













AUTHOR QUERY FORM

LIPPINCOTT WILLIAMS AND WILKINS

JOURNAL NAME: AJP

ARTICLE NO: CJP_D_20_00527

QUERIES AND / OR REMARKS

QUERY NO.	Details Required	Author's Response
GQ1	Please confirm that givennames (coloured in magenta) and surnames (coloured in blue) have been identified correctly and are presented in the desired order.	
Q1	A running head short title was not supplied; please check if this one is suitable and, if not, please supply a short title of up to 50 characters that can be used instead.	
Q2	The academic degree of all authors except for the author 'Thorvaldur Skuli Palsson' have been retained from the title page of PDF as it was not provided in the manuscript, please confirm if okay.	
Q3	Please check and confirm whether italics removed from Table 4 is okay.	
Q4	Please check as we have removed duplicate reference [10 with 13] was present and references are renumbered.	
Q5	Please provide the volume number and page range for this chapter in reference [14,17,33,44,60].	
Q6	Please provide the journal title for reference [37].	
Q7	If this is not a one-page article please supply the first and last pages in reference [39, 64, 65].	
Q8	Asterisk is present in table 1 footnote but not present in table body, please check and provide.	
Q9	Please check and confirm P, PDT and PTT value placement in table 3 is okay.	
Q10	For all institutions mentioned in the Funding footnote, the location (city and state/country) should be listed. Please provide.	
Q11	As per style degrees will be eg, MD, PhD, MSc, BSc, please check and confirm the degree of author Thorvaldur S. Palsson, Mphty and Thomas Graven-Nielsen, DrMed.	

Pain and Disability in Low Back Pain Can be Reduced Despite No Significant Improvements in Mechanistic Pain Biomarkers

AQ11 **AQ2** Thorvaldur S. Palsson, MphD, PhD,* Steffan W.M. Christensen, PhD,*† Enrico De Martino, PhD,‡ and Thomas Graven-Nielsen, DrMed,‡

Objective: Altered balance in nociception in response to noxious stimuli is commonly reported in chronic low back pain (LBP). However, it is unclear whether an improvement in the clinical presentation is contingent on a reduction in pain sensitivity. This study investigated whether the quantitative sensory testing (QST) profile changes in people undergoing rehabilitation for LBP.

Design: A prospective, observational case-control study.

Methods: Forty males and females, 18 to 40 years' old (20 with LBP) participated in 2 sessions. QST was performed at baseline and after discharge from rehabilitation (LBP) or after 3 to 8 weeks (controls). The QST battery consisted of determining pressure-pain thresholds at the low back and shoulder, temporal summation of pain and conditioned pain modulation. Questionnaire data was used to determine pain (Numeric Rating Scale [NRS]), disability (Roland-Morris Questionnaire [RMQ]), Fear Avoidance Beliefs (FABQ) and The Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ) at baseline and discharge. The treatment effect was determined by calculating the Cohen *d*.

Results: No significant group×time interactions or main factor effect was found for any of the QST measures. The LBP group reported a significant reduction in NRS ($P < 0.0002$, $d = 1.23$), RMQ ($P < 0.0001$, $d = 1.58$), FABQ ($P < 0.001$, $d = 0.87$), and in the ÖMPSQ ($P < 0.00001$, $d = 1.44$).

Conclusions: The results indicate that an improvement of clinical LBP is not contingent upon changes in the pain sensory profile. The value of screening pain sensitivity in LBP patients in primary care, needs to

be investigated further, due to the patient population heterogeneity and the sensitivity of assessment methods.

Key Words: conditioned pain modulation, pressure pain threshold, temporal summation, rehabilitation, pain questionnaires

(*Clin J Pain* 2021;00:000–000)

Low back pain (LBP) is common in modern day society¹ where in the majority of cases, the symptoms cannot be related to any specific underlying cause and are therefore described as nonspecific LBP.² One common feature in chronic nonspecific LBP is that the mechanistic pain biomarkers, such as mechanical and thermal pain sensitivity, seem to be facilitated when compared with healthy, asymptomatic controls.^{3–5} Interestingly, this is also seen in other nonspecific musculoskeletal pain conditions, such as neck pain,^{6,7} shoulder pain,⁸ and tendinopathy.⁹ Collectively, those findings suggest that increased pain sensitivity is part of a transition from acute pain, toward ongoing symptoms and that recovery may perhaps be contingent on the normalization of the pain sensory profile.

Pain sensitivity can be assessed in different ways, e.g. by assessing pressure pain thresholds (PPTs), as well as general pain detection and tolerance thresholds.¹⁰ Moreover, it is possible to determine the function of pronociceptive and anti-nociceptive mechanisms by way of assessing the response to repeated painful stimuli (temporal summation of pain, TSP) and conditioned pain modulation.¹¹ Previously, it has been demonstrated that by surgically removing or reducing nociceptive activity in peripheral structures, positive changes of the mechanistic pain biomarkers are found (eg, normalization of widespread hypersensitivity, TSP, and conditioned pain modulation).¹² An important factor is, however, that the pain hypersensitivity (extent and distribution) seems to increase with longer duration and higher pain intensity in the area of the original painful area.¹⁰ Removing the locus of nociceptive activity in chronic LBP, may be challenging, considering the nonspecific nature of the condition. Moreover, such an approach would not account for the multidimensional nature of chronic pain where, for example, emotional, psychological, and social aspects also play an important role in the pathogenesis.¹³

It is recommended that interventions, aimed at reducing pain and improving function in chronic LBP, are patient-centered and focus on advice, exercise and addressing the patient's thought processes, related to the pain condition.¹⁴ This can be puzzling, as the management

Received for publication September 11, 2020; revised December 22, 2020; accepted January 28, 2021.

From the *Department of Health Science and Technology; †Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Aalborg University, Aalborg; and ‡Department of Physiotherapy, University College of Northern Denmark, Hjørring, Denmark.

T.S.P. is supported by the Danish Rheumatism Association. Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Nocitech (pressure algometry) is partly owned by Aalborg University. S.W.M.C. is supported by the Fund for Research, Quality and Education in Physiotherapy Practice (Fysioterapipraksisfonden) and the Lundbeck Foundation for Health Care Research. The remaining authors declare no conflict of interest.

Reprints: Thorvaldur S. Palsson, MphD, PhD, Department of Health Science and Technology, Aalborg University, Faculty of Medicine, Aalborg University, Fredrik Bajers Vej 7D3, Aalborg E 9220, Denmark (e-mail: tsp@hst.aau.dk).

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.clinicalpain.com.

Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/AJP.0000000000000927

1 strategies need to be individually tailored to the patient, and
 3 address factors that may be difficult to quantify such as
 5 unhelpful thoughts and beliefs, as well as identifying
 7 movement patterns and postures that aggravate pain. A part
 9 of the management will then often consist of functionally
 11 challenging and individually tailored activities. It has been
 13 demonstrated that implementing such a multifaceted inter-
 15 vention, has a superior effect when compared to standard
 17 care in the short-term and long-term.¹⁵

11 The aim of the study was to evaluate how and if the
 13 mechanistic pain profile changes in relation to rehabil-
 15 itation. The overall hypotheses were that (1) increased pain
 17 sensitivity seen in participants with chronic LBP would be
 19 reduced/reversed with successful rehabilitation, as measured
 21 in reduced pain and improved function. Moreover, (2) an
 23 association between the change in pain sensitivity and
 25 changes in pain and function was expected.

METHODS

Participants

23 Individuals, in the age range 18 to 40 years, were
 25 recruited through social media, as well as through fliers at
 27 the university campus. People, with a current, chronic, non-
 29 specific LBP, lasting more than 12 weeks, were included.¹⁶
 31 Previous history of treatment for the pain condition was not
 33 an exclusion criterion but any previous treatment and effect
 35 hereof was noted at baseline. A maximum length of
 37 60 months (5 y) with pain was set to limit the potential
 39 spread in pain duration, which may increase the sensitivity
 41 of mechanistic pain biomarkers.¹⁷ Healthy people, whose
 43 age and sex matched to the LBP group, were recruited as
 45 controls. Participants were recruited into the LBP group if
 47 their pain was limited to the area between the posterior
 49 superior iliac spine and the thoracolumbal junction. Partic-
 51 ipants were excluded from the study if their pain was
 caused by a confirmed, specific pathology (eg, spinal
 stenosis, fracture or cancer), had signs of nerve root com-
 pression causing radicular pain, had multiple pain sites in
 areas unrelated to the back (eg, chronic headache, shoulder
 or knee pain), any previous spinal surgery, were pregnant or
 had any systemic diseases. Any habitual use of over-the-
 counter pain medication for the participants in the LBP
 group was noted at inclusion, but not used as an exclusion
 criterion. The healthy control participants were recruited on
 the premise that they were free from any pain, specific to the
 back and/or in general, and had no history of any on-going
 pain defined as pain lasting more than 3 months. For both
 groups, participants were only included if they were naïve to
 the testing procedure.

53 The group size was estimated with Gpower 3.1.9.4
 55 (Kiel University, Germany), by using data from Blumenstiel
 57 et al,⁵ who achieved an effect size of 0.81 when comparing
 59 low back pressure-pain thresholds (PPTs) between chronic
 61 back pain patients and controls. To acquire the desired
 63 power of 0.8 and an α level of 0.05, 20 people were required
 65 for each group (LBP and control). To account for potential
 dropouts and missing data, additional 5 individuals were
 recruited for each group. Participants received a written and
 oral description of the study, before giving their informed
 consent. The protocol was registered on clinicaltrials.gov
 (NCT03748849), conducted in accordance with the Helsinki
 Declaration and approved by the regional Ethics Committee
 (N-20150048).

Experimental Protocol

67 The study was single blinded, and had a prospective,
 69 case-control design. All participants went through 2 exper-
 71 imental sessions, where the pressure pain sensitivity, TSP,
 73 and conditioning pain modulation (CPM) were assessed.
 75 The assessor (E.D.M.) was blinded to group allocation. For
 77 the LBP group, sessions were at baseline and after discharge
 79 from treatment. For the control group, the period between
 81 the 2 sessions was randomized with a roll of a dice (3 to
 83 8 wk) to maintain the blinding of the assessor. First, the
 85 sensitivity to pressure was assessed at 3 body sites, by PPTs.
 87 Next, cuff pressure algometry was used to determine cuff
 89 pressure pain sensitivity, TSP, and to assess the effectiveness
 91 of endogenous pain inhibition by a CPM paradigm. The
 93 study's hypotheses were not revealed to any of the partic-
 95 ipants until all data had been collected.

87 Following measurements at baseline and at discharge,
 89 participants were asked to fill out questionnaires regarding
 91 the levels of disability, fear avoidance behavior, and psy-
 93 chosocial aspects related to pain (LBP group only). These
 95 were completed at baseline and then again at discharge from
 97 the study. Furthermore, all participants were sent an auto-
 99 mated text message once a week, where they were asked to
 101 indicate their average back pain intensity for that week
 103 using a numeric rating scale (NRS, 0 to 10, with 0 defining
 105 no pain and 10 indicated worst pain imaginable). This was
 107 done for monitoring purposes (LBP group) and for screen-
 109 ing purposes (control group) to ensure that participants in
 the control group did not develop LBP after inclusion. All
 questionnaire data and text messages were automatically
 sent to the participants once they were enrolled in the study
 using SmartTrial (SmartTrial, Version 2.6, Medei ApS,
 Aalborg, Denmark). In case a participant did not respond to
 these messages, computer generated reminders were sent
 until the questionnaires had been completed. If the partic-
 ipant did not respond to the reminders, the clinicians could
 contact the respective individual and ask him/her to fill out
 the questionnaires. For blinding purposes, all questionnaire
 data and text messages were kept concealed to the research
 group until all participants in both groups had been through
 the 2 experimental sessions.

Questionnaire Data

109 The Fear Avoidance Beliefs Questionnaire (FABQ)
 111 aims to assess how beliefs about how physical activity and
 113 work may affect symptoms amongst LBP patient.¹⁸ The
 115 questionnaire consists of 16 items, each with the option of
 scoring between 0 and 6 where higher scores will indicate
 greater levels of fear and avoidance beliefs.

117 The Roland Morris Disability Questionnaire (RMDQ)
 119 is designed to assess self-perceived physical disability related
 121 to LBP.¹⁹ The questionnaire consists of 24 statements
 123 relating to functional limitations the respondent has on the
 day of filling out the questionnaire. It works by binary
 responses as the respondent marks only the statements that
 apply. The total number of marked statements can range
 from 0 to 24, where greater levels of disability are reflected
 by higher scores.

125 The Örebro Musculoskeletal Pain Screening Ques-
 127 tionnaire (ÖMPSQ) consists of 20 questions answered by
 129 providing a Likert scale score (0 to 10). The questionnaire
 has been used to screen for the risk of future sick-leave as a
 result of an acute soft tissue injury.^{20,21} A score over 130 has
 been shown to predict for a high-risk of future disability,

1 while moderate to low risk is reflected in scores 105 to 130
2 and below 105, respectively.²²

3 Pressure Pain Sensitivity

5 Assessment of PPTs was done at 5 sites on the back
6 and marked for multiple assessments: (1) 2 cm lateral to the
7 spinous process of L5 (bilateral), (2) 2 cm lateral to the
8 spinous process of L1 (bilateral), and (3) at the infraspinatus
9 muscle (dominant side). The test side was the pain dominant
10 side in CLBP group. In case both sides were affected or
11 unaffected (control group), the dominant side was defined as
12 the test side. The infraspinatus site was identified by locating
13 the intersection between a line lying perpendicular from the
14 medial border of the scapula and a line connecting the
15 middle part of the spine of scapula with the inferior angle of
16 scapula. A handheld pressure algometer (Algometer,
17 Somedic, Sweden) with a 1 cm² probe (covered by a dis-
18 posable latex sheath) was used to apply increasing pressure
19 with a ramp of 30 kPa/s. The PPT was defined to each
20 participant as the moment where the pressure first became
21 painful. Here, the participant pressed a button that stopped
22 the pressure stimulation. Three individual PPTs were
23 acquired at each site with a minimum 30 seconds between
24 assessments. The average of measurements on each side (low
25 back sites) as well as across repetitions at the infraspinatus
26 site, were extracted for statistical analysis.

27 Cuff Pain Detection and Tolerance Thresholds

29 A cuff algometer (NociTech, Aalborg, Denmark and
30 Aalborg University, Aalborg, Denmark) was used to assess
31 the cuff-pressure pain sensitivity.^{11,23,24} A double-chamber
32 cuff (VBM, Sulz, Germany) was placed on the lower leg,
33 with the upper rim of the cuff level with the upper border of
34 the tibialis anterior muscle. Firstly, the cuff-pressure pain
35 sensitivity was determined on the test leg and subsequently
36 on the contralateral leg, using 2 separate pressure cuffs.
37 During the assessment of cuff-pressure pain sensitivity, both
38 chambers of the cuff were inflated gradually at a rate of
39 1 kPa/s. Participants were instructed to continuously rate the
40 pressure-evoked pain intensity until it became intolerable, at
41 which point they were instructed to press a stop button. This
42 stopped the stimulation and the cuff was deflated immedi-
43 ately. The participant used an electronic visual analogue
44 scale (VAS) to indicate the intensity of pressure-induced
45 pain where 0 cm was defined as “no pain” and 10 cm was
46 anchored with “maximal pain.” The pain detection thresh-
47 old (PDT) was defined as the cuff pressure where the VAS
48 score exceeded 1 cm the first time. The pain tolerance
49 threshold (PTT) was the cuff pressure, where the participant
50 stopped cuff inflation. The PDT and PTT were recorded
51 twice for each leg and the average value used for further
52 analysis. In case the PTT was not reached before reaching
53 the safety limit (100 kPa) of the cuff algometer, the PTT was
54 defined as 100 kPa. The values from the test leg were used
55 to evaluate group differences, changes within session (CPM
56 response) and changes between sessions.

57 TSP and CPM

59 TSP was assessed by applying a series of 1-second long
60 cuff pressure stimuli with a 1-second break in between (10
61 stimuli in total) to the test leg. Between each stimulus, a
62 pressure of 5 kPa was kept to maintain cuff position. For
63 standardizing the target stimulation intensity for the TSP
64 paradigm, each individual's PTT was used. The participant
65 was asked to rate the pain intensity from each stimuli during

the repeated stimulations, using the electronic VAS scale,
without returning to 0 between stimulations. For data
analysis, the VAS data was normalized to the first stimulus
and then the ratio of mean VAS score of the first 4 (VAS-I)
and the last 3 (VAS-III) stimuli was calculated as the tem-
poral summation index (TSP-effect).¹¹ The repeated
stimulation protocol was administered once on the test leg only.

For assessment of the CPM, a tonic painful stimulus
was applied by inflating the double cuff on the nontest leg to
80% of PTT for that leg, in the respective sessions.²⁵ Tonic
pressure was maintained while the PDT and PTT were
determined on the test leg. The CPM-effect was determined
by subtracting unconditioned PDT and PTT values from the
PDT and PTT recorded during conditioning in the same
session and comparing between groups.

81 The Rehabilitation Program

83 Following baseline assessments, participants in the
84 LBP group entered the rehabilitation program under the
85 guidance of 2 clinicians (T.S.P. or S.W.M.C.). Both clini-
86 cians had postgraduate training in musculoskeletal physi-
87 otherapy and several years' experience with managing
88 musculoskeletal pain within the primary sector. The clini-
89 cians were blinded to the outcome of the baseline exper-
90 imental session and questionnaire data. All rehabilitation
91 sessions were free of charge and lasted between 45 and
92 60 minutes. In the beginning, the clinical sessions were held
93 weekly. Later in the program, the intervals between sessions
94 increased depending on how the participants responded to
95 the intervention. The intervention followed contemporary
96 guidelines.^{26,27} It was individualized and pragmatic, fol-
97 lowing the subjective and objective assessment. The findings
98 were explained to the participant and plan for the program
99 was designed, together with the participant. The program
100 plan consisted of exercises, selected on the basis of the
101 functional limitations and personal preferences identified
102 during the assessment. These could be, for example, exer-
103 cises in bending forwards, functional tasks, such as lifting,
104 or ways of altering sitting positions, in order to reduce
105 perceived pain. Attention was paid to the participants'
106 thoughts and beliefs related to performing the task, as these
107 may otherwise limit the effect of the intervention.^{28,29}
108 Although most focus was on individualized exercises,
109 manual therapy was provided if it was considered relevant
110 and was delivered with a contemporary explanation of its
111 effect.^{30,31} The relevance and progression of the chosen
112 intervention was re-evaluated and modified during each
113 follow-up session as needed. The program was stopped
114 when (1) the participant had recovered, (2) no more recov-
115 ery was expected by the clinician, or (3) when the participant
116 wanted to stop. The decision to stop was always made in
117 consensus between the clinician and the patient. In a pre-
118 vious study, using a similar approach,¹⁵ participants got 8
119 sessions during the rehabilitation period. In this study,
120 however, no upper limit was set for number of consultations
121 as long as further improvements were to be expected by
122 continuing.

123 Statistics

125 Parametric data are presented as mean and SD and
126 nonparametric data as median and interquartile range
127 [IQR, 0.25 to 0.75]. Normality of data was assessed by the
128 Shapiro-Wilk test.

129 The questionnaire data (NRS, RMDQ, Örebro, and
130 FABQ) were only administered to the LBP group. Paired

1 samples tests (*t* test or Wilcoxon, pending normality) were
 2 used to compare baseline and discharge scores. In case of
 3 incomplete or missing questionnaire data at discharge, the
 4 baseline score from the respective questionnaire was carried
 5 over to the score at discharge. To determine a potential
 6 treatment effect, the effect size for all questionnaire data was
 7 calculated.

8 Pressure pain thresholds were analyzed, using a mixed
 9 model analysis of variance (ANOVA) with *time* (baseline
 10 and discharge) × *sites* (low back and shoulder), set as
 11 repeated factors while *group* (LBP and controls) were set as
 12 a between-group factor. For PDT, PTT, TSP-effect, and
 13 CPM-effect a mixed model ANOVA was used, with *time* as
 14 a repeated factor and *group* as a between-group factor.

15 Associations between significant group differences were
 16 assessed by calculating the Pearson correlation coefficient or
 17 Spearman rank correlation coefficient. Considering that sex
 18 differences exist in healthy populations, for measures of
 19 peripheral and central pain sensitivity,³² additional analyses
 20 were performed, where an adjustment was made for sex. All
 21 analyses were corrected for multiple post-hoc comparisons
 22 using either the Newman-Keuls test (parametric data) or a
 23 Bonferroni correction (nonparametric data). A *P*-value
 24 below 0.05 was considered to reflect a significant difference
 25 or association.

27 **RESULTS**

29 **Participants**

31 Eighty potential participants with LBP were screened
 32 for eligibility, of which 55 were excluded as they failed to
 33 meet the inclusion criteria. The main reasons for exclusion
 34 were age (above 40 y) and too long duration of pain (more
 35 than 5 y). Additional 5 participants (all females) were
 36 excluded, after they had started in the study (see Fig. 1 for
 37 further details). Data from the 5 women were removed
 38 before data analysis. For the control group, there were no
 39 drop-outs and a full data set was available from all partic-
 40 ipants. Therefore, a full data set (baseline and discharge)
 41 from 20 participants with LBP and 20 controls was available
 42 for data analysis. For a demographic description of the
 43 participants, see Table 1. Out of the 20 participants in the

TABLE 1. Demographic Description of the Study Participants and the Mean (±SD) of All Psychometric Variables Measured at Baseline and Discharge Sessions in the Low Back Pain Group (N = 20) and the Control Group (N = 20)

	Control Group (N = 20)	Low Back Pain Group (N = 20)
Age (y)	27.9 ± 5.9	27.4 ± 6.5
Sex (male/females)	10/10	12/8
Occupation	University student (n = 13) IT support (n = 1) Social worker (n = 1) Daycare institution (n = 1) Registered nurse (n = 1) University lecturer (n = 2) Physiotherapist (n = 1)	University student (n = 9) Office worker (n = 3) Daycare institution (n = 1) School teacher (n = 1) Sales and marketing (n = 3) Warehouse (n = 2) Unemployed (n = 1)
Duration of back pain (y)	NA	2.1 ± 1.5
Pain intensity (NRS, 0-10)	NA	4.5 ± 2.3
RMDQ (0-24)	NA	6.8 ± 3.7
ÖMPQ (0-210)	NA	88.4 ± 23.0
FABQ (0-42)	NA	27.2 ± 15.0

44 Values for low back pain intensity (NRS), RMDQ, FABQ, and ÖMPSQ
 45 are shown for the low back pain group only.

46 *Indicates a change > 0.05.

47 FABQ indicates Fear-Avoidance Beliefs Questionnaire; NA, not appli-
 48 cable; NRS, Numeric Rating Scale; ÖMPSQ, Örebro Musculoskeletal Pain
 49 Questionnaire; RMDQ, Roland-Morris Disability Questionnaire.

50 LBP group, only 4 had not sought any care for their condi-
 51 tion (Supplementary material, Appendix i, Supplemental
 52 Digital Content 1, <http://links.lww.com/CJP/A736>). Two of
 53 the participants took prescription medication (paracetamol
 54 500 mg) on a regular basis (4 × 1 g/d) at inclusion; 1 male
 55 and 1 female. Inspection of their QST measures showed that
 56 the data were comparable with the group mean at both
 57 baseline and discharge and were therefore included in all

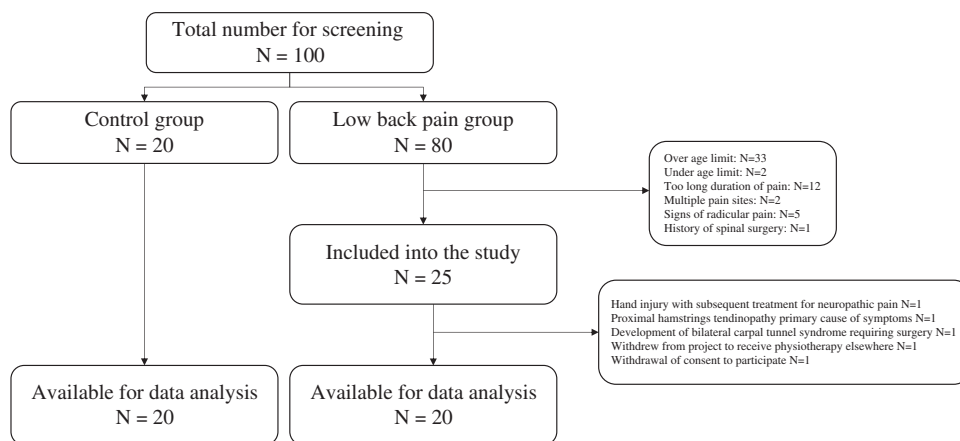


FIGURE 1. A Consort flow diagram demonstrating the screening process for the low back pain (LBP) group. A hundred individuals were screened for eligibility; 20 in the control group and 80 in the LBP group. Twenty-five participants were finally included in the LBP. Five female participants dropped out of the study before finishing the rehabilitation program leaving 20 participants that were included in the LBP group. The 20 matched participants were recruited for the control group.

TABLE 2. The Effect of Treatment in the LBP Group (N=20), Mean (\pm SD), Percentage (%) Change and Effect Size of All Psychometric Variables Measured at Baseline and at Discharge

Low Back Pain Group (N = 20)				
	Baseline Value	Discharge Value	Percentage Change	Effect Size (Cohen <i>d</i>)
Pain intensity (NRS, 0-10)	4.5 \pm 2.3	1.8 \pm 1.8*	62	1.23
RMDQ (0-24)	6.8 \pm 3.7	1.7 \pm 2.3*	76	1.61
ÖMPQ (0-210)	88.4 \pm 23.0	56.9 \pm 30.7*	38	1.44
FABQ (0-42)	27.2 \pm 15.0	17.3 \pm 14.5*	31	0.87

Values for low back pain intensity (NRS), RMDQ, FABQ and ÖMPSQ. *Indicates a change > 0.05.
FABQ indicates Fear-Avoidance Beliefs Questionnaire; NRS, Numeric Rating Scale; ÖMPSQ, Örebro Musculoskeletal Pain Questionnaire; RMDQ, Roland-Morris Disability Questionnaire.

data analyses. The remaining participants used over-the-counter pain medication as needed (paracetamol: n=4), in combination with ibuprofen (combination of paracetamol and ibuprofen: n=7). The remaining participants (n=7) took no pain medication for their back pain. The participants in the LBP group had 5 clinical sessions [IQR 4 to 8] spread over a median of 100.5 days [IQR 82.5 to 119]. The interventions consisted mainly of patient education and home exercises that were adapted to functional limitations, physical capacity and personal preferences. In some cases, manual therapy was used as part of the management strategy.

Questionnaire Data

For the LBP group, a significant improvement (Table 2) was found in pain NRS scores (Wilcoxon: $Z=3.72$, $P<0.0002$), disability (Wilcoxon: $Z=3.8$, $P<0.0001$), FABQ (t test: $t_{(18)}=4.0$, $P<0.001$), and ÖMPSQ (t test: $t_{(18)}=6.2$, $P<0.00001$).

Pressure Pain Sensitivity, PDT and PTT

The mixed model ANOVA on PPTs demonstrated no $group \times time \times sites$ interactions (ANOVA: $F_{2,76}=1.90$, $P<0.16$, Table 3). No significant main factor effects were seen.

For cuff PDT, the mixed model ANOVA demonstrated no $group \times time$ interaction (ANOVA: $F_{1,76}=5.70$, $P<0.31$, Table 3) or a main factor effect. Similarly, no $group \times time$ interaction was found for PTT (ANOVA: $F_{1,37}=0.01$, $P<0.78$, Table 3) or a main factor effect.

A post-hoc power calculation showed that the achieved power was considerably lower (6.6%) than the expected 80% power we had anticipated in our a priori power calculations for PPT values at the low back.

TSP and CPM

For the TSP-effect, the mixed model ANOVA showed no $group \times time$ interaction (ANOVA: $F_{1,34}=0.80$, $P<0.39$, Table 3) or a main factor effect.

For the CPM-effect, the mixed model ANOVA showed no indication of $group \times time$ interactions for PDT (ANOVA: $F_{1,36}=0.41$, $P<0.6$) or PTT (ANOVA: $F_{1,36}=0.68$, $P<0.2$, Table 3). Likewise, no main factor effect was found for the CPM-effect for PDT or PTT.

TABLE 3. Mean (\pm SD) Baseline and Discharge Measures for Pressure Pain Thresholds (PPT), the Effect of Conditioned Pain Modulation (CPM-effect) on Pain Detection Thresholds (PDT), Pain Tolerance Thresholds (PTT), and Temporal Summation of Pain Effect (TSP-effect)

	Low Back Pain Group (N = 20)	Control Group (N = 20)	Analysis of Variance, <i>P</i>
PPT (kPa) baseline			
L5	527.6 \pm 276.0	522.4 \pm 254.4	<0.2
L1	563.3 \pm 234.0	560.9 \pm 252.5	
Infraspinatus	412.2 \pm 185.1	392.8 \pm 149.3	
PPT (kPa) discharge			
L5	562.4 \pm 294.4	535.5 \pm 226.2	
L1	601.8 \pm 304.7	555.5 \pm 258.4	
Infraspinatus	374.1 \pm 189.9	388.4 \pm 200.2	
Cuff pressure (kPa) baseline			
PDT	28.9 \pm 9.4	31.9 \pm 16.8	<0.3
PTT	79.5 \pm 22.8	71.0 \pm 24.1	<0.8
Cuff pressure (kPa) discharge			
PDT	33.6 \pm 13.5	33.26 \pm 17.1	
PTT	77.4 \pm 22.5	70.1 \pm 23.0	
% change in cuff pressure at baseline CPM response			
PDT	45.5 \pm 75.3	31.0 \pm 31.5	<0.4
PTT	11.1 \pm 19.7	11.04 \pm 10.8	<0.3
% change in cuff pressure at discharge CPM response			
PDT	16.8 \pm 30.7	20.4 \pm 32.3	
PTT	9.7 \pm 15.2	16.4 \pm 19.3	
Temporal summation index baseline (cm)	1.90 \pm 1.60	1.20 \pm 1.62	<0.4
Temporal summation index discharge (cm)	1.87 \pm 1.61	1.18 \pm 1.61	

Correlation

A correlation analysis showed no significant associations between changes in any of the variables (Table 4).

DISCUSSION

This is the first study to investigate whether pain sensitivity in people with chronic LBP changes with reduced pain and disability in primary care. Although a significant

TABLE 4. Correlation Analysis (Spearman ρ [S] or Pearson Correlation Coefficient [P]) Showing Associations Between the Variables Pain (Numeric Rating Scale [NRS]), Disability (Roland-Morris Disability Questionnaire [RMDQ]), Fear Avoidance Beliefs (FABQ), and Signs of Yellow Flags (Örebro Musculoskeletal Pain Questionnaire, [ÖMPSQ])

	NRS	RMDQ	FABQ	ÖMPSQ
NRS		0.112 ^P $P<0.65$	0.004 ^S $P<0.99$	0.241 ^P $P<0.32$
RMDQ	0.112 ^P $P<0.65$		0.525 ^S $P<0.84$	0.074 ^P $P<0.76$
FABQ	0.004 ^S $P<0.99$	0.525 ^S $P<0.84$		0.302 ^S $P<0.21$
ÖMPSQ	0.241 ^P $P<0.32$	0.074 ^P $P<0.76$	0.302 ^S $P<0.21$	

The strength of the association between each variable is shown along with the *P*-value (shown below the correlation).

1 reduction in pain and disability were demonstrated, the pain
2 sensitivity and central pain mechanisms were not different at
3 baseline and did not change after completing rehabilitation.

5 A Successful Rehabilitation Strategy

7 A significant improvement was found in pain and function
8 in the LBP group with large effect sizes similar to what
9 has been demonstrated previously when employing a patient-
10 centered approach to managing LBP.^{15,33} Moreover, the
11 improvement in pain and disability were noticeably better than
12 what is considered clinically meaningful.^{34,35} However, these
13 improvements were not aligned with changes in pain sensitivity
14 similar to recent findings by Vaegter et al.³⁶

15 Arguably, the initial symptoms, experienced immediately
16 after the onset of clinical LBP, could reflect tissue injury.
17 However, recovery is not contingent upon the injured struc-
18 tures, reverting to normal or in fact being fully intact.^{37,38} The
19 clinical trajectories of LBP after the initial onset vary from
20 “full recovery” to “fluctuating” to “persistent,”³⁹ where par-
21 ticipants entering this study seemingly belonged to either of the
22 last 2 categories. Acute back pain is known to result in tran-
23 sient changes in motor control, often manifested as increased
24 trunk stiffness.⁴⁰ Despite the protective benefits of decreased
25 movement in the short-term, this may in the long-run become
26 the main catalyst to the pain condition, when tissue recovery
27 has run its course.^{41,42} Based on the inclusion criteria in this
28 study, the assessment methods used and the fact that changes
29 in motor strategies, in response to back pain, vary between
30 individuals,⁴³ it is not possible to determine whether the
31 functional improvements, seen here, can be attributed to
32 changes in tissue loading. Nevertheless, employing a strategy
33 aimed at modifying the patients’ current movement strategy,
34 may be sufficient to change spinal loading and thereby
35 reducing pain.

36 Chronic LBP manifests itself in numerous ways, where
37 patients demonstrate both pro-nociceptive and anti-
38 nociceptive characteristics, as well as psychometric variables
39 and movement patterns being affected in various ways.^{44,45}
40 In that regard, cognitive and emotional factors seem to have
41 a mediating role in the clinical course of LBP.^{37,46,47} This is
42 supported by qualitative findings that indicate, that a suc-
43 cessful outcome in back pain rehabilitation, is related to
44 changes in pain-related beliefs and achieving more inde-
45 pendence in terms of self-managing the pain condition.²⁸ In
46 the present study, the participants reported a significant
47 reduction in fear-avoidance behavior and psychosocial fac-
48 tors, related to their pain condition, in parallel with
49 improvements in pain and function. Nevertheless, no asso-
50 ciations were found between any of the factors where sig-
51 nificant improvements occurred, indicating that although
52 these factors are present, an improvement in one is not
53 contingent on an improvement in the other. The current
54 findings likely reflect the complicated nature of LBP, where
55 multiple domains may contribute to the pain experience to
56 various degrees across patients.

57 Pain Sensitivity in Chronic LBP

58 Interestingly, no baseline differences were found between
59 the groups. Although this has been described before,⁴⁸ it con-
60 trasts the findings of many other studies that have compared
61 people with chronic LBP and controls,^{3,5,49,50} where both local
62 and widespread hyperalgesia was demonstrated. These dis-
63 crepancies in localized and widespread pain hyperalgesia, may
64 be due to several factors. The pain-related functional inter-
65 ference demonstrated in the present study (6.8/24) could be

67 considered moderate^{51,52} and was lower than reported by, for
68 example, Imamura et al⁵³ (12.4/24) in chronic LBP. Even
69 though patients in the current study reported average pain levels
70 above what is considered clinically meaningful to patients (4.5/
71 10),⁵⁴ the pain was lower than what has been seen in other
72 studies assessing pain sensitivity in LBP populations, for
73 example, Vaegter et al (7.7/10),³⁶ Giesecke et al (6.2/10),⁴ Ima-
74 mura et al (6.8/10),⁵³ Mlekusch et al (5.1/10).⁵⁰

75 In the recent findings of Vaegter et al,³⁶ who included
76 people with chronic musculoskeletal pain, with back pain
77 being their main complaint, the PPTs at the low back were
78 considerably lower (221 ± 109.4 kPa) than reported here
79 (527.6 ± 276.0 kPa). Moreover, Blumenstiel et al⁵ (3/10) also
80 demonstrated significantly lower PPTs compared with con-
81 trols. In these 2 studies, it is important to note that the
82 participants were older than here (52.4 and 43.4 y, respec-
83 tively) and had lived with their pain for longer than the
84 participants in this study (14.5 and 15.9 y, respectively).
85 Previously, a conceptual model has been suggested, where
86 an extended duration of pain results in increased sensitivity
87 of central pain mechanisms.¹⁰ Likewise, pain sensitivity
88 increases with age.⁵⁵ It is therefore possible, that baseline
89 differences could not be identified due to the relatively
90 young age (27.4 y) and short duration of pain (2.1 y) of
91 participants in this study.

92 TSP was not different between the groups in the present
93 study at baseline, in contrast to previous findings.⁵⁶⁻⁵⁸ In line
94 with the current findings, Mlekusch et al⁵⁰ found no significant
95 differences in the magnitude of the CPM-effect between their
96 chronic LBP patients and controls. In fact, it has been suggested
97 that endogenous pain inhibition is not deficient in chronic
98 LBP.⁵⁹ A recent large systematic review¹⁷ demonstrated that
99 there is facilitated response to repeated nociceptive stimuli and a
100 reduced efficiency of the CPM response in chronic LBP, and
101 that these changes in pro-nociceptive and anti-nociceptive
102 processing were dependent upon the severity and duration of the
103 pain condition. Although the participants in the LBP group
104 fulfilled all the criteria for the diagnosis of chronic LBP,¹⁶ an
105 upper limit of 5 years was set as inclusion criteria to reduce the
106 heterogeneity in the LBP group. This may have resulted in the
107 participants in this study having shorter average duration of
108 pain (average of 2.1 y) compared with, for example, Imamura
109 et al⁵³ (4.1 y), Giesecke et al⁴ (4.5 y), Mlekusch et al⁵⁰ (7 y), and
110 Blumenstiel et al⁵ (15.9 y). Taken together, the difference in
111 duration of symptoms and the age of participants between the
112 different studies, may have contributed to the lack of baseline
113 differences in the current study.

115 Potential Implications

116 The management strategy used in this study is in line
117 with recent recommendations^{26,27} and it is positive that the
118 intervention significantly improved pain, disability, and
119 pain-related cognitive factors. It is, however, not possible to
120 determine the lasting effect of the intervention, even though
121 long-lasting positive effects have been noted from a com-
122 parable intervention elsewhere.^{15,36,60}

123 The participants in this study reported lower pain and
124 disability levels and shorter duration of pain than many
125 other studies. Nevertheless, the majority of participants
126 (16/20) had previously sought treatment for their condition,
127 with little or no success. Therefore, although the severity
128 profile might indicate that many of the participants only had
129 mild to moderate pain, it seemed to be meaningful enough
130 for them to seek treatment.

The small sample size makes it difficult to fully evaluate how and if an assessment of pain sensitivity in clinical practice is relevant for the target group in this study. This is especially important to consider, as it is likely that individuals comparable to those included in the LBP group had pro-nociceptive characteristics.^{17,61} A larger sample could potentially have revealed clusters with some patient characteristics demonstrating pro-nociceptive mechanisms in the pain system. An investigation of whether such information can inform the clinical decision-making and improve the outcome, is clearly warranted. However, considering the large individual variability as demonstrated in this study (Table 3) and elsewhere (see McPhee et al¹⁷ for an overview), it is questionable whether screening for pain hypersensitivity can be used to guide treatment.

Limitations and Methodological Considerations

The management strategy used here, was not standardized, but instead focused on what was considered the underlying driver for each individual's pain condition. Although this approach mimics standard procedures in clinical practice, and has been used in previous studies,^{36,62} it introduces a risk of improvement being related with the dosage of attention the participants got. The study, however, aimed at investigating potential relationships between the subjective experience of pain and disability on one side and pain sensitivity on the other. Addressing individual characteristics, including functional limitations, unhelpful thought processes and movement strategies is considered important in the management of chronic LBP.¹⁴ For this reason, the management approach was adapted to the individual patient rather than using a standardized intervention.

In previous studies, targeted and efficient management of the nociceptive drive (e.g. total knee replacement in osteoarthritis) resulted in improved anti-nociceptive and pro-nociceptive mechanisms.⁶³ The relative proportion of attention-related improvement in this current study is unknown, but it may affect the actual peripheral nociceptive drive via, for example, changes in tonic muscle activity. This is, however, only speculative and needs to be investigated further.

The clinicians in this study (T.S.P. and S.W.M.C.) were blinded to all outcome measures (questionnaire data, QST measures and pain data) until end of data collection. Likewise, participants were instructed not to reveal their group allocation to the assessor (E.D.M.) in the experimental session. Despite these preventative measures, it was not possible to eliminate the potential source of bias. For example, the intervention was individually tailored and thereby the clinicians addressed the functional limitations the patient reported. Thereby, the clinicians got an insight into the patient's functional capacity at baseline and over time, even though they were blind to the questionnaire scores. Likewise, for the experimental sessions, it cannot be excluded that the assessor discovered which group they belonged to because of pain-related grimacing or pain when moving around in the laboratory (eg, moving from standing to lying down on the plinth). Nevertheless, as all the QST measurements were controlled by the participants (who pressed indicated pain severity and stop stimulation by the control of a button) who all got the same standardized participant information, this is unlikely to have affected the outcome of the measurements.

Socioeconomic factors, such as level of education, work situation and income, are known to be associated with a greater risk of suffering from long-lasting LBP,^{64,65}

whereas the participants in this study seemingly belonged to the upper end of the socio-economic spectrum, considering their educational status and work situation. For this reason, the relatively low age and short duration of pain, compared with other studies, the participants here might have had a greater chance of experiencing improvement than a cohort with a different composition.

Surprisingly, we did not see a baseline difference between the 2 groups similar to what other studies have shown, where patients with chronic LBP appear to be more sensitive than controls.^{3,5,49,50} However, these findings may relate to the methodological approach where a series of paired tests were run, comparing different sites instead of using a repeated measures ANOVA as done here. A post-hoc power calculation of our study sample showed that the achieved power was considerably lower (6.6%) than the expected 80% power we had anticipated in our a priori power calculations. Based on this calculation, a considerably larger cohort (N = 1184) would have been needed to detect a statistically significant difference in PPT's at the shoulder, to demonstrate signs of widespread hyperalgesia. A post-hoc analysis was likewise run to investigate any potential associations between the changes seen in self-reported outcomes with QST data at baseline. In line with the previous findings of Mlekusch et al,⁶⁶ no such relationships were evident. Another potential reason may relate to the upper limit of pain duration which was set to 5 years. This was done to avoid potential inflation of study findings as a longer duration of back pain is known to be associated with higher levels pain sensitivity.¹⁷ It is, therefore, likely that the low levels of sensitization seen in the LBP group can be attributed to the short duration of symptoms.

It is possible that over-the-counter pain medication may affect the sensitivity of pain mechanisms and thereby the QST measurements performed. For blinding purposes, however, it was neither possible to register whether the participants had taken pain medication on the day of QST measurements, nor whether this affected the outcome.

CONCLUSION

The observed positive effect the individually tailored rehabilitation approach had on pain and disability in people with mild to moderate back pain, did not occur in parallel with changes in the pain sensory profile. A larger sample from a population including people with more severe and longer lasting back pain, is needed to qualify the value of screening for pain hypersensitivity in primary care due to the patient heterogeneity and possible sensitivity of assessment methods.

REFERENCES

1. GBD2017. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*. 2018;392:1789-1858.
2. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet*. 2017;389:736-747.
3. Giesbrecht RJ, Battie MC. A comparison of pressure pain detection thresholds in people with chronic low back pain and volunteers without pain. *Phys Ther*. 2005;85:1085-1092.
4. Giesecke T, Gracely RH, Grant MAB, et al. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis Rheum*. 2004;50:613-623.
5. Blumenstiel K, Gerhardt A, Rolke R, et al. Quantitative sensory testing profiles in chronic back pain are distinct from those in fibromyalgia. *Clin J Pain*. 2011;27:682-690.

1 6. La Touche R, Fernandez-de-Las-Penas C, Fernandez-Carnero
 3 J, et al. Bilateral mechanical-pain sensitivity over the trigeminal
 5 region in patients with chronic mechanical neck pain. *J Pain*.
 7 2010;11:256–263.
 9 7. Christensen SW, Hirata RP, Graven-Nielsen T. Altered pain
 11 sensitivity and axioscapular muscle activity in neck pain
 13 patients compared with healthy controls. *Eur J Pain (London,
 15 England)*. 2017;21:1763–1771.
 17 8. Paul TM, Soo Hoo J, Chae J, et al. Central hypersensitivity in
 19 patients with subacromial impingement syndrome. *Arch Phys
 21 Med Rehabil*. 2012;93:2206–2209.
 23 9. Plinsinga ML, Brink MS, Vicenzino B, et al. Evidence of
 25 nervous system sensitization in commonly presenting and
 27 persistent painful tendinopathies: a systematic review. *J Pain*.
 29 2015;45:864–875.
 31 10. Graven-Nielsen T, Arendt-Nielsen L. Assessment of mechanisms
 33 in localized and widespread musculoskeletal pain. *Nat Rev
 35 Rheumatol*. 2010;6:599–606.
 37 11. Graven-Nielsen T, Vaegter HB, Finocchietti S, et al. Assess-
 39 ment of musculoskeletal pain sensitivity and temporal summation
 41 by cuff pressure algometry: a reliability study. *Pain*. 2015;
 43 156:2193–2202.
 45 12. Graven-Nielsen T, Wodehouse T, Langford RM, et al. Normal-
 47 ization of widespread hyperesthesia and facilitated spatial
 49 summation of deep-tissue pain in knee osteoarthritis patients after
 51 knee replacement. *Arthritis Rheum*. 2012;64:2907–2916.
 53 13. Dworkin RH, Bruehl S, Fillingim RB, et al. multidimensional
 55 diagnostic criteria for chronic pain: introduction to the
 57 ACTTION-American Pain Society Pain Taxonomy (AAPT).
 59 *J Pain*. 2016;17:T1–T9.
 61 14. Foster NE, Anema JR, Cherkin D, et al. Prevention and
 63 treatment of low back pain: evidence, challenges, and promising
 65 directions. *Lancet*. 2018;■:■. [Epub ahead of print].
 15. Vibe Fersum K, O’Sullivan P, Skouen JS, et al. Efficacy of
 classification-based cognitive functional therapy in patients with
 non-specific chronic low back pain: a randomized controlled trial.
Eur J Pain (London, England). 2013;17:916–928.
 16. Airaksinen O, Brox JI, Cedraschi C, et al. Chapter 4. European
 guidelines for the management of chronic nonspecific low back
 pain. *Eur Spine J*. 2006;15(suppl 2):S192–S300.
 17. McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in
 pro-nociceptive and anti-nociceptive mechanisms in patients
 with low back pain: a systematic review with meta-analysis.
Pain. 2019;■:■. 10.1097/j.pain.0000000000001737.
 18. Waddell G, Newton M, Henderson I, et al. A Fear-Avoidance
 Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs
 in chronic low back pain and disability. *Pain*. 1993;52:157–168.
 19. Roland M, Fairbank J. The Roland-Morris Disability Question-
 naire and the Oswestry Disability Questionnaire. *Spine*.
 2000;25:3115–3124.
 20. Linton SJ, Hallden K. Can we screen for problematic back
 pain? A screening questionnaire for predicting outcome in acute
 and subacute back pain. *Clin J Pain*. 1998;14:209–215.
 21. Westman A, Linton SJ, Ohrvik J, et al. Do psychosocial factors
 predict disability and health at a 3-year follow-up for patients
 with non-acute musculoskeletal pain? A validation of the
 Orebro Musculoskeletal Pain Screening Questionnaire. *Eur J
 Pain (London, England)*. 2008;12:641–649.
 22. Linton SJ, Boersma K. Early identification of patients at risk of
 developing a persistent back problem: the predictive validity of
 the Orebro Musculoskeletal Pain Questionnaire. *Clin J Pain*.
 2003;19:80–86.
 23. Vaegter HB, Graven-Nielsen T. Pain modulatory phenotypes
 differentiate subgroups with different clinical and experimental
 pain sensitivity. *Pain*. 2016;157:1480–1488.
 24. Skou ST, Graven-Nielsen T, Rasmussen S, et al. Widespread
 sensitization in patients with chronic pain after revision total
 knee arthroplasty. *Pain*. 2013;154:1588–1594.
 25. Palsson TS, Boudreau SA, Krebs HJ, et al. experimental
 referred pain extends toward previously injured location: an
 explorative study. *J Pain*. 2018;19:1189–1200.
 26. Foster NE, Anema JR, Cherkin D, et al. Prevention and
 treatment of low back pain: evidence, challenges, and promising
 directions. *Lancet (London, England)*. 2018;391:2368–2383.
 27. Stochkendahl MJ, Kjaer P, Hartvigsen J, et al. National
 Clinical Guidelines for non-surgical treatment of patients with
 recent onset low back pain or lumbar radiculopathy. *Eur Spine
 J*. 2018;27:60–75.
 28. Bunzli S, McEvoy S, Dankaerts W, et al. Patient perspectives
 on participation in cognitive functional therapy for chronic low
 back pain. *Phys Ther*. 2016;96:1397–1407.
 29. Bunzli S, Smith A, Schutze R, et al. Making sense of low back pain
 and pain-related fear. *J Orthop Sports Phys Ther*. 2017;47:628–636.
 30. Bialosky JE, Bishop MD, Price DD, et al. The mechanisms of
 manual therapy in the treatment of musculoskeletal pain: A
 comprehensive model. *Man Ther*. 2009;14:531–538.
 31. Rabey M, Hall T, Hebron C, et al. Reconceptualising manual
 therapy skills in contemporary practice. *Musculoskel Sci Pract*.
 2017;29:28–32.
 32. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of
 clinical and experimental findings. *Br J Anaesth*. 2013;111:52–58.
 33. Ussing K, Kjaer P, Smith A, et al. Cognitive functional therapy
 for people with nonspecific persistent low back pain in a
 secondary care setting: a propensity matched, case-control
 feasibility study. *Pain Med (Malden, Mass)*. 2020;■:■.
 34. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome
 measures for chronic pain clinical trials: IMMPACT recom-
 mendations. *Pain*. 2005;113:9–19.
 35. Jordan K, Dunn KM, Lewis M, et al. A minimal clinically
 important difference was derived for the Roland-Morris
 Disability Questionnaire for low back pain. *J Clin Epidemiol*.
 2006;59:45–52.
 36. Vaegter HB, Ussing K, Johansen JV, et al. Improvements in
 clinical pain and experimental pain sensitivity after cognitive
 functional therapy in patients with severe persistent low back
 pain. *Pain Rep*. 2019;5:e802–e802.
 37. Panagopoulos J, Magnusson JS. Prospective comparison of
 changes in lumbar spine MRI findings over time between
 individuals with acute low back pain and controls: an
 exploratory study. ■. 2017;38:1826–1832.
 38. Jarvik JG, Hollingworth W, Heagerty PJ, et al. Three-year
 incidence of low back pain in an initially asymptomatic cohort:
 clinical and imaging risk factors. *Spine*. 2005;30:1541–1548;
 discussion 1549.
 39. Gatchel RJ, Bevers K, Licciardone JC, et al. Transitioning
 from acute to chronic pain: an examination of different
 trajectories of low-back pain. *Healthcare (Basel)*. 2018;6:48.
 40. van Dieen JH, Reeves NP, Kawchuk G, et al. motor control
 changes in low back pain: divergence in presentations and
 mechanisms. *J Orthop Sports Phys Ther*. 2019;49:370–379.
 41. Hodges PW, Tucker K. Moving differently in pain: a new
 theory to explain the adaptation to pain. *Pain*. 2011;152:
 S90–S98.
 42. Hodges PW, Moseley GL. Pain and motor control of the
 lumbopelvic region: effect and possible mechanisms. *J Electro-
 myogr Kinesiol*. 2003;13:361–370.
 43. Hodges PW, Coppiters MW, MacDonald D, et al. New insight
 into motor adaptation to pain revealed by a combination of
 modelling and empirical approaches. *Eur J Pain*. 2013;17:
 1138–1146.
 44. Rabey M, Smith A, Kent P, et al. Chronic low back pain is
 highly individualised: patterns of classification across three
 unidimensional subgrouping analyses. *Scand J Pain*. 2019;■:■.
 45. Ippertiel P, Robbins S, Preuss R. Movement variability in
 adults with low back pain during sit-to-stand-to-sit. *Clin
 Biomech (Bristol, Avon)*. 2018;58:90–95.
 46. Lee H, Hubscher M, Moseley GL, et al. How does pain lead to
 disability? A systematic review and meta-analysis of mediation
 studies in people with back and neck pain. *Pain*. 2015;156:
 988–997.
 47. Marshall PWM, Schabrun S, Knox MF. Physical activity and
 the mediating effect of fear, depression, anxiety, and

- 1 catastrophizing on pain related disability in people with chronic
low back pain. *PLoS One*. 2017;12:e0180788.
- 3 48. O'Neill S, Kjær P, Graven-Nielsen T, et al. Low pressure pain
thresholds are associated with, but does not predispose for, low
5 back pain. *Eur Spine J*. 2011;20:2120–2125.
- 7 49. Farasyn A, Meeusen R. The influence of non-specific low back
pain on pressure pain thresholds and disability. *Eur J Pain*.
2005;9:375–375.
- 9 50. Mlekusch S, Nezirli AY, Limacher A, et al. conditioned pain
modulation in patients with acute and chronic low back pain.
Clin J Pain. 2016;32:116–121.
- 11 51. Hirschfeld G, Zernikow B. Variability of “optimal” cut points
for mild, moderate, and severe pain: neglected problems when
13 comparing groups. *Pain*. 2013;154:154–159.
- 15 52. Oldenmenger WH, de Raaf PJ, de Klerk C, et al. Cut points on
0-10 numeric rating scales for symptoms included in the
Edmonton Symptom Assessment Scale in cancer patients: a
17 systematic review. *J Pain Symptom Manage*. 2013;45:1083–1093.
- 19 53. Imamura M, Chen J, Matsubayashi SR, et al. Changes in
pressure pain threshold in patients with chronic nonspecific low
back pain. *Spine*. 2013;38:2098–2107.
- 21 54. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain
numeric rating scale as a screening test in primary care. *J Gen
Intern Med*. 2007;22:1453–1458.
- 23 55. El Tumi H, Johnson MI, Dantas PBF, et al. Age-related
changes in pain sensitivity in healthy humans: a systematic
25 review with meta-analysis. *Eur J Pain*. 2017;21:955–964.
- 27 56. George SZ, Wittmer VT, Fillingim RB, et al. Fear-avoidance
beliefs and temporal summation of evoked thermal pain
influence self-report of disability in patients with chronic low
back pain. *J Occup Rehabil*. 2006;16:95–108.
- 29 57. Owens MA, Bulls HW, Trost Z, et al. An examination of pain
catastrophizing and endogenous pain modulatory processes in
31 adults with chronic low back pain. *Pain Med*. 2016;17:1452–1464.
58. Vaegter HB, Palsson TS, Graven-Nielsen T. Facilitated
pronociceptive pain mechanisms in radiating back pain
compared with localized back pain. *J Pain*. 2017;18:973–983.
59. Roussel NA, Nijs J, Meeus M, et al. Central sensitization and
altered central pain processing in chronic low back pain: fact or
myth? *Clin J Pain*. 2013;29:625–638.
60. Vibe Fersum K, Smith A, Kvale A, et al. Cognitive functional
therapy in patients with non-specific chronic low back pain—a
randomized controlled trial 3-year follow-up. *Eur J Pain*. 2019;
■:■.
61. Rabey M, Slater H, O'Sullivan P, et al. Somatosensory nociceptive
characteristics differentiate subgroups in people with chronic low
back pain: a cluster analysis. *Pain*. 2015;156:1874–1884.
62. Eklund A, Jensen I, Lohela-Karlsson M, et al. The Nordic
Maintenance Care program: effectiveness of chiropractic
maintenance care versus symptom-guided treatment for recur-
rent and persistent low back pain—a pragmatic randomized
controlled trial. *PLoS One*. 2018;13:e0203029.
63. Petersen KK, Graven-Nielsen T, Simonsen O, et al. Preoper-
ative pain mechanisms assessed by cuff algometry are
associated with chronic postoperative pain relief after total
knee replacement. *Pain*. 2016;157:1400–1406.
64. Dionne CE, Von Korff M, Koepsell TD, et al. Formal
education and back pain: a review. *J Epidemiol Community
Health*. 2001;55:455.
65. Fliesser M, De Witt Huberts J, Wippert P-M. Education, job
position, income or multidimensional indices? Associations
between different socioeconomic status indicators and chronic
low back pain in a German sample: a longitudinal field study.
BMJ Open. 2018;8:e020207.
66. Mlekusch S, Schliessbach J, Cámara RJ, et al. Do central
hypersensitivity and altered pain modulation predict the course
of chronic low back and neck pain? *Clin J Pain*. 2013;29:
673–680.