



## Facilitated pronociceptive pain mechanisms in radiating back pain compared with localized back pain

Vaegter, Henrik Bjarke; Palsson, Thorvaldur Skuli; Graven-Nielsen, Thomas

*Published in:*  
Journal of Pain

*DOI (link to publication from Publisher):*  
[10.1016/j.jpain.2017.03.002](https://doi.org/10.1016/j.jpain.2017.03.002)

*Publication date:*  
2017

*Document Version*  
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*  
Vaegter, H. B., Palsson, T. S., & Graven-Nielsen, T. (2017). Facilitated pronociceptive pain mechanisms in radiating back pain compared with localized back pain. *Journal of Pain, 18*(8), 973-983.  
<https://doi.org/10.1016/j.jpain.2017.03.002>

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

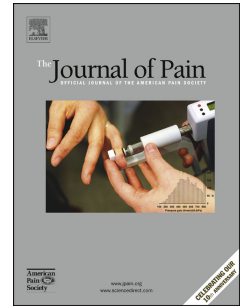
### Take down policy

If you believe that this document breaches copyright please contact us at [vbn@aub.aau.dk](mailto:vbn@aub.aau.dk) providing details, and we will remove access to the work immediately and investigate your claim.

# Accepted Manuscript

Facilitated Pro-Nociceptive Pain Mechanisms in Radiating Back Pain Compared with Localized Back Pain

Henrik Bjarke Vaegter, Thorvaldur Skuli Palsson, Thomas Graven-Nielsen



PII: S1526-5900(17)30516-3

DOI: [10.1016/j.jpain.2017.03.002](https://doi.org/10.1016/j.jpain.2017.03.002)

Reference: YJPAI 3396

To appear in: *Journal of Pain*

Received Date: 7 December 2016

Revised Date: 20 February 2017

Accepted Date: 13 March 2017

Please cite this article as: Vaegter HB, Palsson TS, Graven-Nielsen T, Facilitated Pro-Nociceptive Pain Mechanisms in Radiating Back Pain Compared with Localized Back Pain, *Journal of Pain* (2017), doi: 10.1016/j.jpain.2017.03.002.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## **FACILITATED PRO-NOCICEPTIVE PAIN MECHANISMS IN RADIATING BACK PAIN COMPARED WITH LOCALIZED BACK PAIN**

Henrik Bjarke Vaegter<sup>ab</sup>, Thorvaldur Skuli Palsson<sup>c</sup>, Thomas Graven-Nielsen<sup>c</sup>

<sup>a</sup> *Pain Research Group, Pain Center South, Odense University Hospital, Odense, Denmark*

<sup>b</sup> *Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark*

<sup>c</sup> *Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology,  
Faculty of Medicine, Aalborg University, Aalborg, Denmark*

**Original paper for:** Journal of Pain

**Running title:** Pain profiles in back pain conditions

**Disclosures:** Nocitech is partly owned by Aalborg University. Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). The authors have no conflict of interest.

**Corresponding author:**

Henrik Bjarke Vaegter, PhD

Pain Research Group, Pain Center South, University Hospital Odense

Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark

Heden 9, Indgang 201

DK – 5000 Odense C

Tel.: +45 65413869; fax: +45 65415064.

E-mail address: henrik.bjarke.vaegter@rsyd.dk

**ABSTRACT**

Facilitated pain mechanisms and impaired pain inhibition are often found in chronic pain patients. This study compared clinical pain profiles, pain sensitivity, as well as pro-nociceptive and anti-nociceptive mechanisms in patients with localized low back pain (n=18), localized neck pain (n=17), low back and radiating leg pain (n=18), or neck and radiating arm pain (n=17). It was hypothesized that patients with radiating pain had facilitated pain mechanisms and impaired pain inhibition compared with localized pain patients. Cuff algometry was performed on the non-painful lower leg to assess pressure pain threshold (cPPT), tolerance (cPTT), temporal summation of pain (TSP: increase in pain scores to ten repeated stimulations at cPTT intensity), and conditioning pain modulation (CPM: increase in cPPT during cuff pain conditioning on the contralateral leg). Heat detection (HDT) and heat pain threshold (HPT) at the non-painful hand were also assessed. Clinical pain intensity, psychological distress, and disability were assessed with questionnaires. TSP was increased in patients with radiating back pain compared with localized back pain ( $P<0.03$ ). Patients with radiating arm pain or localized low back pain demonstrated hyperalgesia to heat and pressure in non-painful body areas ( $P<0.05$ ), as well as a facilitated clinical pain profile compared with patients with localized neck pain ( $P=0.03$ ). Patients with radiating pain patterns demonstrated facilitated temporal summation suggesting differences in the underlying pain mechanisms between patients with localized back pain and radiating pain.

**Perspective:** These findings have clinical implications as the underlying mechanisms in different back pain conditions may require different treatment strategies.

**Keywords:** Chronic pain, neck pain, low back pain, pain sensitivity, temporal summation of pain, conditioned pain modulation, cuff algometry

## 1. INTRODUCTION

Chronic musculoskeletal pain, including low back and neck pain, is one of the most severe health problems facing the world today with the costs associated with treatment, sick leave and early retirement comparable to the costs of diabetes and cancer combined [53]. Although the understanding of the pathophysiology underlying chronic musculoskeletal pain has increased significantly over the past decades, it remains a significant clinical problem with few effective therapies [11].

In back pain, degenerative conditions are generally not considered the main cause of symptoms [6] and clinical pain intensity does not correlate well with radiological findings [44]. Recently, sensitization of the central nervous system [20;31] and an imbalance between pro-nociceptive and anti-nociceptive pain mechanisms with amplification of nociceptive signals have been proposed to contribute to the magnitude of clinical symptoms in degenerative musculoskeletal conditions [3;55]. However, research comparing such pain mechanisms in different back pain conditions is sparse. For this purpose, quantification of pain sensitivity and the function of pain modulatory mechanisms may be beneficial [3]. Various modalities, including heat and pressure stimuli can be employed to assess both the sensitivity locally or remote from the pain areas [39], as well as central pain mechanisms including temporal summation of pain (TSP, pro-nociceptive mechanism) [26] and conditioned pain modulation (CPM, anti-nociceptive mechanism) [54]. TSP and CPM are considered to reflect processing of nociceptive signals within the central nervous system; TSP at the dorsal horn neurons at the level of the incoming afferents [2] and CPM at brainstem level [27]. TSP can be reliably assessed in humans by repetitive painful pressure stimulations with identical intensities [17], and is characterized by an increase in subjective pain ratings. Previous studies have demonstrated facilitated TSP in chronic pain patients with local [20;21], and widespread pain conditions [42]. CPM however, is frequently demonstrated as an increase in e.g. pressure pain thresholds at one limb during a painful conditioning stimulus applied on a contralateral limb [35;36]. Reduced CPM has been seen in several chronic pain conditions across pain distribution [16] but patients with larger pain areas seem to demonstrate facilitated TSP [16] and a reduced CPM effect [47]. TSP and CPM may reflect different central pain mechanisms that co-exist in parallel [47], however assessment of TSP and CPM may also indicate the net-effect of central nociceptive processing.

To date, comparison of pain sensitivity and pro-nociceptive and anti-nociceptive pain mechanisms between different back pain conditions with different spatial pain distribution is sparse.

It is therefore not known whether there are differences in the pain sensory profile in patients with localized low back and neck pain, and whether such differences are related to the distance from the assessment sites (e.g. leg and hand) to the painful areas. Moreover, it is unknown whether these are different from back pain conditions with additional radiating pain into the extremities. Increased knowledge regarding this may provide clinicians with an understanding of which factors contribute to the pain condition and thereby potentially be used to guide treatment interventions.

The aim of this study was to investigate the clinical pain profile, pain sensitivity, as well as pro-nociceptive and anti-nociceptive mechanisms in patients 1) with localized chronic back pain at different locations (low back pain compared with neck pain), and 2) with and without radiating pain. Based on previous findings [47], it was hypothesized that patients with radiating back (low back and neck) pain had a facilitated TSP response and a reduced CPM response compared with those with back pain only. Moreover, based on the distance between the pain sensitivity assessment sites (leg and hand) and the painful areas, it was hypothesized that patients with localized low back pain had greater pain sensitivity at the leg compared with localized neck pain and vice versa.

## **2. MATERIALS AND METHODS**

### *2.1 Subjects*

In total, 70 chronic back pain patients (mean age: 48.0 years [range: 20-86]; 43 women) were included in this cross-sectional study after referral to an interdisciplinary pain treatment at a university hospital pain clinic due to neck (n = 34) or low back pain (n = 36). Inclusion criteria were men and women at least 18 years old, chronic nonmalignant pain for minimum 6 months, and patients should speak and understand Danish to ensure they understood the information about the pain testing procedures. Exclusion criterion was pregnancy. Patients were further sub-grouped based on pain distribution into neck pain (pain in the neck without pain referral into the arm or thoracic spine; n = 17), cervical radiating pain (pain in the neck and pain in the right arm below the elbow; n = 17), low back pain (pain in the lower back without pain referral into the legs or thoracic spine; n = 18), or low back radiating pain (pain in the low back and pain in the right leg below the knee; n = 18). No further assessment was performed to confirm the presence of true radiculopathy (MRI, test of muscle strength or reflexes). All patients completed a body chart (pain drawing) indicating their pain areas prior to inclusion. If pain was distributed outside the abovementioned areas patients were not included in this study.

The study was conducted in accordance with the Helsinki Declaration and approved by the local ethical committee (S-20140010). All patients provided written informed consent prior to entering the study. Approximately half of patients included in this study were included in a previous study [47] investigating subgroups based on pain modulatory phenotypes in patients with chronic pain.

## 2.2 Procedure

After referral to the pain clinic, pain sensitivity, as well as pro-nociceptive and anti-nociceptive pain mechanisms were assessed in all patients by the same experienced assessor (HBV). Assessments of pressure pain threshold and tolerance, TSP and CPM were performed on the left lower leg and assessment of heat pain sensitivity was performed on the left hand. These sites were chosen as the main purpose of the study was to investigate the sensitivity of central pain mechanisms in the different sub-groups. Prior to assessments, patients were thoroughly introduced to the pain testing procedures by illustrations and verbal instructions. The pain sensitivity assessments lasted between 20 and 30 minutes and were performed with the patient seated with arms resting on the thighs.

Demographics including age, gender, body mass index (BMI), and clinical pain manifestations were collected via an electronic software system (*PainData, Denmark*). The following pain related data were collected: Duration of pain, use of analgesics, clinical pain intensity for peak pain, and average pain on a 0-10 numerical rating scale (NRS) with 0 defined as “no pain” and 10 “as worst imaginable pain” during the previous 24 hours [8], pain catastrophizing (Pain Catastrophizing Scale, PCS) [43], pain disability (Pain Disability Index, PDI) [34], fear of movement (Tampa Scale of Kinesiophobia, TSK) [24], and health-related quality of life on a 0-100 scale, EQ5D) [14].

## 2.3 Assessment of pressure pain thresholds and tolerance

Pressure pain threshold (cPPT), and pressure pain tolerance (cPTT) were assessed by computer-controlled cuff algometry at the left lower leg (*Nocitech, Denmark and Aalborg University, Denmark*) [33]. A 13-cm wide silicone tourniquet cuff (*VBM, Sulz, Germany*) was mounted with a 5 cm distance between its upper rim and the tibial tuberosity. The rate of the cuff pressure increase was 1 kPa/s and the maximal pressure was 100 kPa. Air was supplied from an external air tank to avoid loud noises from the cuff system during assessment and the maximal pressure was based on the system’s capacity. Patients were instructed to continuously rate their pressure-induced pain

intensity via an electronic visual analogue scale (VAS) from when the pressure was defined as first sensation of pain and to press the pressure release button when the pain was perceived as intolerable. Zero and 10 cm extremes on the VAS were defined as “no pain” and as “maximal pain”, respectively. When beginning to score the cuff-induced pain, patients may make small unintended changes on the electronic VAS which may result in a larger variation in the pain threshold. Therefore, the pressure value, when the patient rated the sensation of pain as 1 cm on the VAS was defined as cPPT. Patients were instructed to terminate the pressure when they could not tolerate the pressure anymore, and when the patient terminated the pressure inflation, the pressure value was defined as the cPTT. In case the maximum pressure stimulation was achieved before reaching the PTT, 100 kPa was used for further analysis as a conservative estimate of the PTT. The VAS score of the pain intensity when patients terminated the pressure inflation was also extracted (VAScPTT). The cuff algometry procedure was repeated twice and the average of parameters was extracted for data analysis. Computer-controlled cuff algometry has previously demonstrated good test-retest reliability in patients with chronic pain [49] and healthy subjects [17;50].

#### *2.4 Assessment of temporal summation of pressure pain*

Temporal summation of pain (TSP) was assessed 1 min after assessment of cPPT and cPTT. Ten repeated cuff pressure stimulations with an intensity equivalent to the cPTT and with duration of 1 s were delivered. For each of the 10 stimulations, the tourniquet is instantaneously inflated by the computer-controlled cuff algometry. This intensity was chosen to ensure that the first stimulation was perceived as painful although not extremely painful due to the short stimulation time. The computer-controlled cuff algometry delivers each stimulation. In the period between stimuli (1 s) a constant non-painful pressure of 5 kPa was kept ensuring that the cuff did not move. During the sequential stimulation, patients rated their pressure pain intensity on the electronic VAS without returning it to zero between stimulations. The VAS score immediately after each stimulus was extracted and the mean VAS scores for stimulation 1-4 (VAS-I), stimulations 5-7 (VAS-II), and stimulations 8-10 (VAS-III) were calculated. TSP was calculated as the ratio between VAS-III and VAS-I, with values above 1 indicating an increase in VAS scores during the sequential stimulation [17].

#### *2.5 Assessment of conditioned pain modulation*

Conditioned pain modulation (CPM) was assessed 2 min after assessment of TSP. The conditioning stimulus (CS) was delivered by a 7.5 cm wide silicone tourniquet cuff (*VBM, Sulz, Germany*) wrapped around the right lower leg. This cuff was mounted 8 cm below the tibial tuberosity. The cuff was inflated to 30 kPa within 1 s and the pressure was kept constant throughout the CPM protocol for a maximum of 100 s. This intensity was chosen a-priori with the prospect to ensure that the CS intensity was above cPPT and would thus be perceived as moderately painful as recommended [41]. Five seconds after CS was induced the test stimulus cuff on the left leg (TS) was inflated with a rate of 1 kPa/s as described above, and the cPPT and cPTT were reassessed. Patients were instructed that the CS would be moderately painful and that they should focus their attention on the TS on the left leg. The CPM response was defined as the percentage change in cPPT recorded during CS compared with baseline assessments of cPPT with positive values indicating a hypoalgesic response [47]. In addition, based on a previous study demonstrating a within-subject coefficient of variation in cPPT between two repeated cuff assessments without the conditioning cuff [47], patients were classified as having impaired CPM if the CPM response was less than or equal to an increase of 20% in cPPT and normal CPM if the response was above 20%.

### *2.6 Assessment of heat detection and heat pain thresholds*

Heat detection threshold (HDT) and heat pain threshold (HPT) at the thenar eminence of the left hand were assessed 3 min after CPM assessment by a computer-controlled contact thermal stimulator (*MSA Thermal Stimulator, SENSELab, Somedic Sales AB, Hörby, Sweden*) with a thermode covering a 25x50 mm skin area. The baseline temperature was 32°C and increased by 1.0°C/s to a maximum of 50°C. Patients were instructed to press a handheld switch first time they detected a change in the temperature (HDT). After assessment of HDT, HPT was assessed. Patients were instructed to press the handheld switch as soon as the heat sensation was defined as the first sensation of pain (HPT). The peak temperature was stored and the thermode decreased its temperature (3.0°C/s) to the baseline temperature. Test stimuli were repeated three times and the averages of HDT and HPT, respectively, were calculated.

Assessment of test-retest reliability for heat pain sensitivity has previously shown acceptable agreement between tests with no systematic mean difference between two sessions [50].

### *2.7 Statistics*

All data are reported as mean and standard deviation (SD) in the text and as mean and standard error of the mean (SEM) in figures. Statistical analyses were run in SPSS Statistics (*Version 21; IBM, Armonk, NY, USA*). Potential differences between the four groups in proportion of gender and use of analgesics were analyzed by Chi-square tests, and potential difference in age was analyzed by one-way analysis of variance (ANOVA). Due to different proportions of women and men between the four groups and previously demonstrated gender-differences in several pain related parameters [47], all pain-related parameters were gender-adjusted (z-transformation) by subtraction of the mean values divided by the standard deviation (SD) for men and women, respectively. Potential differences both in raw values and z-scores for clinical pain, psychological parameters, pain sensitivity, and pro-nociceptive and anti-nociceptive pain mechanisms were examined using two-way ANOVA with *pain location* (neck, low-back) and *distribution* (local, radiating) as between subject factors. In case of significant factors or interactions in the z-scores, Bonferroni-corrected pairwise comparisons were used. *P*-values less than 0.05 were considered significant. Due to significant differences in proportion of patients using opioids and paracetamol, an analysis was conducted to investigate whether patients using analgesics differed in the clinical and experimental variables compared with patients who did not use these analgesics. Independent t-tests were used to investigate if there were any significant differences. Pearson correlations were used to determine the relationship between the z-scores of clinical pain, psychological distress, pain sensitivity, and pro-nociceptive and anti-nociceptive pain mechanisms. Due to multiple correlational analyses, *P*-values equal to or less than 0.001 (0.05 / 36) were considered significant for the correlations.

### 3. RESULTS

#### 3.1 Group characteristics

All patients in the study tolerated and completed the pain sensitivity assessments. Table 1 illustrates raw values for demographics, clinical pain profile, psychological distress, and experimental pain variables in patients with low back pain, neck pain, low back radiating pain, and cervical radiating pain. There was no significant difference in distribution of women and men between groups ( $\chi^2 = 1.85$ ,  $P = 0.60$ ) and no significant group differences in age ( $F(3,69) = 2.32$ ,  $P = 0.083$ ) or BMI ( $F(3,66) = 1.05$ ,  $P = 0.38$ ) were found.

#### 3.2 Heat and pressure pain sensitivity

The ANOVA on HPT at the hand revealed an interaction between pain location and distribution (Table 2;  $F(1,69) = 9.30$ ,  $P = 0.0029$ ) with post-hoc test showing decreased HPT in patients with cervical radiating pain compared with patients with neck pain and low back radiating pain ( $P < 0.01$ ). In patients with low back pain, the HPT demonstrated a tendency for being decreased compared with neck pain ( $P = 0.09$ ).

Three patients reached the maximum pressure of 100 kPa (1 LBP and 2 neck pain patients, respectively). An interaction between pain location and distribution was found in the ANOVA for cPTT (Table 2;  $F(1,69) = 6.93$ ,  $P = 0.01$ ) with post-hoc test showing decreased cPTT in cervical radiating pain patients and low back pain patients compared with neck pain patients ( $P < 0.05$ ).

No significant main effects or interactions were found in the ANOVAs for HDT at the hand ( $F(1,69) < 0.73$ ,  $P > 0.39$ ), cPPT ( $F(1,69) < 1.87$ ,  $P > 0.17$ ), or VAScPTT ( $F(1,69) < 1.30$ ,  $P > 0.25$ ).

### 3.3 Pro- and anti-nociceptive pain mechanisms

The ANOVA for TSP demonstrated a main effect of pain distribution (Table 2;  $F(1,69) = 4.92$ ,  $P = 0.029$ ) with post-hoc test showing increased TSP in patients with radiating pain (low back or neck) compared with patients with localized low back or neck pain ( $P < 0.03$ ).

An interaction between pain location and distribution was found in the ANOVA for CPM (Table 2;  $F(1,69) = 4.50$ ,  $P = 0.038$ ) with post-hoc test showing decreased CPM in cervical radiating pain patients compared with neck pain patients ( $P = 0.006$ ).

### 3.4 Clinical pain profile

An interaction between pain location and distribution was found in the ANOVA for the NRS score of clinical average pain intensity (Table 2;  $F(1,69) = 6.66$ ,  $P = 0.012$ ) with post-hoc test showing increased NRS pain scores in patients with cervical radiating pain compared with patients with neck pain ( $P < 0.001$ ). Moreover, compared with low back radiating pain patients, the average NRS pain scores demonstrated a tendency for being increased in patients with cervical radiating pain ( $P = 0.06$ ). Compared with neck pain patients, the average NRS pain scores demonstrated a tendency for being increased in patients with low back pain ( $P = 0.08$ ).

The ANOVA for the NRS score of clinical peak pain intensity demonstrated an interaction between pain location and distribution (Table 2;  $F(1,69) = 24.65$ ,  $P < 0.001$ ) with post-hoc test showing increased NRS of peak pain intensity in patients with cervical radiating pain compared

with local neck pain and low back radiating pain patients ( $P < 0.002$ ). Compared with patients with neck pain, the peak NRS pain scores were significantly higher in patients with low back pain ( $P < 0.001$ ).

There was a significant difference in proportion of patients using opioids (Table 2;  $X^2 = 9.26$ ,  $P = 0.026$ ) and paracetamol ( $X^2 = 9.09$ ,  $P = 0.028$ ) between groups and Bonferroni corrected between-group comparisons showed that significantly more patients with low back radiating pain used opioids and paracetamol compared with patients with localized neck pain ( $P < 0.004$ ). No significant differences were found in clinical and experimental pain profiles in the sensitivity analysis for opioids ( $t(68) = 1.33$ ,  $P > 0.19$ ) or paracetamol ( $t(68) = 1.79$ ,  $P > 0.08$ ), respectively.

No significant main effects or interactions were found in the ANOVA for pain duration ( $F(1,69) < 3.38$ ,  $P > 0.06$ ).

### 3.5 Psychological parameters

The ANOVA carried out on PCS showed an interaction between pain location and distribution (Table 2;  $F(1,63) = 8.31$ ,  $P = 0.006$ ) with post-hoc test showing increased pain catastrophizing in cervical radiating pain patients compared with neck pain and low back radiating pain patients ( $P < 0.006$ ).

A significant interaction between pain location and distribution was found in the ANOVA for TSK (Table 2;  $F(1,64) = 7.88$ ,  $P = 0.007$ ) with post-hoc test showing increased fear of movement in cervical radiating pain patients compared with neck pain patients ( $P = 0.007$ ). Moreover, compared with neck pain patients, TSK was increased in patients with low back pain ( $P = 0.004$ ).

The ANOVA for PDI demonstrated a significant interaction between pain location and distribution (Table 2;  $F(1,64) = 12.02$ ,  $P < 0.001$ ) with post-hoc test showing increased pain-related disability in cervical radiating pain patients compared with neck pain and low back radiating pain patients ( $P < 0.009$ ). Moreover, compared with neck pain patients, disability was increased in patients with low back pain ( $P = 0.03$ ).

An interaction between pain location and distribution was found in the ANOVA for quality of life (Table 2;  $F(1,68) = 4.71$ ,  $P = 0.034$ ) with post-hoc test showing reduced quality of life in cervical radiating pain patients compared with neck pain patients ( $P = 0.046$ ).

### 3.6 Correlational analysis

As illustrated in Table 3, positive correlations for all patients were found between clinical pain intensity and PCS, as well as between TSK and PDI indicating that patients reporting higher clinical pain intensity also reported higher psychological distress and more pain-related disability.

#### 4. DISCUSSION

The sensory and clinical pain profiles in different subtypes of back pain indicated that 1) patients with localized pain in the low back had in general more cuff pain hypersensitivity than pain patients with localized neck pain, and 2) patients with radiating back (neck and low back) pain had facilitated pro-nociceptive pain mechanisms compared with patients with localized back pain. Moreover, patients with cervical radiating pain demonstrated hyperalgesia to heat, reduced CPM response, and increased levels of clinical pain, psychological distress and disability compared with patients with neck pain only. Similar findings between radiating pain and localized pain were not found in patients with low back pain.

##### *4.1 Effects of pain distribution on pro-nociceptive and anti-nociceptive pain profile*

Patients with radiating pain patterns demonstrated facilitated temporal summation of pain suggesting mechanistic differences in the underlying pain mechanisms between patients with localized pain and radiating pain. It is possible, that radiating back pain in this cohort to some extent is driven by hypersensitivity of central pain mechanisms that from a treatment perspective may require different strategies than localized back pain. In this regard, it is important to note that individuals suffering from chronic low back pain are known to demonstrate enlarged pain areas from experimental pain [31], suggesting facilitated central pain mechanisms similar to patients with larger pain areas. Moreover, it has recently been shown that individuals suffering from chronic low back pain [37;38] have varying pain characteristics, with some demonstrating a pro-nociceptive response to experimental pain stimuli, manifested by a facilitated TSP and reduced efficiency of the CPM effect. However, the current dichotomous differentiation in back pain with or without radiating limb pain cannot differentiate between referred pain of neural origin or initiated from the periphery. Experimental pain studies have shown that peripheral structures in the low back [4;22] and cervical regions [10] are capable of extensive pain referral. However, cervical pain from e.g. zygapophyseal joints seems to predominantly refer pain in the neck/shoulder region [15] in a diffuse pattern [13] whereas a stimulation of similar structures at various spinal segments in the low back is in most cases capable of causing pain extending beyond the knee [4]. To increase the diagnostic

certainty in this regard, medical imaging would have been needed but this was neither available in this study nor is it commonly used in everyday clinical practice.

An interesting finding in this study was that patients with cervical radiating pain had a reduced CPM response compared with patients with localized neck pain. This finding agrees with a previous study showing more pain areas in patients who presented with a facilitated TSP, and a reduced CPM response [48], suggesting that cervical radiating pain is linked with an imbalance between pro-nociceptive modulation at spinal [2] and anti-nociceptive modulation at brainstem [27] levels. This hypothesis is further supported by the reduced heat pain threshold demonstrated in a non-painful body area indicating more widespread hyperalgesia. In fact, individuals with cervical radiating pain without a specific peripheral cause seem to be more prone to heat pain hypersensitivity than those with specific cervical radicular pain [30]. Moreover, patients with true cervical radiculopathy become less sensitive to heat [45]. No significant difference in heat detection threshold was found between groups which could be due to the sample size, but one suggestion is that significant changes in pain sensitivity between groups were not due to reduced neural transduction (sensory loss).

#### *4.2 Effects of pain location on pro-nociceptive and anti-nociceptive pain profiles*

As hypothesized, patients with localized pain in the low back demonstrated increased cuff pain hypersensitivity than pain patients with localized neck pain. This finding could be related to the segmental levels stimulated by the cuff (L4/L5) is more directly related to the lower back, whereas the stimulation is extra-segmental to the neck. However, in contrast to the hypothesis, heat pain sensitivity was not increased in localized neck pain patients compared with low back pain patients. Although the difference did not reach significance, the heat pain sensitivity was increased in low back pain patients compared with neck pain patients. Combined, these findings may suggest that low back pain patients had more generalized pain hypersensitivity compared with neck pain patients.

#### *4.3 Clinical pain profile*

Patients included in this study were considerably affected by their pain condition as demonstrated by high levels of pain, psychological distress, and pain-related disability. The current and previous [12] findings show that cervical radiating pain affects patients more than neck pain only. Unexpectedly, this pattern was not found between patients with low back radiating pain and

localized low back pain, which in contrast to what has previously been reported [18;23]. The reason for this difference is currently unclear. Moreover, low back pain patients had increased pain intensity compared with neck pain patients.

In addition to pain, differences were found for fear of movement and pain catastrophizing which are the key cognitive elements in the fear-avoidance model [52]. Patients with low back pain showed increased levels of fear of movement which could influence the difference in pain [5] and pain-related disability [19;28] between groups. As a result of a painful injury, some individuals develop fear of movement or kinesiophobia, which has been defined as an excessive, irrational, and debilitating fear of physical movement [24]. In accordance with the current findings, a recent comparison of patients with low back pain and patients with neck pain showed significantly higher levels of kinesiophobia in low back pain despite comparable pain levels [46]. The influence of fear of movement is further supported by the fact that all groups except the neck pain group were above the threshold for high values of kinesiophobia [51], and by the moderately strong associations between fear of movement, pain intensity, and pain-related disability.

In addition to fear of movement, patients in this study reported varying degrees of pain catastrophizing but interestingly, only the cervical radiating pain group had scores above 30 which is considered a clinically relevant level of pain catastrophizing [43]. This should be noted given the relationship between pain catastrophizing and perceived pain and pain-related disability.

#### *4.4 Clinical implications*

Guidelines for the management of chronic back pain [1;7;9;25;40] consistently recommend supervised exercises, and cognitive behavioral therapy, whereas recommendations regarding manual- and pharmacology treatment have some discrepancies between guidelines. The current findings illustrate differences in the clinical and sensory pain profile in patients suffering from different types of back pain which could have implications for clinical assessment and choice of treatment strategy. Especially pharmacological and non-pharmacological treatment strategies targeting facilitated central pain mechanisms may show better efficacy in patients with radiating back pain compared with localized back pain.

Diagnosis and treatment of musculoskeletal pain within a mechanism-based framework has been proposed [29;32] but it is unclear which mechanisms should direct treatment. It seems possible that underlying mechanisms may to some degree be identified from clinical presentation [41] but a more detailed investigation of the somatosensory profile of back pain patients shows varying pro-

nociceptive and anti-nociceptive traits [38]. It is possible that such knowledge, on an individual level, might be helpful in directing the choice of treatment but the therapeutic options are many and therefore of importance to identify the mechanism(s) to target before choosing the intervention.

#### *4.5 Limitations*

The cross-sectional design is a major limitation, as judgement on causality and definite directions of the associations cannot be made. Patients were not trained in the sensory testing but received oral explanations and a thorough neurological examination including diagnostic tests excluding potential nerve lesions was not performed in this study. Although significant group differences were found, this study is limited by the small sample size within each subgroup and larger studies should confirm the findings. Increasing group size would enable an investigation of pro-nociceptive and anti-nociceptive tendencies within each group. Tests to exclude true radiculopathy were not performed which may indicate that the radiating pain groups consisted of individuals both with and without the nerve roots affected. This study did not include a healthy control group which may affect the interpretation of findings because deviations from normative pain profiles cannot be established. Further research is warranted, accounting for differences in ongoing pain and psychological distress between chronic pain patients and healthy controls. Pain sensitivity was only evaluated at non-painful sites, and not at the primary site of pain (neck or low back) which could have strengthened the interpretation of the results.

#### *4.6 Conclusion*

This study compared the clinical and sensory pain profiles in four subgroups of patients with back pain, with and without radiating pain components. The results indicate that patients with radiating pain patterns demonstrated facilitated temporal summation of pain suggesting mechanistic differences in the underlying pain mechanisms between patients with localized pain and radiating pain. Furthermore, patients with localized low back pain demonstrated hyperalgesia to heat and pressure pain, as well as increased levels of clinical pain, psychological distress and disability compared with patients with localized neck pain only. These exploratory findings may have implications for future studies on clinical assessment and choice of treatment strategy.

**REFERENCES**

- [1] Airaksinen O, Brox JJ, Cedraschi C, Hildebrandt J, Klüber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G: Chapter 4 - European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J*, 15:S192-300, 2006
- [2] Arendt-Nielsen L, Graven-Nielsen T: Translational musculoskeletal pain research. *Best Pract Res Clin Rheumatol*, 25:209-226, 2011
- [3] Arendt-Nielsen L, Skou ST, Nielsen TA, Petersen KK: Altered Central Sensitization and Pain Modulation in the CNS in Chronic Joint Pain. *Curr Osteoporos Rep*, 13:225-234, 2015
- [4] Bogduk N: On the definitions and physiology of back pain, referred pain, and radicular pain. *Pain*, 147:17-19, 2009
- [5] Branstrom H, Fahlstrom M: Kinesiophobia in patients with chronic musculoskeletal pain: differences between men and women. *J Rehabil Med*, 40:375-380, 2008
- [6] Brinjikji W, Luetmer PH, Comstock B, Bresnahan BW, Chen LE, Deyo RA, Halabi S, Turner JA, Avins AL, James K, Wald JT, Kallmes DF, Jarvik JG: Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *AJNR Am J Neuroradiol*, 36:811-816, 2015
- [7] Childs JD, Cleland JA, Elliott JM, Teyhen DS, Wainner RS, Whitman JM, Sopyk BJ, Godges JJ, Flynn TW: Neck pain: Clinical practice guidelines linked to the International Classification of Functioning, Disability, and Health from the Orthopedic Section of the American Physical Therapy Association. *J Orthop Sports Phys Ther*, 38:A1-A34, 2008
- [8] Cleland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore*, 23:129-138, 1994
- [9] Cohen SP: Epidemiology, diagnosis, and treatment of neck pain. *Mayo Clin Proc*, 90:284-299, 2015
- [10] Cooper G, Bailey B, Bogduk N: Cervical zygapophysial joint pain maps. *Pain Med*, 8:344-353, 2007
- [11] Costa Lda C, Maher CG, McAuley JH, Hancock MJ, Herbert RD, Refshauge KM, Henschke N: Prognosis for patients with chronic low back pain: inception cohort study. *BMJ*, 339:b3829, 2009
- [12] Daffner SD, Hilibrand AS, Hanscom BS, Brislin BT, Vaccaro AR, Albert TJ: Impact of neck and arm pain on overall health status. *Spine*, 28:2030-2035, 2003

- [13] Dalton PA, Jull GA: The distribution and characteristics of neck-arm pain in patients with and without a neurological deficit. *Aust J Physiother*, 35:3-8, 1989
- [14] EuroQol: EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy*, 16:199-208, 1990
- [15] Fukui S, Ohseto K, Shiotani M, Ohno K, Karasawa H, Naganuma Y, Yuda Y: Referred pain distribution of the cervical zygapophyseal joints and cervical dorsal rami. *Pain*, 68:79-83, 1996
- [16] Gerhardt A, Eich W, Janke S, Leisner S, Treede RD, Tesarz J: Chronic Widespread Back Pain is Distinct from Chronic Local Back Pain: Evidence from Quantitative Sensory Testing, Pain Drawings, and Psychometrics. *Clin J Pain*, 32:568-579, 2016
- [17] Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L: Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: A reliability study. *Pain*, 156:2193-2202, 2015
- [18] Hider SL, Whitehurst DG, Thomas E, Foster NE: Pain location matters: the impact of leg pain on health care use, work disability and quality of life in patients with low back pain. *Eur Spine J*, 24:444-451, 2015
- [19] Huis 't Veld RM, Vollenbroek-Hutten MM, Groothuis-Oudshoorn KC, Hermens HJ: The role of the fear-avoidance model in female workers with neck-shoulder pain related to computer work. *Clin J Pain*, 23:28-34, 2007
- [20] Izumi M, Petersen KK, Laursen MB, Arendt-Nielsen L, Graven-Nielsen T: Facilitated temporal summation of pain correlates with clinical pain intensity after hip arthroplasty. *Pain*, 158:323-332, 2017
- [21] Jespersen A, Amris K, Graven-Nielsen T, Arendt-Nielsen L, Bartels EM, Torp-Pedersen S, Bliddal H, Danneskiold-Samsøe B: Assessment of pressure-pain thresholds and central sensitization of pain in lateral epicondylalgia. *Pain Med*, 14:297-304, 2013
- [22] Kellgren JH: On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clinical Science*, 4:35-46, 1939
- [23] Konstantinou K, Dunn KM, Ogollah R, Vogel S, Hay EM: Characteristics of patients with low back and leg pain seeking treatment in primary care: baseline results from the ATLAS cohort study. *BMC Musculoskeletal Disord*, 16:332, 2015
- [24] Kori SH, Miller RP, Todd DD: Kinisophobia: a new view of chronic pain behavior. *Pain Manag*, 1:35-43, 1990

- [25] Laerum E, Storheim K, Brox JI: New clinical guidelines for low back pain. *Tidsskr Nor Laegeforen*, 127:2706, 2007
- [26] Latremoliere A, Woolf CJ: Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain*, 10:895-926, 2009
- [27] Le Bars D, Villanueva L, Bouhassira D, Willer JC: Diffuse noxious inhibitory controls (DNIC) in animals and in man. *Patol Fiziol Eksp Ter*, 4:55-65, 1992
- [28] Lentz TA, Barabas JA, Day T, Bishop MD, George SZ: The relationship of pain intensity, physical impairment, and pain-related fear to function in patients with shoulder pathology. *J Orthop Sports Phys Ther*, 39:270-277, 2009
- [29] Malfait AM, Schnitzer TJ: Towards a mechanism-based approach to pain management in osteoarthritis. *Nat Rev Rheumatol*, 9:654-664, 2013
- [30] Moloney N, Hall T, Doody C: Sensory hyperalgesia is characteristic of nonspecific arm pain: a comparison with cervical radiculopathy and pain-free controls. *Clin J Pain*, 29:948-956, 2013
- [31] O'Neill S, Manniche C, Graven-Nielsen T, Arendt-Nielsen L: Generalized deep-tissue hyperalgesia in patients with chronic low-back pain. *Eur J Pain*, 11:415-420, 2007
- [32] O'Sullivan PB, Beales DJ: Diagnosis and classification of pelvic girdle pain disorders--Part 1: a mechanism based approach within a biopsychosocial framework. *Man Ther*, 12:86-97, 2007
- [33] Polianskis R, Graven-Nielsen T, Arendt-Nielsen L: Computer-controlled pneumatic pressure algometry--a new technique for quantitative sensory testing. *Eur J Pain*, 5:267-277, 2001
- [34] Pollard CA: Preliminary validity study of the pain disability index. *Perceptual and motor skills*, 59:974, 1984
- [35] Pud D, Granovsky Y, Yarnitsky D: The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. *Pain*, 144:16-19, 2009
- [36] Pud D, Sprecher E, Yarnitsky D: Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. *Neurosci Lett*, 380:209-213, 2005
- [37] Rabey M, Poon C, Wray J, Thamajaree C, East R, Slater H: Pro-nociceptive and anti-nociceptive effects of a conditioned pain modulation protocol in participants with chronic low back pain and healthy control subjects. *Man Ther*, 20:763-768, 2015
- [38] Rabey M, Slater H, O'Sullivan P, Beales D, Smith A: Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis. *Pain*, 156:1874-1884, 2015

- [39] Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B: Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*, 123:231-243, 2006
- [40] Rossignol M, Poitras S, Dionne C, Tousignant M, Truchon M, Arsenault B, Allard P, Cote M, Neveu A: An interdisciplinary guideline development process: the Clinic on Low-back pain in Interdisciplinary Practice (CLIP) low-back pain guidelines. *Implement Sci*, 2:36, 2007
- [41] Smart KM, Blake C, Staines A, Doody C: Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. *Man Ther*, 15:80-87, 2010
- [42] Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ, Jr: Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. *Pain*, 102:87-95, 2003
- [43] Sullivan MJ, Bishop SR, Pivik J: The pain catastrophizing scale: development and validation. *Psychol Assess*, 7:524-532, 1995
- [44] Suri P, Boyko EJ, Goldberg J, Forsberg CW, Jarvik JG: Longitudinal associations between incident lumbar spine MRI findings and chronic low back pain or radicular symptoms: retrospective analysis of data from the longitudinal assessment of imaging and disability of the back (LAIDBACK). *BMC Musculoskeletal Disord*, 15:152, 2014
- [45] Tampin B, Slater H, Hall T, Lee G, Briffa NK: Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck-arm pain. *Pain*, 153:2403-2414, 2012
- [46] Ulug N, Yakut Y, Alemdaroglu I, Yilmaz O: Comparison of pain, kinesiophobia and quality of life in patients with low back and neck pain. *J Phys Ther Sci*, 28:665-670, 2016
- [47] Vaegter HB, Graven-Nielsen T: Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity. *Pain*, 157:1480-8, 2016
- [48] Vaegter HB, Handberg G, Emmeluth C, Graven-Nielsen T: Preoperative Hypoalgesia after Cold Pressor Test and Aerobic Exercise is Associated with Pain Relief Six Months after Total Knee Replacement. *Clin J Pain*, Epub ahead of print, Aug 12 2016.

- [49] Vaegter HB, Handberg G, Graven-Nielsen T: Hypoalgesia After Exercise and the Cold Pressor Test is Reduced in Chronic Musculoskeletal Pain Patients With High Pain Sensitivity. *Clin J Pain*, 32:58-69, 2016
- [50] Vaegter HB, Hoeger Bement M, Madsen AB, Fridriksson J, Dasa M, Graven-Nielsen T: Exercise increases pressure pain tolerance but not pressure and heat pain thresholds in healthy young men. *Eur J Pain*, 21:73-81, 2017
- [51] Vlaeyen JW, Kole-Snijders AM, Rotteveel AM, Ruesink R, Heuts PH: The role of fear of movement/(re)injury in pain disability. *J Occup Rehabil*, 5:235-252, 1995
- [52] Vlaeyen JW, Linton SJ: Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, 85:317-332, 2000
- [53] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basanez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fevre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S,

Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA, 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leon FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA: Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380:2163-2196, 2012

- [54] Yarnitsky D, Bouhassira D, Drewes AM, Fillingim RB, Granot M, Hansson P, Landau R, Marchand S, Matre D, Nilsen KB, Stubhaug A, Treede RD, Wilder-Smith OH:

Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain*, 19:805-806, 2015

[55] Yarnitsky D, Granot M, Granovsky Y: Pain modulation profile and pain therapy: Between pro- and antinociception. *Pain*, 155:663-665, 2014

ACCEPTED MANUSCRIPT

## FIGURE AND TABLE LEGENDS

**Fig. 1:** Mean (+ SEM, N = 70) heat pain threshold (HPT; **A**) at the thenar eminence on the left hand, and pressure pain tolerance (cPTT; **B**) at the lower left leg in patients with Low Back Pain (LBP; white bars), Neck Pain (hatched bars), Low Back Radicular Pain (grey bars) and Cervical Radicular Pain (black bars). Raw values are illustrated but gender-adjusted values (z-scores) are used for statistics presented in this figure. Significantly different between groups (\*, NK:  $P < 0.05$ ).

**Fig. 2:** Mean (+ SEM, N = 70) ratio between VAS-III and VAS-I reflecting temporal summation of pain assessed by computerized cuff algometry (**A**), and percentage change in cPPT at the lower left leg during painful conditioning cuff stimulation on the contralateral leg reflecting conditioned pain modulation (**B**) in patients with Low Back Pain (LBP; white bars), Neck Pain (hatched bars), Low Back Radicular Pain (grey bars) and Cervical Radicular Pain (black bars). Raw values are illustrated but gender-adjusted values (z-scores) are used for statistics presented in this figure. Significantly different between groups (\*, NK:  $P < 0.05$ ).

**Table 1:** Raw scores for demographics, clinical pain profile, psychological distress, experimental pain sensitivity, and pro-nociceptive and anti-nociceptive mechanisms in patients with neck pain, low back pain, low back radiating pain, and cervical radiating pain. ‘BMI’: Body Mass Index. ‘NRS’: Numerical Rating Scale. ‘PCS’: Pain Catastrophizing Scale. ‘TSK’: Tampa Scale of Kinesiophobia. ‘PDI’: Pain Disability Index. ‘HDT’: Heat Detection Threshold. ‘HPT’: Heat Pain Threshold. ‘cPPT’: Cuff Pressure Pain Threshold. ‘cPTT’: Cuff Pressure Pain Tolerance. ‘VAScPPT’: VAS score at cPTT. ‘TSP’: Temporal summation of pain. ‘CPM’: Conditioned pain modulation. ‘Y/N, CPM > 20%’: Proportion of patients with a CPM response over 20%). P-values are based on by Chi-square tests for categorical variables and two-way analysis of variance (ANOVA) for continuous variables.

**Table 2:** Mean ( $\pm$  SD) z-scores of clinical pain, psychological distress, experimental pain sensitivity, and pro-nociceptive and anti-nociceptive mechanisms in patients with neck pain, low back pain, low back radiating pain, and cervical radiating pain. Negative Z-scores indicate reduced parameters compared with the group mean. ‘NRS’: Numerical Rating Scale. ‘PCS’: Pain Catastrophizing Scale. ‘TSK’: Tampa Scale of Kinesiophobia. ‘PDI’: Pain Disability Index. ‘HDT’: Heat Detection Threshold. ‘HPT’: Heat Pain Threshold. ‘cPPT’: Cuff Pressure Pain Threshold.

‘cPTT’: Cuff Pressure Pain Tolerance. ‘VAScPTT’: VAS score at cPTT. ‘TSP’: Temporal summation of pain. ‘CPM’: Conditioned pain modulation. P-values are based on two-way ANOVA on gender adjusted variables (z-scores) and post-hoc effects are indicated in parenthesis.

**Table 3:** Pearson correlations between clinical pain intensity, pain sensitivity as well as pro-nociceptive and anti-nociceptive mechanisms. Due to multiple correlational analyses, P-values equal to or less than 0.001 (0.05 / 36) were considered significant for the correlations. ‘HPT’: Heat Pain Threshold. ‘cPPT’: Cuff Pressure Pain Threshold. ‘cPTT’: Cuff Pressure Pain Tolerance. ‘TSP’: Temporal summation of pressure pain. ‘CPM’: Conditioned pain modulation.

**Table 1.** Raw scores for demographics, clinical pain profile, psychological distress, experimental pain sensitivity, and pro-nociceptive and anti-nociceptive mechanisms in patients with neck pain, low back pain, low back radiating pain, and cervical radiating pain. ‘BMI’: Body Mass Index. ‘NRS’: Numerical Rating Scale. ‘PCS’: Pain Catastrophizing Scale. ‘TSK’: Tampa Scale of Kinesiophobia. ‘PDI’: Pain Disability Index. ‘HDT’: Heat Detection Threshold. ‘HPT’: Heat Pain Threshold. ‘cPPT’: Cuff Pressure Pain Threshold. ‘cPTT’: Cuff Pressure Pain Tolerance. ‘VAScPTT’: VAS score at cPTT. ‘TSP’: Temporal summation of pain. ‘CPM’: Conditioned pain modulation. ‘Y/N, CPM > 20%’: Proportion of patients with a CPM response over 20%). P-values are based on by Chi-square tests for categorical variables and two-way analysis of variance (ANOVA) for continuous variables.

Variable	Total (n=70)	Low Back Pain (n=18)	Neck Pain (n=17)	Low back radiating pain (n=18)	Cervical radiating pain (n=17)	P-value
Gender (Women/Men)	43/27	9/9	12/5	12/6	10/7	0.60
Age (years)	48.0±12.9	49.7±14.8	42.8±9.4	53.3±14.5	45.9±10.1	0.083
BMI (kg/m <sup>2</sup> )	27.1±5.5	25.8±3.2	28.8±6.9	26.2±5.0	27.5±6.1	0.38
Pain duration (years)	6.3±7.3	5.3±5.2	7.1±10.5	8.9±7.9	3.9±2.8	0.06
Peak pain intensity (NRS: 0-10)	8.2±1.7	8.6±1.0	6.8±1.9	7.9±1.6	9.4±1.0	< 0.001
Average pain intensity (NRS: 0-10)	6.7±1.9	6.7±1.7	5.6±1.6	6.7±2.0	7.8±1.6	0.010
Analgesic users (Y/N)	63/7 (90%)	16/2 (88.9%)	13/4 (76.5%)	18/0 (100%)	16/1 (94.1%)	0.12
Opioid users (Y/N)	40/30 (57.1%)	12/6 (66.7%)	5/12 (29.4%)	14/4 (77.8%)	9/8 (52.9%)	0.03
Antidepressant users (Y/N)	15/55 (21.4%)	1/17 (5.6%)	6/11 (35.3%)	2/16 (11.1%)	6/11 (35.3%)	0.07
Anticonvulsive users (Y/N)	19/51 (27.1%)	2/16 (11.1%)	5/12 (29.4%)	7/11 (38.9%)	5/12 (29.4%)	0.30
NSAID users (Y/N)	15/55 (21.4%)	4/14 (22.2%)	5/12 (29.4%)	4/14 (22.2%)	2/15 (11.8%)	0.66
Paracetamol users (Y/N)	42/28 (60.0%)	12/6 (66.7%)	6/11 (35.3%)	15/3 (83.3%)	9/8 (52.9%)	0.028
Muscle relaxants (Y/N)	19/51 (27.1%)	2/16 (11.1%)	7/10 (41.2%)	6/12 (33.3%)	4/13 (23.5%)	0.21
Pain Catastrophizing (PCS: 0-52)	25.9±13.0	27.2±11.1	21.7±11.2	21.3±14.1	34.3±12.9	0.004
Fear of movement (TSK: 17-68)	42.1±9.3	43.6±6.4	34.8±8.3	43.8±8.3	47.1±10.2	0.005
Disability (PDI: 0-50)	37.2±8.1	38.6±6.0	32.6±8.6	35.1±9.9	42.1±4.7	0.001
Quality of Life (EQ5D: 0-100)	44.0±26.6	37.8±23.3	55.2±22.8	48.4±31.1	34.6±25.7	0.016
HDT Hand (°C)	35.1±1.4	35.0±1.0	34.9±1.5	35.3±1.5	35.2±1.6	0.95
HPT Hand (°C)	43.5±3.7	43.7±3.9	45.6±2.4	43.8±3.0	41.0±4.2	0.006
cPPT (0-100 kPa)	23.6±10.4	21.9±9.7	26.1±11.7	24.2±10.3	22.5±10.2	0.25
cPTT (0-100 kPa)	49.3±18.8	48.2±19.1	58.7±19.5	50.1±17.0	40.2±16.2	0.021
VAScPTT (VAS: 0-10 cm)	8.3±1.9	8.3±2.2	8.7±1.8	8.5±2.0	7.8±1.9	0.27
TSP (ratio)	2.4±1.8	2.3±1.8	1.7±0.8	2.8±2.2	2.9±2.1	0.048
CPM (absolute, kPa)	5.37±7.97	5.03±6.10	9.48±8.50	5.71±9.49	1.25±5.51	0.017
CPM (%)	20.6±32.7	20.7±30.4	33.7±24.9	21.9±37.9	5.9±32.8	0.062
CPM (Y/N, CPM > 20%)	36/34 (51.4%)	10/8 (55.6%)	14/3 (82.4%)	9/9 (50.0%)	3/14 (17.6%)	0.002

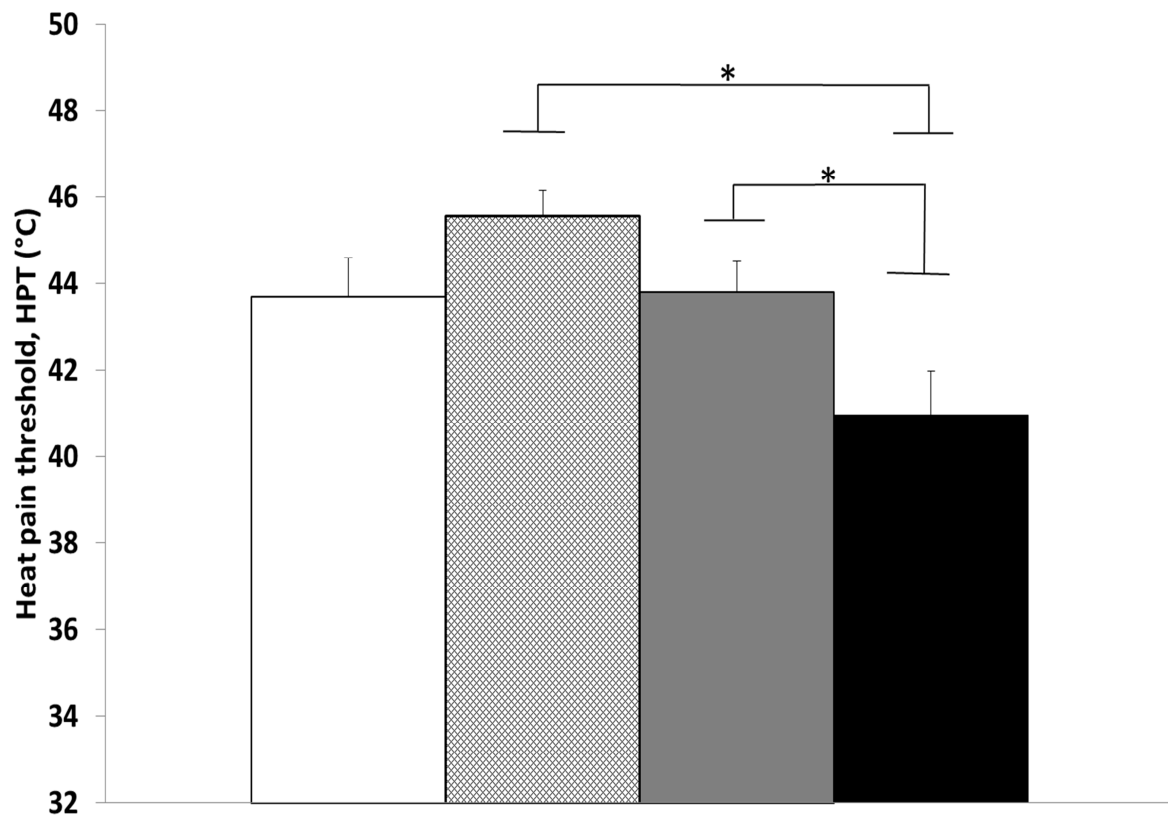
**Table 2.** Mean ( $\pm$  SD) z-scores of clinical pain, psychological distress, experimental pain sensitivity, and pro-nociceptive and anti-nociceptive mechanisms in patients with neck pain, low back pain, low back radiating pain, and cervical radiating pain. Negative Z-scores indicate reduced parameters compared with the group mean. ‘NRS’: Numerical Rating Scale. ‘PCS’: Pain Catastrophizing Scale. ‘TSK’: Tampa Scale of Kinesiophobia. ‘PDI’: Pain Disability Index. ‘HDT’: Heat Detection Threshold. ‘HPT’: Heat Pain Threshold. ‘cPPT’: Cuff Pressure Pain Threshold. ‘cPTT’: Cuff Pressure Pain Tolerance. ‘VAScPTT’: VAS score at cPTT. ‘TSP’: Temporal summation of pain. ‘CPM’: Conditioned pain modulation. P-values are based on two-way ANOVA on gender adjusted variables (z-scores) and post-hoc effects are indicated in parenthesis.

Variable	Low Back Pain (a) (n=18)	Neck Pain (b) (n=17)	Low back radiating pain (c) (n=18)	Cervical radiating pain (d) (n=17)	P-value
Pain duration	-0.10 $\pm$ 0.78	0.09 $\pm$ 1.43	0.35 $\pm$ 1.05	-0.34 $\pm$ 0.36	0.07
Peak pain intensity	0.25 $\pm$ 0.55	-0.83 $\pm$ 1.13	-0.19 $\pm$ 0.94	0.72 $\pm$ 0.60	< 0.001 (d>b,c), (a>b)
Average pain intensity	-0.03 $\pm$ 0.88	-0.59 $\pm$ 0.86	0.003 $\pm$ 1.04	0.59 $\pm$ 0.89	0.012 (d>b)
Pain Catastrophizing	0.07 $\pm$ 0.85	-0.30 $\pm$ 0.84	-0.34 $\pm$ 1.07	0.65 $\pm$ 0.99	0.006 (d>b,c)
Fear of movement	0.20 $\pm$ 0.69	-0.75 $\pm$ 0.88	0.18 $\pm$ 0.87	0.53 $\pm$ 1.11	0.007 (a,d>b)
Disability	0.12 $\pm$ 0.81	-0.56 $\pm$ 1.13	-0.23 $\pm$ 1.04	0.65 $\pm$ 0.55	0.001 (d>b,c), (a>b)
Quality of Life	-0.17 $\pm$ 0.92	0.34 $\pm$ 0.74	0.16 $\pm$ 1.19	-0.34 $\pm$ 0.99	0.034 (d<b)
HDT	-0.11 $\pm$ 0.80	-0.10 $\pm$ 0.98	0.17 $\pm$ 1.13	0.04 $\pm$ 1.08	0.39
HPT	0.04 $\pm$ 1.04	0.56 $\pm$ 0.64	0.09 $\pm$ 0.81	-0.70 $\pm$ 1.06	0.003 (d<b,c)
cPPT	-0.21 $\pm$ 0.89	0.26 $\pm$ 1.15	0.07 $\pm$ 1.02	-0.12 $\pm$ 0.92	0.17
cPTT	-0.10 $\pm$ 0.96	0.53 $\pm$ 1.05	0.06 $\pm$ 0.95	-0.50 $\pm$ 0.81	0.011 (a,d<b)
VAScPTT	0.003 $\pm$ 1.10	0.20 $\pm$ 0.90	0.06 $\pm$ 1.01	-0.28 $\pm$ 0.96	0.25
TSP	-0.09 $\pm$ 0.86	-0.43 $\pm$ 0.45	0.23 $\pm$ 1.13	0.29 $\pm$ 1.25	0.03 (c,d>a,b)
CPM	-0.01 $\pm$ 0.93	0.43 $\pm$ 0.75	0.06 $\pm$ 1.12	-0.48 $\pm$ 0.99	0.038 (d<b)

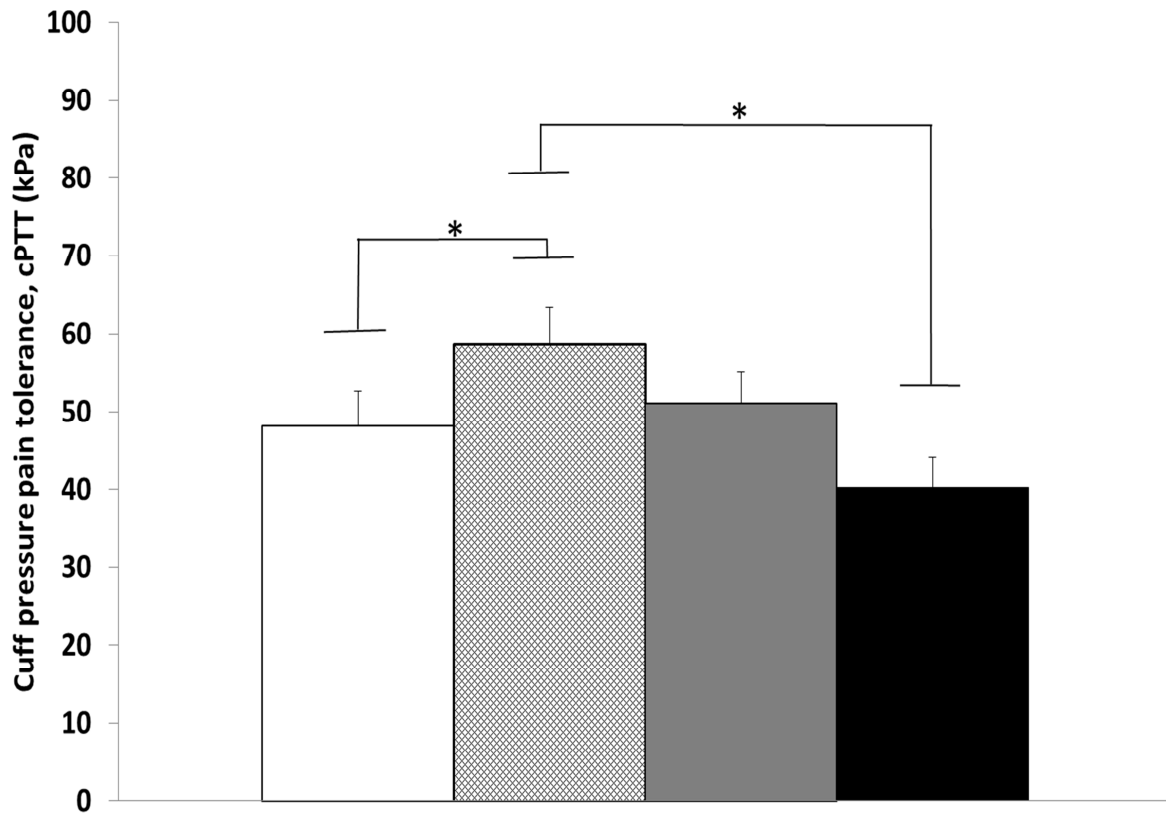
**Table 3:** Pearson correlations between clinical pain intensity, pain sensitivity as well as pro-nociceptive and anti-nociceptive mechanisms. Due to multiple correlational analyses, P-values equal to or less than 0.001 (0.05 / 36) were considered significant for the correlations. 'HPT': Heat Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance. 'TSP': Temporal summation of pressure pain. 'CPM': Conditioned pain modulation.

Variables	Correlation	Clinical pain intensity	PCS	TSK	PDI	HPT	cPPT	cPTT	TSP	CPM
Clinical pain intensity	R P-value	-	<b>0.604</b> < <b>0.001</b>	<b>0.559</b> < <b>0.001</b>	<b>0.413</b> <b>0.001</b>	-0.241 0.046	-0.091 0.456	-0.185 0.128	0.148 0.225	-0.284 0.018
PCS	R P-value	<b>0.604</b> < <b>0.001</b>	-	<b>0.599</b> < <b>0.001</b>	<b>0.663</b> < <b>0.001</b>	-0.238 0.038	0.003 0.980	-0.081 0.526	0.183 0.150	-0.317 0.011
TSK	R P-value	<b>0.559</b> < <b>0.001</b>	<b>0.599</b> < <b>0.001</b>	-	<b>0.471</b> < <b>0.001</b>	-0.234 0.063	-0.183 0.149	-0.294 0.018	0.199 0.115	-0.325 0.009
PDI	R P-value	<b>0.413</b> <b>0.001</b>	<b>0.663</b> < <b>0.001</b>	<b>0.471</b> < <b>0.001</b>	-	-0.090 0.476	0.102 0.419	0.029 0.818	0.114 0.366	-0.207 0.099
HPT	R P-value	-0.241 0.046	-0.238 0.038	-0.234 0.063	-0.090 0.476	-	<b>0.435</b> < <b>0.001</b>	<b>0.447</b> < <b>0.001</b>	-0.055 0.650	0.134 0.270
cPPT	R P-value	-0.091 0.456	0.003 0.980	-0.183 0.149	0.102 0.419	<b>0.435</b> < <b>0.001</b>	-	<b>0.780</b> < <b>0.001</b>	-0.064 0.600	0.127 0.296
cPTT	R P-value	-0.185 0.128	-0.081 0.526	-0.294 0.018	0.029 0.818	<b>0.447</b> < <b>0.001</b>	<b>0.780</b> < <b>0.001</b>	-	-0.266 0.026	0.312 0.009
TSP	R P-value	0.148 0.225	0.183 0.150	0.199 0.115	0.114 0.366	-0.055 0.650	-0.064 0.600	-0.266 0.026	-	-0.120 0.322
CPM	R P-value	-0.284 0.018	-0.317 0.011	-0.325 0.009	-0.207 0.099	0.134 0.270	0.127 0.296	0.312 0.009	-0.120 0.322	-

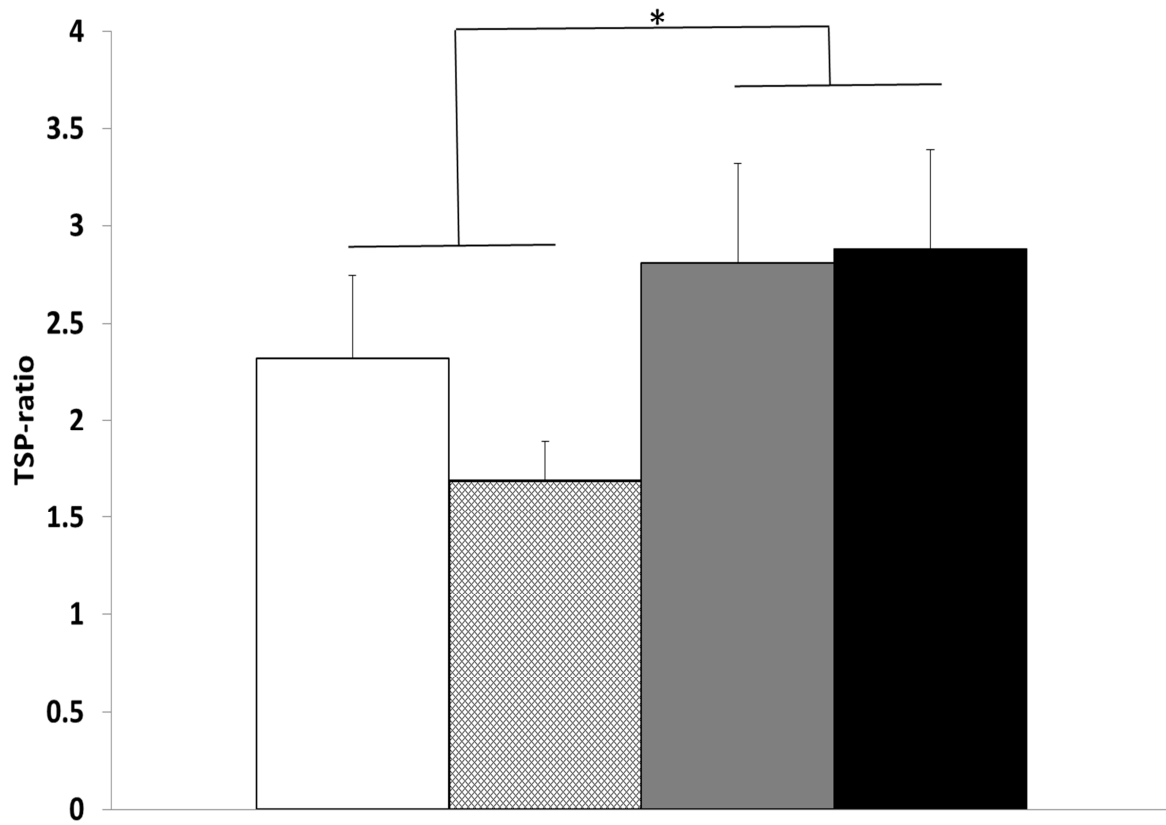
A  Low Back Pain  Neck Pain  Low Back Radiating Pain  Cervikal Radiating Pain



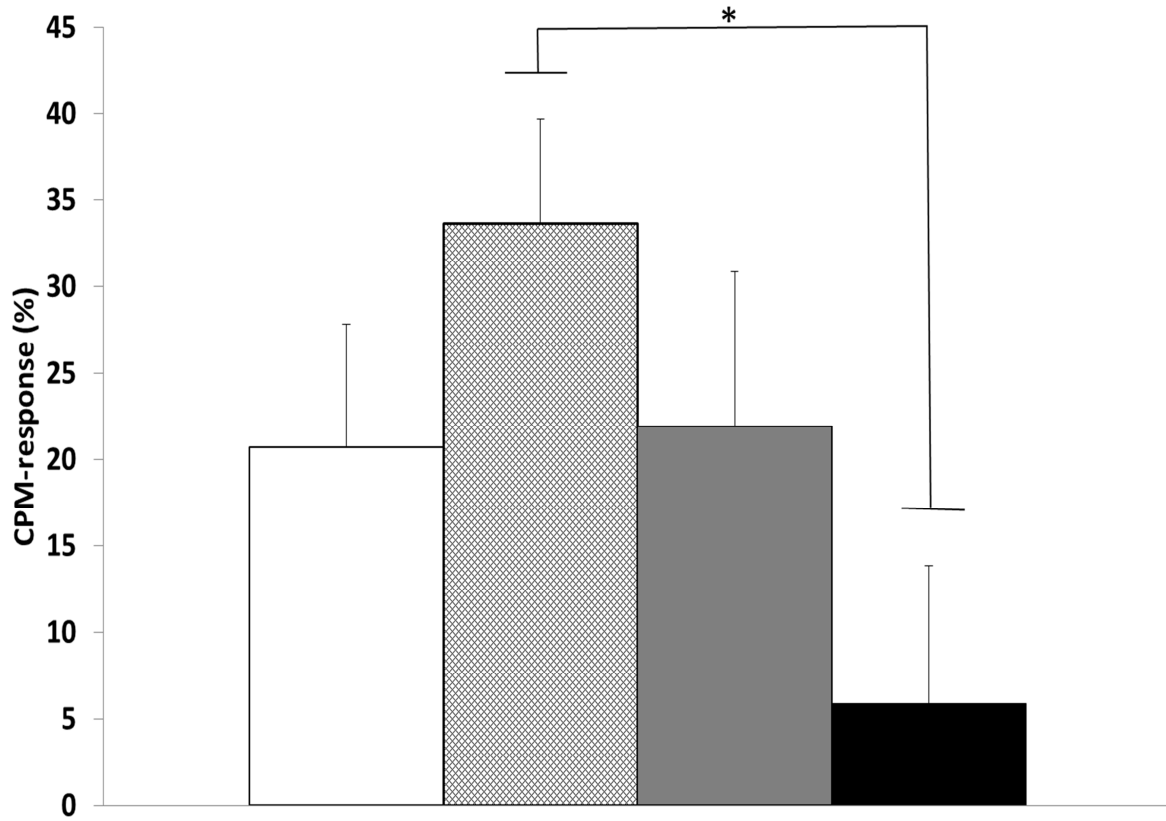
**B**    □ Low Back Pain    ▨ Neck Pain    ▩ Low Back Radiating Pain    ■ Cervikal Radiating Pain



A  Low Back Pain  Neck Pain  Low Back Radiating Pain  Cervikal Radiating Pain



**B**    □ Low Back Pain    ▨ Neck Pain    ■ Low Back Radiating Pain    ■ Cervikal Radiating Pain



**Highlights**

- Sensory and clinical pain profiles are different in subtypes of back pain
- Patients with radiating pain demonstrated facilitated temporal pain summation
- Different back pain conditions may require different treatment strategies