part-time working	5 (24)	6 (26)	8 (40)
Not working/homemaker	1 (5)	8 (35)	2 (10)
Retired	6 (26)	0	0
Unemployed	2 (9)	0	0
Not specified	2 (9)	1 (5)	0
Pain intensity before QST, mean (SD)	5.8 (1.8)	3.0 (2.2)	0
Pain duration in years, mean (SD)	13.4 (10.4)	15.9 (11.5)	0
Painful tender points	15.2 (2.3)	4.7 (3.8)	0
FFbH (disability), % (SD)	60 (18)	70 (16)	

Pain intensity before QST was assessed on a numeric rating scale 0 to 10. "0" indicating "no pain," "10" indicating "worst pain imaginable." Painful tender points were identified by tenderness examination using ACR criteria. FFbH (Hannover Functional Ability Questionnaire): measures pain-related disability (80% to 100% = no functional disability; about 70% = moderate disability; < 60% = relevant disability).

(Optihair$_2$-Set, Marstock Nervetest, Germany) that exert forces between 0.25 and 256 mN.[29] The contact area was of uniform size and shape (round, 0.5 mm diameter). The threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical Pain Threshold

Mechanical pain threshold (MPT) was measured using a set of weighted pinprick stimulators with a flat contact area of 0.25 mm diameter that exert forces between 8 and 512 mN.[30] Again using the method of limits, the threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical Pain Sensitivity Including Dynamic Mechanical Allodynia

Mechanical pain sensitivity (MPS) was tested using the same weighted pinprick stimuli as that for MPT. To obtain stimulus response function, these 7 pin pricks were applied in balanced order, 5 times each. The participant was asked to rate each stimulus for pain on a 0 to 100 numerical rating scale (0 indicating "no pain," and 100 indicating "most intense pain imaginable"). The geometric mean of the 35 pain ratings was the final value for MPS. Stimulus response functions for dynamic mechanical allodynia (DMA) were determined using a set of 3 light tactile stimulators.[30,31] They were intermingled with the pin-prick stimuli in balanced order and participants were asked to give a rating on the same numeric rating scale.

Wind-up Ratio

The ratings of single pin-prick stimulation were compared with those of a series of 10 repeated pin-prick stimuli of the same force (256 mN) over the same area. Wind-up ratio (WUR) was calculated by dividing the mean ratings of series by the mean pain ratings of single stimuli.

Vibration Detection Threshold

Vibration detection threshold (VDT) was determined with a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale), which was placed 3 times over a bony prominence of the tested body area. Participants indicated the disappearance of vibratory sensations.

PPT

The PPT was measured using an Algometer (Somedic, Sweden) with a probe diameter of 1.1 cm that exerts pressure up to 2000 kPa. The PPT is determined by 3 ramped stimuli, each applied with a slope of 50 kPa/s.

Statistical Analysis

Most QST parameters cold detection threshold (CDT), warmth detection threshold (WDT), thermal sensory limen, PPT, MPT, MPS, DMA, WUR, and MDT) are log-normally distributed and were therefore log-transformed.[26] The QST values of each tested body area of the control group were averaged across both sides of the body. To compare QST measures at both sides (most painful area in the back and hand dorsum) between the 3 groups, analyses of covariance (ANCOVA) were calculated for each modality, followed by Fisher least significant difference tests (Tables 2 and 3). QST values were entered as dependent variables and pain group (FMS, CBP, and HC) was entered as the independent variable. As the 3 groups significantly differed in age ($P < 0.001$), age was included as a covariate, because QST parameters are age dependent.[32]

To compare the 2 test sites within each patient group (localized vs. generalized QST aberrations), all QST measures were standardized by z-transformation referring to the group of pain-free controls (QST profiles in Figs. 1, 2). This is carried out through z-transformation of all QST measures of the FMS and CBP groups, referring to the

TABLE 2. Analysis of Covariance, Mean Values, and Confidence Intervals for Quantitative Sensory Testing of the Most Painful Area in the Back

		ANCOVA		Fibromyalgia		Chronic Back Pain		Pain-free Controls	
		F	P	Mean	95% CI	Mean	95% CI	Mean	95% CI
CDT	Δ°C	0.650	0.526	1.55	1.13-2.10	1.72	1.31-2.25	1.37	1.02-1.85
WDT	Δ°C	1.36	0.264	2.72	2.18-3.38	3.22	2.66-3.90	2.61	2.12-3.21
CPT	°C	5.70	< 0.01	22.96†,‖	18.46-27.47	13.97	10.05-17.90	12.89	8.59-17.20
HPT	°C	3.88	< 0.05	41.60*,§	39.82-43.39	44.73	43.17-46.29	44.65	42.94-46.36
PPT	kPa	7.15	< 0.01	199‡ = 0.001	161-244	239.3†	200-287	352	286-432
MPT	mN	7.26	< 0.01	21.38‡ = 0.001‖	14.52-31.48	45.71	32.89-63.68	61.94	42.36-90.57
MPS	NRS_{100}	9.73	< 0.001	1.82‡,¶	0.99-3.37	0.35	0.21-0.60	0.31	0.17-0.57
WUR		2.03	0.141	2.36	1.67-3.32	2.36	1.74-3.21	3.61	2.56-5.11
MDT	mN	1.05	0.355	6.10	3.45-10.79	6.05	3.75-9.77	3.67	2.09-6.43
VDT	/8	3.41	< 0.05	7.10	6.72-7.47	6.69*	6.36-7.02	7.31	6.93-7.69

Values of CDT, WDT, PPT, MPT, MPS, WUR, and MDT were calculated by back transformation from the log-means.
*$P < 0.05$ vs. controls.
†$P < 0.01$ vs. controls.
‡$P < 0.001$ vs. controls.
Significant test results for fibromyalgia vs. chronic back pain are denoted.
§$P < 0.05$.
‖$P < 0.01$.
¶$P < 0.001$, respectively.
CDT indicates cold detection threshold; CI, confidence interval; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WDT, warmth detection threshold; WUR, wind-up ratio.

mean and standard deviation of the pain-free control group. Whenever log-transformed scores were calculated, the log scores were used for z-standardization. The representation of QST profiles as z-transformed data allows the direct comparison between sensory tests that are measured in different units (eg, °C and mN) and the comparison of test sites that have different ranges of normal values. To compare standardized QST measures of the most painful area in the back with standardized QST measures of the hand dorsum, paired t tests were calculated for both disease groups. Moreover, to compare QST parameters of the hand and back in FMS and CBP patients with that of HCs (Figs. 1 and 2), t tests were applied. Sensory findings on the hand were also compared with the published DFNS reference data,[32] both by group comparison and by counting the number of patients who were outside the 95% confidence interval (CI); DFNS reference data for the back are not yet available.

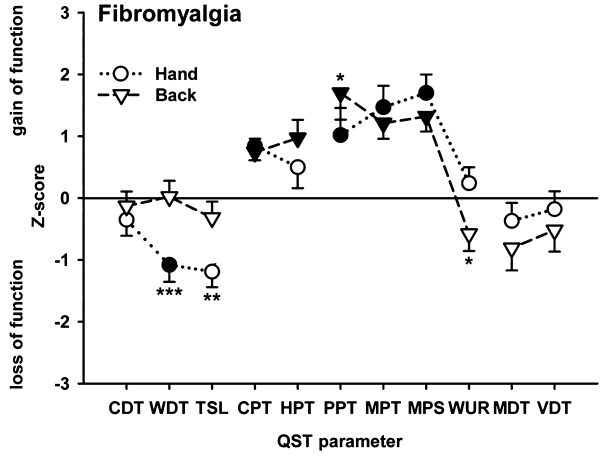

FIGURE 1. QST profiles in fibromyalgia syndrome. Circles: hand, triangles: back. Filled symbols: significant versus healthy controls (open symbols: n.s.; *t* test). *$P<0.05$, **$P<0.01$, ***$P<0.001$, paired *t* test hand versus back. Parallel profiles between hand and back indicate generalized sensory changes. 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; Values are mean±SEM.

RESULTS

In FMS patients, the mean duration of pain was 13.4 ± 10.4 years (mean ± SD). The average duration of

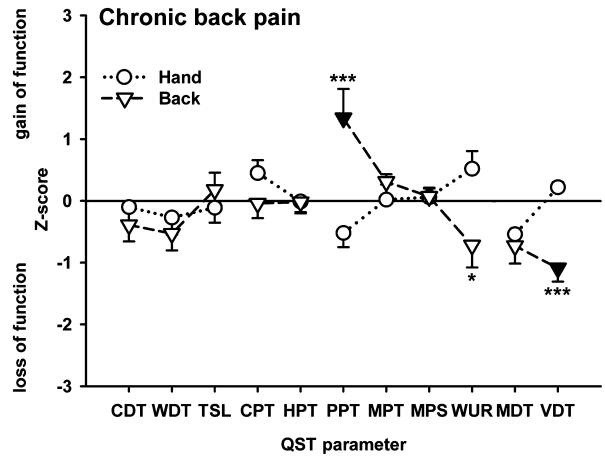

FIGURE 2. QST profiles in chronic back pain. Circles: hand, triangles: back. Filled symbols: significant versus healthy controls (open symbols: n.s.; *t* tests). *$P<0.05$, ***$P<0.001$, paired *t* test hand versus back. Significant differences indicate that sensory changes are localized to the back. For abbreviations, see legend to Figure 1. Values are mean±SEM.

CBP was 15.9 ± 11.5 years (mean ± SD). FMS patients rated pain intensity (directly before QST investigation) higher on a numeric rating scale (0 to 10) compared with CBP participants (mean ± SD 5.8 ± 1.8 vs. 3.0 ± 2.2, $P < .001$). Moreover, measuring disability showed that FMS patients were more severely burdened in daily activities than were CBP patients (relevant vs. moderated, respectively, *n.s.*). FMS patients showed 15.2 ± 2.3 painful tender points, whereas the CBP group revealed 4.7 ± 3.8 painful tender points (mean ± SD).

Comparison of QST Values on the Most Painful Area in the Back

As shown in Table 2, ANCOVA revealed significant group differences for all pain thresholds [cold pain threshold (CPT), heat pain threshold (HPT), PPT, and MPT], as well as for suprathreshold pin-prick pain (MPS) and vibration detection (VDT). Compared with pain-free HCs, FMS patients showed higher sensitivity toward cold and heat pain (CPT $P < 0.01$, HPT, $P < 0.05$) and toward mechanical pain induced by pin-prick stimulation (MPT $P = 0.001$, MPS $P < 0.001$) and by blunt pressure (PPT $P = 0.001$). In addition, CPT ($P < 0.01$), HPT ($P < 0.05$), and MPT ($P < 0.01$) were lower and MPS ($P < 0.001$) ratings were higher than those in CBP participants. Compared with pain-free HCs, CBP participants showed higher sensitivity with regard to PPT levels ($P < 0.01$) and lower sensitivity toward VDT ($P < 0.05$).

Comparison of QST Values on Hand Dorsum

As shown in Table 3, ANCOVA revealed significant group differences for all mechanical pain parameters (MPT, MPS, and PPT) and for cold pain sensitivity (CPT). Compared with pain-free HCs, FMS patients showed an elevated pain sensitivity for pin-prick stimulation (MPT $P < 0.01$, MPS $P < 0.01$), pressure pain (PPT $P < 0.05$), and cold pain (CPT $P < 0.01$). Compared with CBP participants, FMS patients were more sensitive toward pin-prick pain (MPS $P < 0.001$, MPT $P < 0.01$) and pressure pain (PPT $P = 0.001$). CBP participants did not differ from controls with regard to QST values on the hand dorsum.

Comparison of QST Values With DFNS Reference Data

A group comparison between FMS patients and pain-free HCs with regard to DFNS reference data[32] revealed a significantly lower sensitivity to nonpainful warming ($P = 0.02$) and 5 of 21 FMS individuals ranged outside the 95% CI of the published reference data. Increased sensitivity to cold pain (CPT $P < 0.001$), pin-prick pain (MPT $P < 0.001$, MPS $P < 0.001$), and pressure pain (PPT $P < 0.001$) was also significantly different from the DFNS reference data. Several individual values were outside the 95% CI of the published reference data: 4/21 for CPT, 7/21 for MPT, 8/21 for MPS, and 9/21 for PPT.

DMA and PHS

Allodynia on the back occurred in 6 FMS patients, in none of the back pain participants, and in none of the HCs ($P < 0.01$, Fisher exact test). On the hand dorsum, allodynia occurred in 2 FMS patients, in none of the CBP participants, and in 1 HC (not significant). Because of this lack of variance, the allodynia score could not be included in the ANCOVA. Similarly, only 3 FMS patients reported PHS, 1 on hand dorsum, 1 on the back, and 1 on both sites. None of the CBP participants and HCs reported PHS.

Localized Versus Generalized Sensory Changes

To distinguish between localized and generalized QST aberrations, we compared the sensitivity of the hand dorsum with that of the most painful area in the back. As there are regional differences between these 2 test sites in normal participants, the QST values of FMS and CBP participants were standardized in relation to the QST values of the pain-free control group using z-transformation. As allodynia and PHS did not occur in the control group, the respective values could not be standardized.

TABLE 3. Analysis of Covariance, Mean Values, and Confidence Intervals for Quantitative Sensory Testing of the Dorsum of the Hand

		ANCOVA		Fibromyalgia		Chronic Back Pain		Pain-free Controls	
		F	P	Mean	95% CI	Mean	95% CI	Mean	95% CI
CDT	Δ°C	0.187	0.830	1.05	0.84-1.32	1.09	0.90-1.33	1.16	0.93-1.45
WDT	Δ°C	1.44	0.245	2.51	1.86-3.38	1.85	1.42-2.4	1.79	1.33-2.4
CPT	°C	4.73	< 0.05	21.03†	17.21-24.85	16.80	13.46-20.14	12.22	8.45-15.98
HPT	°C	0.990	0.378	43.43	41.55-45.32	45.02	43.37-46.68	45.19	43.33-47.06
PPT	kPa	6.53	< 0.01	238*,‖ = 0.001	204-278	345	301-394	318	273-370
MPT	mN	6.18	< 0.01	26.73†,§	17.86-39.90	64.27	45.50-90.57	65.01	43.75-96.61
MPS	NRS_{100}	10.57	< 0.001	2.13‡,‖	1.24-3.67	0.45	0.28-0.71	0.46	0.27-0.78
WUR		0.764	0.470	3.08	2.27-4.17	3.57	2.74-4.67	2.81	2.07-3.82
MDT	mN	0.699	0.502	2.22	1.37-3.60	2.78	1.85-4.18	1.96	1.22-3.16
VDT	/8	0.691	0.505	7.90	7.78-8.02	7.97	7.87-8.07	7.89	7.77-8.00

Values of CDT, WDT, PPT, MPT, MPS, WUR, and MDT were calculated by back transformation from the log-means.
*$P < 0.05$ vs. controls.
†$P < 0.01$ vs. controls.
‡$P < 0.001$ vs. controls.
Significant test results for fibromyalgia vs. chronic back pain are denoted.
§$P < 0.01$.
‖$P < 0.001$, respectively.
CDT indicates cold detection threshold; CI, confidence interval; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; PPT, pressure pain threshold; VDT, vibration detection threshold; WDT, warmth detection threshold; WUR, wind-up ratio.

All other QST parameters were standardized for all individuals and mean z-scores for both disease groups were calculated separately (Figs. 1, 2).

FMS patients showed similar QST profiles for both areas, indicating that their hyperalgesia was generalized and not local (Fig. 1). WDT was only significantly elevated in the hand, whereas PPT was decreased significantly more in the back than in the hand. In addition, there was a significant difference in WURs, although both areas did not differ significantly from those of control participants (Tables 2 and 3). WUR varied around 3.0, but this variation was in the opposite direction in control participants. In CBP participants, the lowered vibratory sensitivity and the enhanced pressure pain sensitivity of the back were significant compared with the hand, indicating a localized sensory alteration (Fig. 2). As for FMS, WUR varied opposite to that of control subjects.

Punctate Mechanical Hyperalgesia

Fibromyalgia patients exhibited an increased pain sensitivity to pin-prick stimulation (MPT) and enhanced ratings to pinprick stimuli on a numeric rating scale (MPS), both on the back and on the hand dorsum. We calculated a repeated-measure ANCOVA comparing the 3 groups with regard to MPS, including the single stimulus intensity as a covariate. We detected overall differences between FMS patients and both HC and CBP participants (back: $F = 18.63$ $P < 0.001$; hand dorsum: $F = 23.93$ $P < 0.001$).

These data are analyzed in more detail by plotting stimulus-response functions for the 7 stimulus intensities used (Fig. 3). These functions were shifted upward by a factor of 5. All participants were able to discriminate the stimulus intensities. There was also a stimulus effect, indicating higher pain ratings for more intense pin-prick stimuli. There was no interaction effect between the groups and the stimulus intensity, indicating that the profiles of the 3 groups are almost parallel (Fig. 3).

DISCUSSION

The present study used a comprehensive QST protocol to assess the somatosensory profiles of FMS patients, CBP participants, and HCs. FMS patients showed hyperalgesia generalized in space and including both superficial and deep pain modalities, whereas CBP participants revealed a profile of a localized pain condition with a decreased threshold only for deep pain and only at the affected area. Thus, we can conclude that there are distinct sensory profiles in FMS and CBP participants.

Somatosensory Profiles in FMS

FMS patients showed increased mechanical and thermal pain sensitivity (with the exception of HPT over hand dorsum) compared with CBP and HC participants,

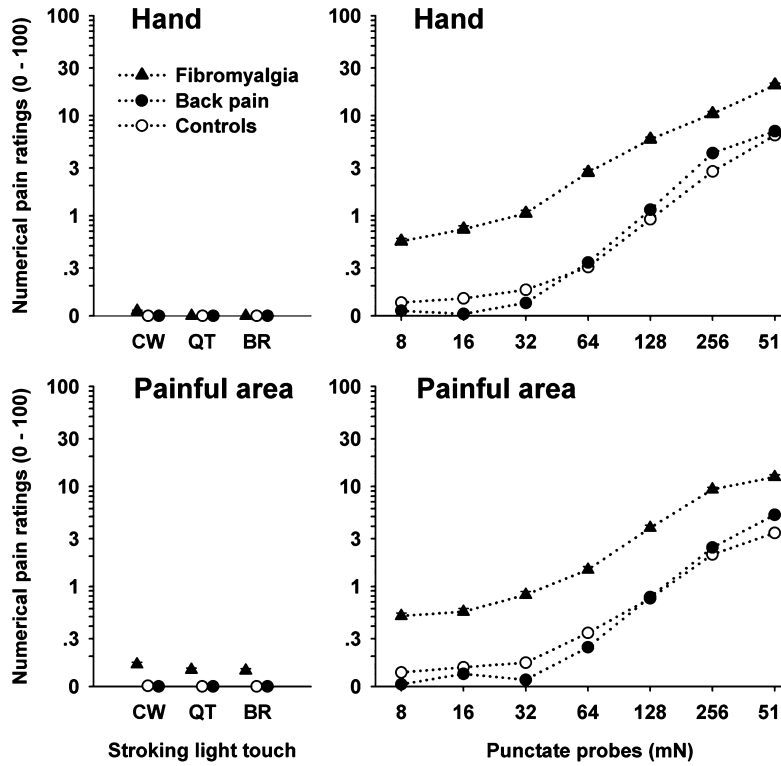

FIGURE 3. Stimulus-response functions of pin-prick pain and dynamic mechanical allodynia in the hand and back of patients with fibromyalgia (closed triangles), chronic back pain (closed circles), and control participants (open circles). Patients with fibromyalgia exhibit static hyperalgesia to pinprick, both over the pain-free hand and the most painful area of the back. Pain evoked by the same set of graded punctate probes (numbers indicate force in mN) was about 5-fold stronger in fibromyalgia patients than in chronic back pain or control participants. Stroking with gentle tactile stimuli (BR, brush; CW, cotton whisp; QT, cotton wool tip) elicited a slight amount of pain (dynamic mechanical allodynia) in fibromyalgia patients only. Patients with chronic back pain and healthy control participants showed similar SR functions.

whereas detection sensitivity was not increased. Our sensory profile suggests that hyperalgesia in FMS may involve all nociceptive submodalities. Pin-prick sensitivity and DMA have not been addressed before. Moreover, pain sensitivity is increased over back and hand dorsum (parallel profiles for back and hand in Fig. 1). Thus, increased sensitivity in FMS is generalized in space (superficial and deep pain, back and hand) and across nociceptive submodalities, but not to other somatosensory functions. The best possible explanation for such a generalized hyperalgesia is a deficient pain inhibitory system.[33] Mechanisms of descending control of pain also include descending facilitation.[34,35] The term "central sensitization" often used in the context of FMS[6,14] does not describe the clinical picture sufficiently. It implies an increased excitability of central neurons, but its effects are restricted in space to the receptive fields and often limited to mechanical test stimuli.[36,37] Disinhibition, in contrast, strikes the entire body and may explain a generalized pain syndrome such as FMS adequately. Thus, disinhibition should be addressed in future studies.[38,39] Possibly, multiple neuronal mechanisms such as disinhibition, central sensitization, and lack of habituation[12] work together.

The presence of DMA, usually interpreted as an indicator for a central sensitization of the nociceptive system, in a relevant number of FMS patients suggests that a deficit in pain inhibitory systems may facilitate the occurrence of central sensitization. Yet, this sensory sign was significantly present only over the back. Sensory findings on the hand in FMS were characterized by a pronounced pin-prick hyperalgesia in the absence of DMA. This type of finding has also been observed in patients with restless legs syndrome. In restless legs syndrome, pinprick hyperalgesia is slowly reversed by dopaminergic treatment.[40] Notably, a recent positron emission tomography study demonstrated a dopaminergic hyporesponsivity in FMS patients,[41] pointing to a possible pathophysiological commonality between these 2 disorders.

The decreased sensitivity to nonpainful warmth (WDT) in FMS, which has not been described so far, is difficult to interpret. In fact, Hurtig et al[7] found no differences in CDT and WDT compared with HCs. Considering this, the mismatch in age distribution between FMS patients and HCs has to be taken into account. On the one hand it is a likely explanation, as the comparison with age-matched and sex-matched control participants in the DFNS reference database[32] yielded the same result. On the other hand, however, the difference in WDT was no longer significant in an ANCOVA with age as a covariate. A thermal hypoesthesia is usually interpreted as a sign of disturbed small fiber function, but recently a correlation between ongoing pain intensity and suppressed sensitivity to nonpainful thermal stimuli has been reported in chronic non-neuropathic pain.[42] Ongoing pain in FMS patients may thus contribute to the decreased sensitivity in nonpainful warmth (WDT) in FMS. Anyway, our data clearly show that the sensitivity toward nonpainful warmth is not increased, supporting the view that the elevated sensitivity in FMS is specific to painful stimuli and not generalized for all somatosensory stimuli.

The wind-up of pain and wind-up after sensations are often described in FMS patients[10,43] and are thought to denote altered CNS processing. This feature, however, is missing in our results, and the WUR for the back was even lower than that for the hand. Magerl et al[44] revealed that, in a capsaicin model, the difference between the first and last stimuli of trains of pin-pricks was increased, but the ratio was unchanged. Our findings are consistent with these results. FMS patients already rate the first (single) stimulus significantly higher than do controls or CBP participants, and thus the relative increase in pain rating after the series of 10 stimuli is not as high. Hence, wind-up was present in our FMS patients, but its magnitude was unchanged as the denominator and numerator of the WUR change by a similar amount.

Somatosensory Profiles in CBP

In this population-based sample of CBP participants, we found features of a localized pain condition with no evidence of spatial generalization, although pain duration was as long as in FMS patients. Significant differences in pain thresholds compared with HCs were only seen for pressure pain, which primarily reflects muscle nociception and peripheral sensitization.[45,46] Moreover, the alterations were limited to the painful area at the back, meaning that there were no signs for a pain generalization. CBP participants differed from FMS patients in all modalities in the same way as HCs, except for PPT at the back, where CBP and FMS both showed decreased PPT. These results suggest localized alterations in muscles and joints. There was no evidence of central sensitization or disinhibition in this sample of CBP participants, indicating that chronic pain per se is not a sufficient condition for these abnormalities. This finding appears intriguing as other studies, for example,[17] suggested central sensitization in both FMS and CBP. As our CBP sample was drawn from the general population, widespread pain sensitivity observed in pain clinic samples may not be representative for all patients with CBP. Therefore, parameters other than chronic ongoing nociceptive pain are likely to be the predisposing factors for widespread pain and FMS. Such factors may be pain intensity, the subtype of CBP, and psychosocial factors. In our CBP sample, the average pain intensity before QST was nearly 50% lower than in the FMS group. The broad range of pain intensity is probably due to the heterogeneity of the CBP sample comprising 1 episode of CBP, intermittent, and continuous CBP according to the distribution in the general population. This is consistent with epidemiological data[47] showing that only a subgroup of a population with localized pain developed FMS later on.

An interesting result was a lower sensitivity toward vibration at the back of CBP participants. In fact, VDT was, on average, 6.7/8 in CBP participants, 7.1/8 in FMS patients, and 7.4/8 in HCs. This result is in line with secondary tactile hypoesthesia in other painful conditions.[48,49] It describes the phenomenon that, in a painful body area, nonpainful stimuli are suppressed. A recent QST study showed decreased VDT in patients with pseudoradicular back pain as well.[50]

Technical Considerations

There are several limitations of the study that should be mentioned. One limitation is the small group size, with about 20 participants in each group. Further, the groups significantly differed in age. In future research, it would be desirable to match patient groups according to age. However, our results are controlled for age by ANCOVA. Besides, QST may be described as a "semi-objective"

procedure, as it still includes the subjective rating of the participants.[51] This raises the question whether QST would rather measure health behavior than pain thresholds. On the other hand, we used 2 methods to assess pain thresholds (method of limits, and direct scaling using randomized stimuli). Patients with FMS perform consistently at different body sites in both paradigms and specifically in the randomized paradigm (Fig. 3). Similarly, brain imaging techniques with FMS patients show fitting activated areas/patterns in the brain when compared with QST.[17,52]

A critical problem consists of the testing sites at the back. CBP participants suffered from pain especially at the lower back, whereas FMS patients indicated the most painful area predominantly at the upper back. The test site in HCs (trapezius muscle) matches the FMS group better than the CBP group. Nevertheless, the FMS group had more sensory aberrations, suggesting that inhomogeneity in test sites had no major effect on our data. This pitfall becomes even less important, given that both FMS and CBP participants revealed abnormal QST profiles at the painful areas; however, only FMS patients showed abnormal QST profiles at the pain-free control site as well, indicating the phenomenon of generalization.

CONCLUSIONS

There is ongoing debate about the classification of FMS [See discussion in Baillieres Best Practice and Research: Clinical Rheumatology Vol. 13 (1999)]. Some authors emphasize the entity of FMS as a distinct and circumscribed disease[53]; others argue that FMS is 1 end of a continuous spectrum of pain diseases.[54,55] The other end of the spectrum may constitute localized pain syndromes such as CBP. Within this spectrum, a switch between pain syndromes is possible[20,47] and common pathogenetic pathways may be assumed. Our data suggest that FMS pathogenesis may be explained at least partly by disinhibition, which can explain the spatial generalization of pain and the involvement of multiple pain modalities. In contrast, CBP offered features of a local pain condition with peripheral sensitization. Given that pain duration did not differ in CBP participants and FMS patients, our population-based data suggest that CBP may persist as a localized pain condition for many years without turning into widespread pain or FMS. Thus, if CBP is a pre-stage to FMS and findings show involvement of central nervous pathways in some patients, as observed in pain clinics, factors other than ongoing peripheral nociceptive pain itself are likely to account for this generalization in place of the ongoing pain.

ACKNOWLEDGMENT

The authors thank Esther Weppelmann for her assistance in quantitative sensory testing.

REFERENCES

1. Andersson HI, Ejlertsson G, Leden I, et al. Musculoskeletal chronic pain in general practice. Studies of health care utilisation in comparison with pain prevalence. *Scand J Prim Health Care*. 1999;17:87–92.
2. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain*. 2000;84:95–103.
3. Kalauokalani D, Cherkin DC, Sherman KJ, et al. Lessons from a trial of acupuncture and massage for low back pain: patient expectations and treatment effects. *Spine*. 2001;26:1418–1424.
4. Karjalainen K, Malmivaara A, van Tulder M, et al. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. *Cochrane Database Syst Rev*. 2000;2:CD001984.
5. Dadabhoy D, Crofford LJ, Spaeth M, et al. Biology and therapy of fibromyalgia. Evidence-based biomarkers for fibromyalgia syndrome. *Arthritis Res Ther*. 2008;10:211.
6. Desmeules JA, Cedraschi C, Rapiti E, et al. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis Rheum*. 2003;48:1420–1429.
7. Hurtig IM, Raak RI, Kendall SA, et al. Quantitative sensory testing in fibromyalgia patients and in healthy subjects: identification of subgroups. *Clin J Pain*. 2001;17:316–322.
8. Kosek E, Ekholm J, Hansson P. Sensory dysfunction in fibromyalgia patients with implications for pathogenic mechanisms. *Pain*. 1996;68:375–383.
9. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain*. 1996;64:415–423.
10. Staud R, Vierck CJ, Cannon RL, et al. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain*. 2001;91:165–175.
11. Henriksson K. Hypersensitivity in muscle pain syndromes. *Curr Pain Headache Rep*. 2003;7:426–432.
12. Smith BW, Tooley EM, Montague EQ, et al. Habituation and sensitization to heat and cold pain in women with fibromyalgia and healthy controls. *Rheumatology (Oxford)*. 2008;140:420–428.
13. Arendt-Nielsen L, Graven-Nielsen T. Central sensitization in fibromyalgia and other musculoskeletal disorders. *Curr Pain Headache Rep*. 2003;7:355–361.
14. Price DD, Staud R. Neurobiology of fibromyalgia syndrome. *J Rheumatol Suppl*. 2005;75:22–28.
15. Krismer M, van Tulder M. Strategies for prevention and management of musculoskeletal conditions. Low back pain (non-specific). *Best Pract Res Clin Rheumatol*. 2007;21:77–91.
16. Flor H, Diers M, Birbaumer N. Peripheral and electrocortical responses to painful and non-painful stimulation in chronic pain patients, tension headache patients and healthy controls. *Neurosci Lett*. 2004;361:147–150.
17. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum*. 2004;50:613–623.
18. Baraniuk JN, Whalen G, Cunningham J, et al. Cerebrospinal fluid levels of opioid peptides in fibromyalgia and chronic low back pain. *BMC Musculoskelet Disord*. 2004;5:48.
19. Lapossy E. The frequency of transition of chronic low back pain to fibromyalgia. *Scand J Rheumatol*. 1995;24:29–33.
20. Müller A, Hartmann M, Eich W. Inanspruchnahme medizinischer Versorgungsleistungen: Untersuchung an Patienten mit Fibromyalgiesyndrom. *Schmerz*. 2000;14:77–83.
21. Nijs J, van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: application of pain neurophysiology in manual therapy practice. *Man Ther*. 2009;14:3–12.
22. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. *Pain*. 2003;102:1–8.
23. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet*. 1999;353:959–1964.
24. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33:160–172.
25. Kohlmann T, Raspe H. Der Funktionsfragebogen Hannover zur alltagsnahen Diagnostik der Funktionsbeeinträchtigung durch Rückenschmerz FFbH-R [FFbH-R: a questionnaire assessing functional limitations in patients with musculoskeletal disorders]. *Rehabilitation*. 1996;35:1–8.

26. Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain*. 2006;10:77–88.
27. Rolke R, Andrews CK, Magerl W, et al. Deep pain thresholds in the distal limbs of healthy human subjects. *Eur J Pain*. 2005; 9:39–48.
28. Yarnitsky D, Sprecher E, Zaslansky R, et al. Heat pain thresholds: normative data and repeatability. *Pain*. 1995; 60:329–332.
29. Fruhstorfer H, Gross W, Selbmann O. Von Frey hairs: new materials for a new design. *Eur J Pain*. 2001;5:341–342.
30. Baumgärtner U, Magerl W, Klein T, et al. Neurogenic hyperalgesia versus painful hypoalgesia: two distinct mechanisms of neuropathic pain. *Pain*. 2002;96:141–151.
31. LaMotte RH, Shain CN, Simone DA, et al. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *J Neurophysiol*. 1991;66:190–211.
32. Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*. 2006;123:231–243.
33. Villanueva L, Le Bars D. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. *Biol Res*. 1995;28:113–125.
34. Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002; 66:355–474.
35. Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends Pharmacol Sci*. 2004;25:613–617.
36. Treede RD, Meyer RA, Raja SN, et al. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol*. 1992; 38:397–421.
37. Treede RD, Handwerker HO, Baumgärtner U, et al. Hyperalgesia and allodynia: taxonomy, assessment, and mechanisms. In: Brune KHH, ed. *Hyperalgesia: Molecular Mechanisms and Clinical Implications*. Seattle: IASP Press; 2005:1–15.
38. Pud D, Granovsky Y, Yarnistky D. The methodology of experimentally induced Diffuse Noxious Inhibitory Control (DNIC)-like effect in humans. *Pain*. 2009;144:16–19.
39. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. *Eur J Pain*. 2010;14:339.
40. Stiasny-Kolster K, Magerl W, Oertel WH, et al. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. *Brain*. 2004;127: 773–782.
41. Wood PB, Schweinhardt P, Jaeger E, et al. Fibromyalgia patients show an abnormal dopamine response to pain. *Eur J Neurosci*. 2007;25:3576–3582.
42. Agostinho CM, Scherens A, Richter H, et al. Habituation and short-term repeatability of thermal testing in healthy human subjects and patients with chronic non-neuropathic pain. *Eur J Pain*. 2009;8:779–785.
43. Price DD, Staud R, Robinson ME, et al. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain*. 2002;99:49–59.
44. Magerl W, Wilk SH, Treede RD. Secondary hyperalgesia and perceptual wind-up following intradermal injection of capsaicin in humans. *Pain*. 1998;74:257–268.
45. Kilo S, Schmelz M, Koltzenburg M, et al. Different patterns of hyperalgesia induced by experimental inflammation in human skin. *Brain*. 1994;117:385–396.
46. Kosek E, Ekholm J, Hansson P. Pressure pain thresholds in different tissues in one body region. The influence of skin sensitivity in pressure algometry. *Scand J Rehabil Med*. 1999;31:89–93.
47. Forseth KO, Husby G, Gran JT, et al. Prognostic factors for the development of fibromyalgia in women with self-reported musculoskeletal pain. A prospective study. *J Rheumatol*. 1999; 26:2458–2467.
48. Leffler AS, Kosek E, Hansson P. Injection of hypertonic saline into musculus infraspinatus resulted in referred pain and sensory disturbances in the ipsilateral upper arm. *Eur J Pain*. 2000;4:73–82.
49. Magerl W, Treede RD. Secondary tactile hypoesthesia: a novel type of pain-induced somatosensory plasticity in human subjects. *Neurosci Lett*. 2004;361:136–139.
50. Freynhagen R, Rolke R, Baron R, et al. Pseudoradicular and radicular low-back pain–a disease continuum rather than different entities? Answers from quantitative sensory testing. *Pain*. 2008;135:65–74.
51. Petzke F, Clauw DJ, Ambrose K, et al. Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. *Pain*. 2003;105:403–413.
52. Staud R, Craggs JG, Perlstein WM, et al. Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. *Eur J Pain*. 2008;12:1078–1089.
53. Rau CL, Russell IJ. Is fibromyalgia a distinct clinical syndrome? *Curr Rev Pain*. 2004;4:287–294.
54. Makela MO. Is fibromyalgia a distinct clinical entity? The epidemiologist's evidence. *Baillières Best Pract ResClin Rheumatol*. 1999;13:415–419.
55. Schochat T, Raspe H. Elements of fibromyalgia in an open population. *Rheumatology (Oxford)*. 2003;42:829–835.

