

Cross-Sectional Study

Differences in Pain Processing Between Patients with Chronic Low Back Pain, Recurrent Low Back Pain, and Fibromyalgia

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Background: The impairment in musculoskeletal structures in patients with low back pain (LBP) is often disproportionate to their complaint. Therefore, the need arises for exploration of alternative mechanisms contributing to the origin and maintenance of non-specific LBP. The recent focus has been on central nervous system phenomena in LBP and the pathophysiological mechanisms underlying the various symptoms and characteristics of chronic pain. Knowledge concerning changes in pain processing in LBP remains ambiguous, partly due to the diversity in the LBP population.

Objective: The purpose of this study is to compare quantitative sensory assessment in different groups of LBP patients with regard to chronicity. Recurrent low back pain (RLBP), mild chronic low back pain (CLBP), and severe CLBP are compared on the one hand with healthy controls (HC), and on the other hand with fibromyalgia (FM) patients, in which abnormal pain processing has previously been reported.

Study Design: Cross-sectional study.

Setting: Department of Rehabilitation Sciences, Ghent University, Belgium.

Methods: Twenty-three RLBP, 15 mild CLBP, 16 severe CLBP, 26 FM, and 21 HC participated in this study. Quantitative sensory testing was conducted by manual pressure algometry and computer-controlled cuff algometry. A manual algometer was used to evaluate hyperalgesia as well as temporal summation of pain and a cuff algometer was used to evaluate deep tissue hyperalgesia, the efficacy of the conditioned pain modulation and spatial summation of pain.

Results: Pressure pain thresholds by manual algometry were significantly lower in FM compared to HC, RLBP, and severe CLBP. Temporal summation of pain was significantly higher in FM compared to HC and RLBP. Pain tolerance thresholds assessed by cuff algometry were significantly lower in FM compared to HC and RLBP and also in severe CLBP compared to RLBP. No significant differences between groups were found for spatial summation or conditioned pain modulation.

Limitations: No psychosocial issues were taken into account for this study.

Conclusion: The present results suggest normal pain sensitivity in RLBP, but future research is needed. In mild and severe CLBP some findings of altered pain processing are evident, although to a lesser extent compared to FM patients. In conclusion, mild and severe CLBP presents within a spectrum, somewhere between completely healthy persons and FM patients, characterized by pain augmentation.

Key words: Low back pain, fibromyalgia, pain assessment, quantitative sensory testing, central sensitization, hypersensitivity, temporal summation, spatial summation, conditioned pain modulation

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The impairments in musculoskeletal structures in patients with low back pain (LBP) are often disproportionate to their complaints (1). By consequence, the need arises to explore alternative mechanisms contributing to the origin and maintenance of non-specific LBP. In addition to potential peripheral mechanisms, the recent focus has been on central nervous system phenomena in LBP research and the pathophysiological mechanisms underlying the various symptoms and characteristics of chronic pain. Sensitized central pain mechanisms are the result of prolonged and strong activation of dorsal horn neurons, which leads to increased neuronal responsiveness of nociceptive mechanisms (2). Moreover, an imbalance between enhanced pain facilitation and decreased endogenous pain inhibition is demonstrated in different chronic pain conditions, leading to widespread pain and hyperalgesia (3-5).

Sensitized central pain mechanisms may potentially be involved in the transition from acute to chronic widespread pain (6). In whiplash patients, altered pain processing rather than impaired motor control, has been identified as one of the prime prognostic factors for developing chronic whiplash complaints (7). In fibromyalgia (FM) patients, it is suggested that central pain mechanisms can be dependent on abnormal peripheral input(s) for development and maintenance of the chronic condition (8). Until now, only conflicting results for the involvement of sensitized central pain mechanisms in LBP are available in literature. Some studies found generalized hyperalgesia in patients with chronic low back pain (CLBP) (9-12), whereas others found no differences in pain perception or modulation in CLBP (13,14). These inconsistent results might be the consequence of the heterogeneity within the LBP population as proposed by O'Sullivan et al (15). In recurrent low back pain (RLBP), to our knowledge, no research on altered pain processing is performed. Besides, often there is no clear distinction between CLBP and RLBP.

Consequently, the challenge is to compare subgroups of LBP with different levels of chronicity for possible signs of malfunctioning in pain processing. Therefore, next to defining RLBP patients, 2 subgroups of CLBP, based on the frequency of pain days in one week, were defined: a group with mild CLBP and a group with severe CLBP. In the current study, it is hypothesized that while RLBP may be mainly characterized by musculoskeletal dysfunctions (explaining the intermittent/fluctuating nature of the complaints), the transition to chronic pain may be complicated with sensitized pain

processing mechanisms. Therefore, in contrast to RLBP and asymptomatic controls, severe CLBP patients and FM were hypothesized to have widespread hyperalgesia, facilitated spatial summation of pain (SS), facilitated temporal summation of pain (TS), and impaired conditioning pain modulation.

Manifestations of pro- and anti-nociceptive mechanisms are examined by quantitative somatosensory testing. Handheld pressure algometry is a frequently used, valid, and reliable method to evaluate subcutaneous pain sensitivity in the local area and in distant structures (16,17). Alternatively, computer controlled cuff algometry is a standardized and examiner-independent tool to assess deep tissue pain sensitivity (18). It is able to assess a larger tissue volume and is in that way less influenced by local pain sensitivity (6). In this study, manual algometry is used to assess hyperalgesia and bottom up processing, while cuff algometry is used to assess deep tissue hyperalgesia, spatial summation, and endogenous pain inhibition.

METHODS

Participants

All participants were recruited through co-workers and students of the University Hospital of Ghent. The recruitment occurred through announcements on social media (Facebook and Twitter) and by advertisements (posters and flyers) in the different hospitals in Ghent and in private practices of the co-workers. Healthy controls (HC) are matched to the patient groups for gender. All in- and exclusion criteria can be found in Table 1 (19-24).

This cross-sectional study is part of a larger study. The complete study was approved by the local ethical committee (EC UZ 22012/791) and all subjects gave written informed consent to participate.

Procedure

An anamnesis was performed to control for all in- and exclusion criteria. To evaluate the LBP disability on the day of testing, all patient groups were asked to fill in the Roland-Morris Disability Questionnaire. The items in this questionnaire represent the execution of daily physical activities and functions that may be affected by LBP complaints (25). Afterwards, the pain measurements were assessed.

First, pressure pain thresholds (PPT) and TS were measured by manual algometry on the lower back, quadriceps, trapezius, and hand. TS started 2 minutes

Table 1. In- and exclusion criteria of all participants. HC=healthy controls; RLBP=recurrent low back pain; CLBP=chronic low back pain; FM=fibromyalgia; NRS=numeric rating scale.

GROUP	GENERAL IN- AND EXCLUSION CRITERIA	SPECIFIC IN- AND EXCLUSION CRITERIA
RLBP	<ul style="list-style-type: none"> males and females 18-65 years old ≥1 years post-natal no neurological, respiratory, circulatory or severe orthopaedic diseases no pregnancy no back surgery no previous cognitive exercise therapy for their low back pain no use of antidepressants or analgesics (except for NSAID's or paracetamol), taken 2 weeks prior to the testing 	<ul style="list-style-type: none"> non-specific RLBP ≥6 months a frequency of ≥2 episodes in the past year (19) a pain flare of ≥24 hours(20), characterized by an increase of ≥2 on a NRS scale and/or ≥5 on the Roland-Morris Disability Questionnaire (21) followed by a pain free episode of ≥1 month, characterized by a 0/10 on an NRS scale and/or <2 on the Roland-Morris disability questionnaire (22) applicate for medical help concerning low back complaints
Mild CLBP		<ul style="list-style-type: none"> non-specific CLBP ≥3 months (23) 3 to 4 pain days a week
Severe CLBP		<ul style="list-style-type: none"> non-specific CLBP ≥3 months (23) 7 pain days a week
FM		<ul style="list-style-type: none"> diagnosed by the 2010 ACR-criteria for primary FM (24)
HC		<ul style="list-style-type: none"> healthy persons no physical pain complaints never asked for help or advice concerning low back pain

after the PPT assessment and was provoked by 10 consecutive pressure stimuli delivered at the previously determined PPT (26). Next, the pressure pain detection threshold (cPDT) and the pressure pain tolerance threshold (cPTT) were measured by the cuff algometer. SS was assessed by recordings of cPDT and cPTT for 2 different stimulation areas (inflation of 1 and 2 chambers in the cuff). Afterwards, 2 minutes of rest were inserted. Finally, to evaluate endogenous pain inhibition, conditioned pain modulation (CPM) was assessed. To assess a baseline for CPM, 15 repetitive cuff stimulation pulses were applied and the pain intensity was recorded, followed by 5 minutes of rest (27). Afterwards, this procedure was repeated, by adding the conditioning stimulus (immersion of the hand in a hot water bath of 46°C) for eliciting CPM. Standardized instructions were used for all subjects. An overview of all algometry parameters and the assigned abbreviations can be found in Table 2.

On the day of testing, all subjects were asked to refrain from alcohol, nicotine, caffeine, and all medication, including NSAIDs and paracetamol. Subjects were also instructed not to perform exhausting physical activities the day before.

Manual Pressure Algometry

A hand held pressure algometer (Wagner Force Ten) with a circular probe of one cm diameter was used to assess PPTs. Pressure was applied perpendicular and at

a constant rate (1kg/s) to the tissue surface, bilaterally at 4 spots: erector spinae muscle (lower back) at 5 cm laterally of the processus spinosus vertebrae at L3 (28), quadriceps muscle (quadriceps) at the middle between anterior superior iliac spine and basis patella (26), trapezius muscle (trapezius) at the middle between acromion and processus spinosus at C7 (29-31), and the web (hand) between the index finger and thumb at the dorsal hand side (13,32). For each site, 2 PPT measurements were taken with a 30 second interval (29) and the mean of both recordings was used for further analysis. Lower back and quadriceps sites were measured in prone and supine position respectively (Fig. 1A and 1B). Trapezius and hand sites were measured when sitting on a chair. For trapezius, both arms hung relaxed beside the trunk (Fig. 1C) and for the hand site, both hands were placed on a table (Fig. 1D).

Pressure pain threshold: Participants were instructed to say 'stop' when the sensation became uncomfortable. The minimal amount of pressure that induces an uncomfortable pain, resembles PPT (15).

Temporal summation: TS was used to evaluate endogenous pain facilitation. The previous determined mean PPT intensity was applied 10 repetitive times at each assessment site and was maintained one second before being released. Pressure was increased, during one second, until the previously determined mean PPT intensity was reached (27, 31), followed by one second

Table 2. The elucidation of the used abbreviations of the algometry parameters.

MEASURED BY	ABBREVIATION	COMPLETE TERM	CALCUATION
Digital Algometer	PPT	Pressure pain threshold	The moment of the first uncomfortable sensation.
	TS	Temporal summation of pain	Area under the curve of pain sensation during pulse 1, 5, 10 when mean PPT was applied 10 repetitive times.
Cuff Algometer	cPDT	Pressure pain detection threshold	The moment when the visual analogue scale exceeds 0.5.
	cPTT	Pressure pain tolerance threshold	The moment when the sensation gets unbearable.
	SS	Spatial summation of pain	A lower PPDT and/or PPTol during inflation of both chambers compared to inflation of a single chamber.
	CPM	Conditioned pain modulation	Area under the curve of the condition, in which a combination of a test stimulus and conditioning stimulus were applied, minus the area under the curve of the condition, in which a singular test stimulus was applied.



Fig.1. The test sites for manual pressure algometry: at lumbar level L3 (top left), at the middle of the quadriceps (top right), at the middle of the trapezius (bottom left), and at the first web (bottom right).

of rest. After the first, fifth, and tenth stimulus, a numeric rating score (NRS) of the pressure induced pain sensation was recorded.

Cuff pressure algometry

Computer-controlled cuff algometry (Nocitech and Aalborg University, Denmark) was used to assess cPDT, cPTT, SS, and CPM. The device consists of a computer controlled compressor, connected with a 13 cm wide silicone tourniquet cuff (VBM Medizintechnik GmbH, Sulz, Germany) and an electronic VAS scale allowing continuous recording of the pain intensity (18). The electronic VAS contains a stop-button and a 10 cm bar, indicating the amount of experienced pain: 0 cm is 'no pain' and 10 cm represents 'the worst pain imaginable'. The inflatable cuff was separated into 2 equal-sized chambers which were positioned directly onto the skin at the thickest point of the right calf (Fig. 2A).

Pressure pain detection threshold and pressure pain tolerance threshold: In order to evaluate cPDT and cPTT, the distal chamber of the cuff was gradually inflated (1kPa/s) until a maximum of 100kPa. Participants constantly scored their sensation during inflation on the electronic VAS. They started shifting the bar at the point when feeling uncomfortable and pushing the stop-button when the pressure stimulation got intolerable (cPTT), after which immediate deflation was initiated. A VAS-value of 0.5 cm was set as cPDT (18). Inflation of one chamber and inflation of 2 chambers, respectively, were done. Assessments were repeated 3 times with 30 seconds of rest in between, and the mean of the 2 last recordings was used for further analysis.

Spatial summation: To assess SS, the cPDT and cPTT during inflation of the double-chamber cuff was compared by cPDT and cPTT during inflation of the single-chambered cuff. The sequence of one or both chamber compressions was randomized and subjects were blinded for which condition was applied.

Conditioned pain modulation: Fifteen repetitive cuff compressions of both chambers (one second stimulation and one second pause) were used as a test stimulus (33), but only the third pulse of both conditions was used for further analysis in this study. The intensity of the compression was set as the mean value of cPDT and cPTT (33,34). As a painful conditioning stimulus, the subjects immersed their right hand in a hot water bath of 46°C. Participants were asked to immerse the hand in the water at 10 cm above the wrist (35), 20 seconds prior to the administration of the test stimulus. Participants scored the sensation of the cuff compressions on the electronic VAS and for each stimulus a VAS-score was extracted. They were instructed to focus on and rate the pain intensity of the leg and to ignore the sensation on the hand. CPM was quantified by calculating the amount of pain reduction in the test stimulus evoked by a painful conditioning stimulus (36) (Fig. 2B).

Data Analysis and Statistics

Statistics were performed on Windows 10 Software using IBM SPSS Statistics 22 (SPP Inc., Chicago, IL, USA). In all analysis by manual algometry, a mean value of left and right measurements was calculated and used.

For TS, the area under the curve was calculated by summation of NRS during pulse 1, 5, and 10. For SS, the

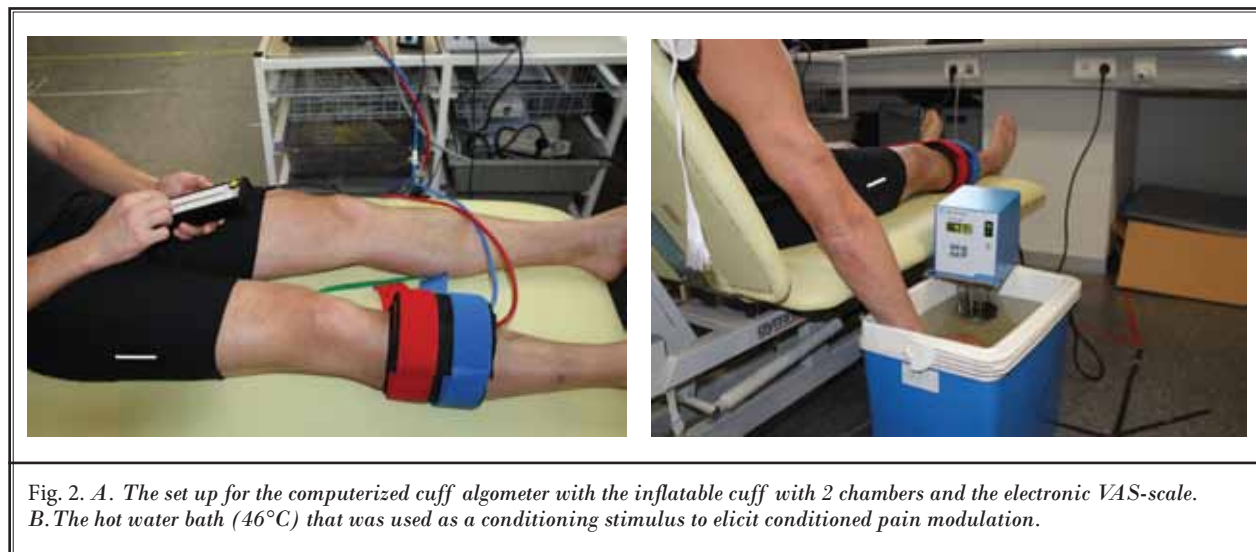


Fig. 2. A. The set up for the computerized cuff algometer with the inflatable cuff with 2 chambers and the electronic VAS-scale. B. The hot water bath (46°C) that was used as a conditioning stimulus to elicit conditioned pain modulation.

Table 3. Participants characteristics

	HC (n=21)		RLBP (n=23)				CLBP mild (n=15)				CLBP severe (n=16)				FM (n=26)			Total (n=101)			
	mean (SD)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)		
Gender	9 m; 12 f		9 m; 14 f		7 m; 8 f		8 m; 8 f		7 m; 19 f		40 m; 61 f										
Symptomatic Side	/		- L: 2 - R: 4 - bilat: 17		- R: 1 - bilat: 14		- L: 2 - R: 2 - bilat: 12		- R: 1 - bilat: 18 - centr: 5 - no LBP: 2		- L: 4 - R: 8 - bilat: 61 - centr: 4 - no LBP: 23										
Age (years)	38 (13)	20 - 55	31 (10)	27 (12)	21 - 53	34 (10)	31 (14)	20 - 54	46 (14)	50 (28)	23 - 64	45 (9)	46; (11)	22 - 58	39 (13)	39 (24)					
BMI	23.00 (3.02)	18.25-30.22	22.88 (2.33)	22.80 (2.59)	18.59-28.83	23.29 (1.60)	23.07 (1.13)		25.00 (3.07)	24.07 (3.53)	19.66-31.74	26.14 (5.07)	24.99 (6.70)	19.49-37.84	24.14 (3.62)	23.30 (4.12)					
Symptom Duration (months)	/	/	112 (81)	84 (120)	24 - 300	104 (74)	78 (138)	24 - 240	199 (169)	156 (213)	30 - 552	159 (124)	150 (144)	20 - 508	141 (118)	102 (132)					
RMDQ (max 24)	/	/	1.52 (1.44)	1.00 (1)	0 - 6	4.93 (2.69)	5.00 (3)	1 - 11	5.56 (2.90)	5.00 (4)	1 - 12	10.19 (4.77)	11.50 (7)	1 - 21	4.65 (4.79)	3.00 (6)					

SD=standard deviation; IQR=interquartile range; n=number of subjects included; m=male; f=female; L=left; R=right; bilat=bilateral; centr=central; no LBP=no low back pain; RMDQ=Roland-Morris disability questionnaire; HC=healthy controls; RLBP=recurrent low back pain; CLBP=chronic low back pain; FM=fibromyalgia.

ratio of cPDT and cPTT, respectively were calculated; the threshold from the double-chamber cuff was divided by the threshold from the single-chamber cuff. For CPM, a delta-value was calculated; the condition with conditioning stimulus minus the condition without conditioning stimulus resulted in CPM. The lower this CPM value, the less efficient the pain inhibition works.

Since the data was observed to deviate from normally, a non-parametric Kruskal-Wallis Analysis of Variance test was performed to evaluate differences between groups in demographic variables, the Roland-Morris Disability Questionnaire, PPT by manual pressure algometer, and cPDT, cPTT, SS, and CPM by cuff algometer. Mann-Whitney U tests were used post hoc for group comparisons in case of a significant Kruskal-Wallis test. To evaluate the functionality of SS and CPM, a Wilcoxon Signed Ranks test was performed. A Chi-Square test was used to evaluate gender distribution between groups. TS measured by manual algometer, which was observed to be not normally distributed, was examined using a general linear model (GLM) followed by post hoc tests of which p-values and 95% confidence intervals are presented (Bonferroni corrected). Age and body mass index were initially used as covariates in GLM, but were observed to be of no influence in gathered data, so these covariates were no longer taken into account for further analysis. Homogeneity of variances was tested using the Levene's test. In order to examine the influence of the applied pressure on TS and CPM, respectively, a Pearson and Spearman correlation was assessed for each group. Hence, in order to improve the interpretation of the results, a post hoc power analysis by the 'GPower' program (By Franz Faul, Universitat Kiel, Germany, Version 3.1.9.2) was performed. A P-value of 0.05 was considered significant.

RESULTS

Demographics

A total of 101 participants between 20 and 64 years of age participated in this study (Table 3). No difference in gender was seen between groups (Chi-Square: $P > 0.05$). The mean age was significantly lower in RLBP, compared with severe CLBP and FM (Mann-Whitney U: $P = 0.002$; $P < 0.05$). The mean age was also significantly lower in mild CLBP compared to respectively severe CLBP and FM

(Mann-Whitney U: $P = 0.021$; $P = 0.002$). The body mass index was significantly higher in FM compared to HC and RLBP (Mann-Whitney U: $P = 0.027$; $P = 0.018$) and in severe CLBP compared respectively to HC, RLBP, and mild CLBP (Mann-Whitney U: $P = 0.029$; $P = 0.020$; $P = 0.041$). The score on the Roland-Morris Disability Questionnaire was significantly lower in RLBP compared to mild CLBP, severe CLBP, and FM ($P < 0.05$), as well as in FM compared to severe CLBP ($P = 0.002$) and to mild CLBP ($P = 0.001$). None of the subjects used alcohol, nicotine, caffeine, or any medication (including NSAIDs and paracetamol) on the day of testing.

Manual Pressure Algometry

Significant differences between groups were found for PPT in quadriceps and lower back, and a borderline significant difference was found for trapezius (Kruskal-Wallis: $P = 0.044$; $P = 0.035$; $P = 0.052$). Mean values for PPT were significantly lower in FM compared to respectively HC, RLBP, and severe CLBP for quadriceps (Mann-Whitney U: $P = 0.004$; $P = 0.029$; $P = 0.049$), lower back (Mann-Whitney U: $P = 0.011$; $P = 0.005$; $P = 0.038$) and trapezius (Mann-Whitney U: $P = 0.006$; $P = 0.026$; $P = 0.039$).

Significant differences between groups were found for VAS scores to repeated pressure stimulation in quadriceps, lower back, trapezius, and first web (ANOVA: $P = 0.001$; $P = 0.006$; $P < 0.05$; $P = 0.003$). TS was significantly higher in FM compared with HC and RLBP for quadriceps (Bonferroni: $P = 0.047$, [0.21, 10.12]; $P < 0.05$, [2.95, 12.49]) and trapezius (Bonferroni: $P = 0.023$, [0.45, 9.31]; $P < 0.05$, [3.08, 11.72]). The mean TS was also significantly higher in FM compared to RLBP for lower back and hand (Bonferroni: $P = 0.002$, [2.01, 11.92]; $P = 0.001$, [2.12, 11.68]). No correlations were found between TS and the intensity of the applied pressure (Pearson: $P > 0.05$).

Cuff Algometry

Significant differences between groups were found for cPTT (Kruskal-Wallis: $P = 0.006$), but not for cPDT (Kruskal-Wallis: $P = 0.496$) when assessing one chamber. The mean cPTT was significantly lower in FM compared with HC and RLBP (Mann-Whitney U: $P = 0.005$; $P = 0.041$) and in severe CLBP compared to RLBP (Mann-Whitney U: $P = 0.041$).

Significantly lower cPTT (Wilcoxon Signed-Ranks: $P < 0.012$) was found in all groups when compression in both chambers was applied compared to compression in one chamber, resembling a well-functioning SS. Also,

significantly lower cPDT was found in all groups (Wilcoxon Signed-Ranks: $P < 0.042$) when inflation in both chambers was applied, except in severe CLBP ($P > 0.05$). The SS-ratio although, was not significantly different between groups for cPDT or cPTT (Kruskal-Wallis: $P > 0.05$; $P > 0.05$) (Fig. 3A and 3B).

For CPM, mean values when the conditioning stimulus was applied were lower compared to the condition when no conditioning stimulus was applied, although not significant (Wilcoxon Signed-Ranks $P > 0.05$). Also, no significant differences between groups were established for CPM nor for the baseline condition without conditioning stimulus (Kruskal-Wallis: $P = 0.683$; $P = 0.478$). No correlations were found between CPM and the intensity of the applied pressure (Spearman: $P > 0.05$).

Post hoc power analysis demonstrated a power of 0.29 for the difference between HC and severe CLBP (expected effect size = 0.5; $P = 0.05$).

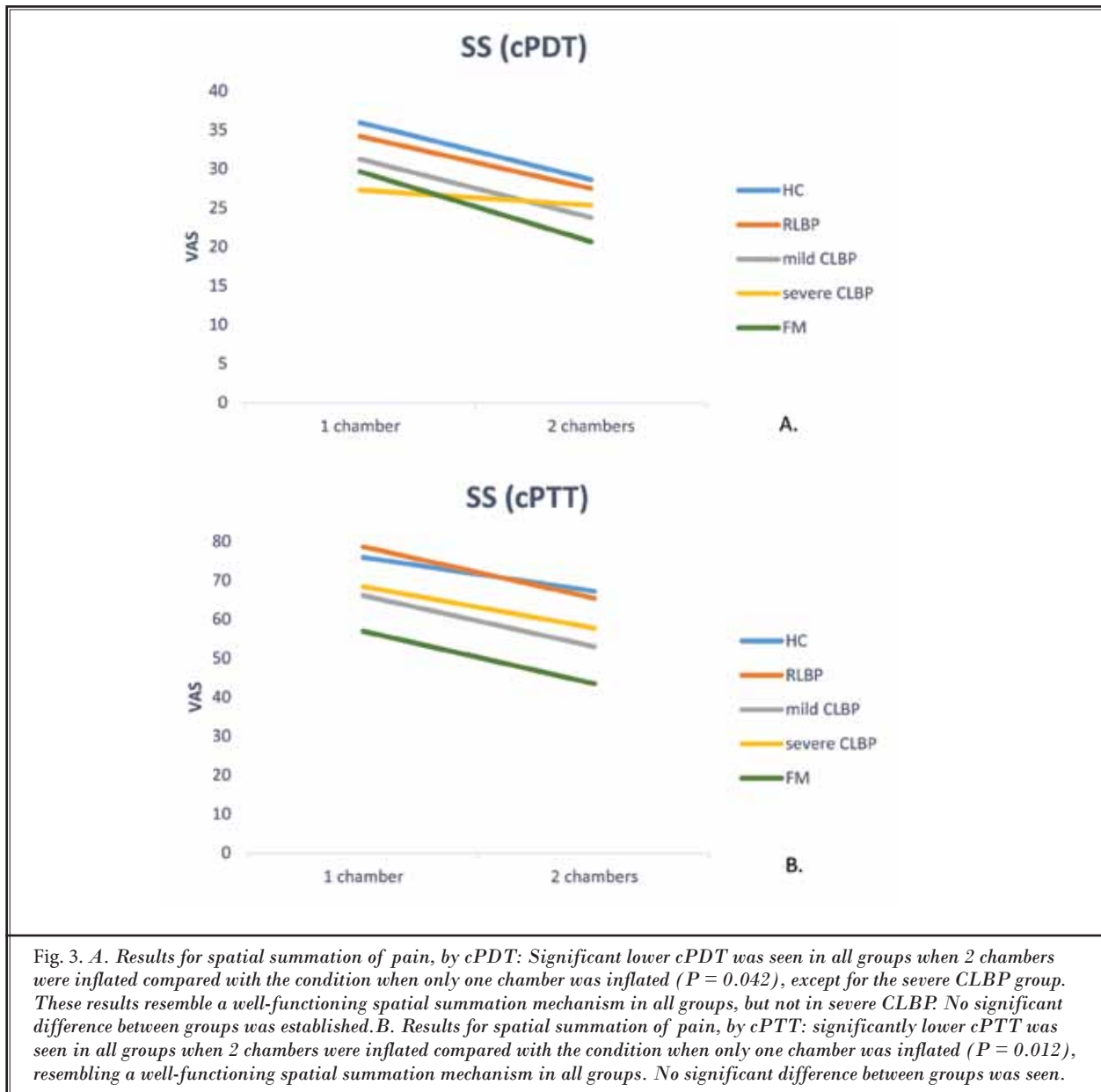
A summary of all presented data can be found in Table 4.

DISCUSSION

The current study aimed at evaluating pain processing mechanisms in 3 LBP groups, compared to FM and HC. To our knowledge, this is the first study that aimed at investigating pain processing in RLBP and in different CLBP populations with defined degrees of chronicity, in comparison to the 2 extremes of the musculoskeletal pain spectrum, with HC suffering from no pain and FM characterized by widespread pain and hyperalgesia. This study hypothesized altered pain processing in severe CLBP, but not in RLBP. Mild CLBP were expected to float between RLBP and severe CLBP.

PPT measured by manual pressure algometry is significantly lower in FM compared to HC, RLBP, and severe CLBP at the quadriceps, lower back, and trapezius, indicating widespread hyperalgesia in FM. These results confirm the generally widespread hypersensitivity in FM (8,37,38). In the LBP groups, no clear primary hypersensitivity at the lower back is found. Because of standardization, PPT was measured at level L3, which might be different from the exact pain location. Also, PPT values localized in distant structures in RLBP, mild CLBP, and severe CLBP appear to not be different from HC. Thus, localized and widespread hyperalgesia is found in FM, but cannot be established in RLBP, mild CLBP, and severe CLBP.

Cuff pressure algometry reveals significantly lower cPTT in FM compared to HC and RLBP, and in severe



CLBP compared to RLBP. These results indicate deep tissue hypersensitivity at the leg, away from the pain location, and are suggestive for maladaptive pain processing in both FM and severe CLBP, but not in RLBP. These results are in line with another study, which found generalized and localized hyperalgesia in participants with long-lasting LBP (>30 days pain in the previous year), but not in patients with recent LBP (pain within the last 7 days) (10). These findings support the hypothesis that generalized hyperalgesia develops over time, as a con-

sequence of long lasting pain (6). In the current study, severe CLBP patients are older compared to RLBP. Previous research by cuff algometer established enhanced pain sensitivity in older healthy subjects compared to younger persons. Therefore, age might contribute to the differences between severe CLBP and RLBP (39).

In the current study, RLBP scores better on the Roland-Morris Disability Questionnaire compared with mild and severe CLBP and FM. As a consequence, the perceived disability because of LBP is lower in RLBP

Table 4. Summary statistics of PPT and TS by manual algometer and outcome variables by cuff algometer. SD=standard deviation; IQR=interquartile range; mini=minimum; max=maximum; HC=healthy controls; RLBP=recurrent low back pain; CLBP=chronic low back pain; FM=fibromyalgia; PPT=pressure pain threshold; TS=temporal summation; cPDT=pressure pain detection threshold by cuff algometer; cPTT=pressure pain tolerance threshold by cuff algometer; SS=spatial summation; CPM=conditioned pain modulation (the delta value of the condition without conditioning stimulus minus with the condition with conditioning stimulus).

	HC			RLBP			Mild CLBP			Severe CLBP			FM		
	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max	mean (SD)	median (IQR)	min-max
MANUAL PPT															
quadriceps	7.48 (4.68)	6.24 (4.19)	2.63 -24.70	6.46 (3.15)	5.00 (3.41)	2.89 -16.38	6.19 (3.08)	5.58 (4.22)	2.20 -14.00	6.25 (2.53)	6.09 (4.32)	1.24 -10.05	4.70 (2.54)	4.46 (3.03)	1.32 -12.00
lower back	7.30 (4.42)	5.83 (4.23)	2.36 -19.76	6.89 (3.32)	5.57 (3.82)	2.91 -16.94	6.14 (3.07)	5.16 (3.84)	1.94 -14.27	6.36 (3.47)	5.31 (3.79)	0.86 -13.87	4.44 (2.12)	4.26 (2.99)	1.16 -8.70
trapezius	5.22 (3.76)	4.27 (3.15)	1.29 -19.54	4.27 (1.84)	3.55 (2.55)	1.67 -7.74	4.33 (2.18)	3.94 (1.43)	0.95 -9.43	4.04 (1.71)	3.69 (2.05)	1.00 -7.78	3.18 (1.57)	2.87 (2.15)	1.07 -6.93
hand	5.79 (4.16)	4.59 (4.21)	1.78 -19.26	4.87 (2.49)	3.90 (3.45)	2.01 -10.42	4.78 (3.04)	4.20 (3.10)	1.45 -13.88	4.56 (2.28)	4.54 (2.60)	1.27 -10.44	3.77 (1.48)	3.71 (2.03)	0.98 -6.66
MANUAL TS															
quadriceps	11.30 (6.17)	10.25 (11.25)	2.50 -22.50	8.74 (6.35)	6.00 (8.00)	0.50 -24.00	12.13 (6.23)	13.00 (7.50)	1.50 -22.50	12.5 (5.48)	13.75 (9.00)	4.00 -21.00	16.45 (5.73)	16.75 (9.75)	7.00 -27.00
lower back	11.13 (6.38)	9.25 (11.00)	3.00 -23.50	8.15 (6.77)	6.50 (10.50)	0.50 -22.00	12.53 (6.19)	11.50 (10.00)	3.00 -24.00	12.46 (5.57)	10.25 (10.00)	5.50 -23.00	15.12 (6.08)	14.75 (9.25)	3.00 -27.50
trapezius	11.35 (5.10)	10.75 (8.63)	4.50 -21.00	8.70 (4.48)	7.50 (8.50)	0.50 -15.50	13.50 (6.92)	14.50 (10.00)	2.50 -24.00	12.79 (5.58)	12.75 (9.38)	3.50 -22.00	16.10 (5.50)	16.75 (9.13)	7.00 -25.50
hand	11.98 (5.38)	10.25 (8.75)	3.00 -23.50	8.02 (5.91)	7.00 (8.50)	0.00 -22.00	13.40 (7.13)	13.00 (10.50)	1.50 -27.00	12.29 (6.88)	12.25 (12.75)	1.50 -25.00	14.92 (5.32)	16.25 (9.00)	6.00 -22.50
CUFF															
cPDT	35.94 (18.31)	40.01 (30.68)	7.27 -68.46	34.17 (18.36)	29.70 (20.43)	9.96 -76.68	31.23 (17.85)	25.58 (20.54)	12.65 -71.97	27.25 (11.25)	25.98 (18.29)	12.23 -52.43	29.64 (12.89)	27.24 (15.08)	9.09 -58.07
cPTT	75.87 (20.64)	70.13 (40.88)	40.24 -100	78.61 (20.51)	80.30 (32.08)	25.61 -100	66.09 (23.05)	60.43 (51.84)	35.49 -100	68.39 (17.67)	67.31 (20.02)	40.82 -100	56.92 (23.36)	52.46 (34.47)	22.68 -100
SS (cPDT)	0.89 (0.33)	0.82 (0.55)	0.44 -1.70	0.85 (0.37)	0.78 (0.38)	0.26 -2.12	0.83 (0.30)	0.84 (0.48)	0.39 -1.42	0.97 (0.26)	0.92 (0.32)	0.53 -1.58	0.74 (0.19)	0.74 (0.32)	0.46 -1.13
SS (cPTT)	0.88 (0.21)	0.91 (0.25)	0.52 -1.32	0.84 (0.16)	0.87 (0.26)	0.48 -1.09	0.80 (0.12)	0.81 (0.14)	0.59 -1.01	0.85 (0.19)	0.85 (0.26)	0.60 -1.35	0.77 (0.16)	0.74 (0.29)	0.50 -1.03
CPM (no CS)	1.11 (1.61)	0.00 (20.13)	0.00 -6.32	0.30 (0.48)	0.00 (0.37)	0.00 -1.76	0.93 (1.24)	0.55 (1.58)	0.00 -4.51	0.58 (0.93)	0.00 (1.11)	0.00 -3.26	0.43 (0.75)	0.00 (0.62)	0.00 -2.76
CPM (no CS minus CS)	0.32 (0.72)	0.00 (0.74)	-0.47 -1.90	-0.03 (0.25)	0.00 (0.17)	-0.83 -0.37	-0.09 (1.01)	0.00 (0.45)	-3.44 -0.94	0.01 (0.35)	0.00 (0.15)	0.72 -1.36	-0.01 (0.34)	0.00 (0.20)	-0.57 -0.86

compared to mild and severe CLBP. Other factors, like psychosocial issues in CLBP, might also influence local and global pain perception and pain expression (9) and might be related to the initiation and maintenance of physical symptoms. Psychosocial factors may indeed play a role in the difference between RLBP and CLBP. The ability to cope, self-efficacy, social support, sense of control, etc. might help RLBP patients to recover after a pain episode and prevent it from becoming chronic. In RLBP, as far as we know, no extensive studies examined psychosocial factors yet.

The results of cPDT are not different between groups. Similar results were established in an earlier study between HC and patients with chronic whiplash-associated disorders, with differences in cPTT but not in cPDT (34). In the current study, the cuff pressure algometer was unable to detect differences between groups in cPDT, whereas PPT by manual pressure algometer established differences between FM and HC, RLBP and severe CLBP. This inconsistency can be explained by differences in procedure: cPDT is defined as the pressure associated with the first increase on the VAS, while the PPT is defined as the pressure at which the patient indicates a feeling of discomfort. Therefore, the pain intensity at cPDT is probably lower compared to the PPT. Consequently, 2 different constructs are measured by cPDT by cuff algometer and PPT by manual algometer. Cuff pressure algometry was, however, able to reveal differences in cPTT between severe CLBP and RLBP. Therefore, cPTT by the computerized cuff algometer might be a sensitive tool to evaluate secondary hyperalgesia in LBP patients.

Repetitive noxious stimulation at the same intensity, also known as TS, is experienced as increased pain and is a proxy for the level of central sensitization (6). TS is facilitated in FM compared to HC for quadriceps and trapezius, and also compared to RLBP for quadriceps, trapezius, lower back, and hand. These results confirm results in earlier studies (3,40). TS in mild and severe CLBP was more provocative compared to HC and RLBP. However, it was not significant and less provocative compared to FM. As indicated in previous research, a shorter interstimulus interval evokes a higher pain sensation (41). Since the PPT was the lowest in FM, the aimed intensity at which TS is applied, is reached sooner. As a consequence, the interstimulus interval, in theory, is shorter in FM compared to the other groups and might influence the TS result. The applied intensity itself, was of no influence on TS. As a consequence, these results suggest enhanced pain facilitation in CLBP

groups, but not as clearly as in FM. These results should be confirmed in future studies. Conclusively, the results of the present study show clear enhanced TS of pain in FM patients, but could not establish TS in CLBP groups.

Interestingly, although not significant, RLBP in remission demonstrates less TS and a higher mean cPTT compared to HC. Besides, no local hyperalgesia is established in RLBP and TS in RLBP is significantly lower compared to FM. All of these results illustrate a properly working pain processing in RLBP. Possibly, pain processing in RLBP works in a very efficient way, and maybe even more efficient compared to HC. This efficiency might help the participants to recover after every pain episode instead of developing chronicity. In general, little research has been done on pain processing in RLBP. A single study applying pain assessment on female workers with and without RLBP indicated no significant differences in pressure pain thresholds between subjects with RLBP and HC (42) confirming the results of the present study. The results of the current study suggest normal pain sensitivity in the RLBP group.

Besides TS, SS is also an important mechanism to represent altered pain processing (43). Doubling the tissue volume under the cuff evokes pain earlier and faster during constant compression (34, 44). In the present study, lowered cPDT and cPTT is seen when the surface is doubled, indicating SS is working properly. However, no differences are found between groups, as confirmed in earlier research (34). These results indicate no clear enhanced SS in FM or LBP groups, however a larger study is warranted to reconsider these results.

Reduced descending pain inhibition contributes to maintaining pain conditions and are seen in different chronic pain populations (29,45,46). In FM, a deficiency in pain inhibition is well recognized (45,47,48). In the current study, the experienced pain intensity from the test stimulus is decreased when a conditioning stimulus is applied, compared to baseline, although not significantly. This might indicate that the CPM assessment paradigm did not work properly. Possibly, the applied intensity during the baseline measurement might be too weak to elicit pain or likewise the conditioning stimulation was insufficient.

The current study divided the non-specific CLBP group into a mild CLBP and a severe CLBP, based on the amount of pain days in one week. Other criteria may also be appropriate to define both groups and are warranted to subdivide the heterogeneous CLBP group. Future research should look for other parameters characterizing the different CLBP groups more accurately.

By this classification however, a whole spectrum of subjects is created: starting from completely healthy persons, to RLBP suffering from pain episodes altered by pain free episodes, to mild CLBP suffering of LBP for 3-4 days a week, to severe CLBP suffering every day of LBP, and to FM patients who are known to have generalized pain hypersensitivity. This study established differences between RLBP and severe CLBP for cPTT by cuff algometry. By manual pressure algometry, differences were seen between FM and RLBP and severe CLBP, but not with mild CLBP. As a matter of fact, mild CLBP didn't differ from HC or FM for PPT by manual pressure algometer. These results might indicate that mild CLBP floats between the 2 extremes of the spectrum and underline the diversity in pain sensitivity within the LBP population.

The results of the current study must be seen in the light of some statistical limitations. Since this study did not correct for multiple comparison, statistical type-I errors cannot be excluded for the measurements analysed by non-parametric tests. After correction, differences remain for PPT in the quadriceps and trapezius and for cPTT between FM and HC, as well as for PPT in the lower back between FM and RLBP. Also, the lack

of statistical power might influence the results of this study; to detect an expected effect of medium size, only a power of 0.29 was found. As a consequence, true differences between groups might be missed. A larger study exploring pain processing in CLBP patients is therefore needed. For RLBP, results are promising and point in the direction of normal pain processing, but further research is warranted to confirm these results.

CONCLUSION

Generalized hyperalgesia, deep-tissue hypersensitivity, and enhanced pain facilitation was clearly seen in FM. In both mild and severe CLBP, some indications of altered pain processing were evident, although not to the extent of FM patients. The present results also suggest that normal pain sensitivity is observed in RLBP, but future research is needed. In conclusion, we propose that both mild and severe CLBP are situated in a spectrum, somewhere between completely healthy persons, with no altered pain processing and FM patients, which are established to have altered pain processing. Further research should unravel at which extent pain processing deficiencies are present in CLBP.

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