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# Experimental pain measurements do not relate to pain intensity and pain cognitions in people scheduled for surgery for lumbar radiculopathy

## Experimental pain measurements versus pain cognitions

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## Abstract

**Objective.** The present cross-sectional study aims to unravel associations between pain intensity and cognitions versus quantitative sensory testing in people scheduled for surgery for lumbar radiculopathy. Additionally, insight will be provided in the presence of dysfunctional nociceptive processing and maladaptive pain cognitions in this population.

**Design.** Cross-sectional study.

**Setting.** Data from three hospitals in Belgium.

**Subjects.** The final sample comprised 120 participants with lumbar radiculopathy scheduled for surgery, included between March 2016 and April 2019.

**Methods.** Self-reported pain intensity was assessed using a visual analogue scale and pain cognitions were assessed using self-reported questionnaires (Pain Catastrophizing Scale, Tampa Scale for Kinesiophobia and Pain Vigilance and Awareness Questionnaire). Quantitative sensory testing (detection thresholds, pain thresholds, temporal summation and conditioned pain modulation) was evaluated as well.

**Results.** Evidence was found for the presence of an impaired inhibitory response to nociceptive stimuli and maladaptive pain cognitions in this population. Kinesiophobia was found to be present to a maladaptive degree in the majority of the patients (n=106 (88%)). Significant, but weak, associations between electrical pain thresholds at the Sural nerves and leg pain intensity (Sural nerve symptomatic side: r=-0.23; p=0.01; non-symptomatic side: r=-0.22; p=0.02) and kinesiophobia levels (Sural nerve non-symptomatic side: r=-0.26; p=0.006) were identified.

**Conclusions.** Electrical detection thresholds and correlates for endogenous nociceptive facilitation and inhibition were not found to be related with any of the pain cognitions, nor with pain intensity in people scheduled to undergo surgery for lumbar radiculopathy.

**Keywords.** Quantitative sensory testing; pain; pain cognitions; neurophysiology; radiculopathy

## Introduction

Low back pain is a highly prevalent condition (point prevalence for Belgium: 24.8%(1)) and one of the leading causes of disability globally(2). A subgroup of people with low back pain (5-10%) are also suffering from radiating leg pain(3), also known as lumbar radiculopathy. In people presenting with lumbar radiculopathy, a surgical intervention to decompress the symptomatic lumbar nerve root is often indicated when conservative care fails(4). Although these surgical interventions are often anatomically successful (75-80% success rate(5)), 23-28% of the patients end up with chronic low back and leg pain(6), and this is associated with high socio-economic burden(7).

Several perioperative factors have been associated with the development of (chronic) postsurgical pain, including, maladaptive cognitive-emotional factors(8), preoperative pain intensity(9), psychological disorders(9, 10), among others. It has been suggested that the relationship between preoperative pain intensity and the occurrence of chronic postsurgical pain is due to preexisting peripheral nociceptor sensitization in the surgical field combined with structural and physiological changes in the central nervous system(9, 11). The latter comprise neurophysiological processes and changes related to peripheral and central nervous system sensitization, such as decreased pain thresholds, enhanced wind-up (temporal summation) and impaired endogenous nociceptive inhibition(12). The latter two have also been found to be related with persistent post-surgical pain and disability following various surgical procedures when present during the preoperative period(9, 13). For research purposes, neurophysiological processing of nociceptive stimuli is often measured by quantitative sensory testing (QST)(13). Although it has been suggested that the predictive value of preoperative pain intensity might be due to the occurrence of neurophysiological changes related to central sensitization(9), there is still no conclusive evidence for a relationship between pain intensity and QST outcomes in people with spinal pain(14-16).

One of the key features of postoperative pain is dysfunctional endogenous nociceptive inhibition(9), which further underscores the importance of a functional endogenous analgesic system to achieve

acceptable postoperative health. In people with chronic pain, it has been confirmed that the (mal)functioning of endogenous analgesia is at least partially caused by maladaptive cognitive and/or emotional factors such as pain catastrophizing(17), anxiety(18) and (activity) avoidance(19). Such maladaptive cognitive and emotional factors have been found to be present to a clinically relevant degree in a subgroup of people undergoing surgery for lumbar radiculopathy(20, 21). However, to the best of our knowledge, the relationship between QST outcomes and cognitive and emotional factors was not extensively studied in this population yet. This knowledge gap is especially relevant because of the fact that these maladaptive cognitive and emotional factors can be improved by targeted interventions, such as pain neuroscience education which has been found to significantly decrease pain catastrophizing (i.e., an exaggerated negative mental set brought to bear during actual or anticipated painful experience(22))(23), kinesiophobia (i.e., fear of movement and/or (re-)injury(24))(25) and pain hypervigilance (i.e., constant scanning of the body for somatic, and particularly, pain sensations(26))(25).

The present study aims to unravel associations between pain intensity and cognitions (i.e., pain catastrophizing, kinesiophobia and pain vigilance/awareness) versus experimental pain measurements (i.e., QST) in people scheduled for surgery for lumbar radiculopathy. Additionally, this study will provide further insight in the presence of dysfunctional nociceptive processing and maladaptive pain cognitions in this population.

## Methods

Study design

This cross-sectional study, comprises a secondary analysis of the baseline data of a multicenter double-blind randomized controlled trial (n=120). The study was conducted in accordance with the revised Declaration of Helsinki (1998) and reported following the STROBE (Strengthening The Reporting of

OBservational studies in Epidemiology) Statement (Appendix A: STROBE checklist). The study protocol was approved by the Ethics Committee of the Universitair Ziekenhuis Brussel (B.U.N.143201526926) and prospectively registered on ClinicalTrials.gov (NCT02630732) at December 15, 2015. The protocol of the randomized controlled trial has been published elsewhere(27).

Participants

People scheduled for surgery for lumbar radiculopathy (aged 18–65 years) were recruited from the Department of Neurosurgery at the Universitair Ziekenhuis Brussel (Brussels, Belgium), AZ Sint Dimpna (Geel, Belgium) and AZ Sint-Maarten (Mechelen, Belgium) between March 2016 and April 2019. Participants needed to be able to read and speak Dutch fluently and had to continue their usual care 3 weeks before surgery. Exclusion criteria were, having symptoms of spinal cord compression, having chronic pain other than the symptoms related to lumbar radiculopathy, having rheumatologic, neurological, or psychiatric disorders, presenting cognitive impairments, and being pregnant or having given birth in the past year. Moreover, participants were not allowed to start new treatments during the 3 weeks preceding the scheduled surgery. All participants had to provide written informed consent before study participation.

Study protocol

Data collection was performed by 2 researchers trained in quantitative sensory testing during the week prior to surgery. Participants were first asked to complete a set of self-reported questionnaires on a computer to assess pain cognitions and intensity. Afterwards, electrical detection thresholds (EDTs), electrical pain thresholds (EPTs) and temporal summation (TS) were determined consecutively at both Sural nerves and at the Median nerve of the symptomatic side. Afterwards, a conditioned pain modulation (CPM) protocol was conducted on the three test locations with electrical stimulation and a cold pressor task, as often used in research settings(28, 29). The order of test locations was randomized. No instructions or restrictions regarding medication use were provided due to ethical considerations and to avoid withdrawal symptoms.

Outcome measurements

*Pain intensity and cognitions*

The Pain Catastrophizing Scale (PCS) was used to measure the level of pain catastrophizing. This self-reported questionnaire consists of 13 pain-related cognition items that are scored on a 5-point Likert scale (0= not at all, 4= all the time; total score range: 0-52))(30). The higher the score, the higher the level of pain catastrophizing. Scores ≥30/52 indicate a clinically relevant level of catastrophizing(30). Next to the PCS total score, subscale scores for rumination (PCS_R), magnification (PCS_M) and helplessness (PCS_H) were calculated. The Dutch version of the PCS has established clinimetric properties(31, 32).

Attention to pain was assessed with the Pain Vigilance and Awareness Questionnaire (PVAQ) which comprises 16 items that assess awareness, consciousness, vigilance and observation of pain and are rated on a 6-point scale (total score range: 0-80). The PVAQ shows good internal consistency reliability (26).

To assess the level of Kinesiophobia, the Tampa Scale for Kinesiophobia (TSK) was used. The clinimetric properties of this 17-item questionnaire (score range: 17-68) are well-established in people with low back pain (33, 34). Scores ≥37/68 indicate a clinically relevant level of kinesiophobia.

The Visual Analogue Scale (VAS) was used to measure pain intensity for low back pain and leg pain separately. Patients were asked to rate their average pain intensity on a VAS ranging from “no pain” (score 0) to “worst pain imaginable” (score 100).

*Electrical detection and pain thresholds*

EDTs and EPTs were determined on both Sural nerves and on the Median nerve. For the stimulation of the Sural nerves, the electrode was placed on the skin posterior of the lateral malleolus at the symptomatic and non-symptomatic side(35). For the Median nerve, the electrode was placed on the skin 5 cm from the wrist in the anatomical region of the Median nerve(36).

At each test location, electrical stimuli (constant current pulse train of 5 pulses at 250 Hz) were given through a bipolar felt pad electrode (Surpass LT Stimulator (EMS Biomedical, Korneuburg, Austria)). Stimuli were gradually increased by steps of 0.5 mA, starting from 0 mA. The participant was asked to inform the researcher once a faint sensation was experienced, which was registered as the EDT. Stimuli were then further increased, and the participant was asked to indicate when the stimuli became unpleasant. The intensity of the first unpleasant stimulus was then registered as the EPT(37). At each location, the measurement was performed 3 times with a 30 seconds rest interval in between. The mean of those 3 measurements was calculated as the final EDT and EPT for each location(38).

*Temporal summation*

Endogenous nociceptive facilitation was evaluated by applying a TS protocol for which 20 stimuli(37) were delivered at the previously determined intensity of the EPT for that specific location at a frequency of 2 Hz. Participants provided a verbal numeric rating scale (vNRS) score for pain intensity ranging from 0 (= no pain) to 10 (= worst imaginable pain)(37) after the 1st, the 10th and the 20th stimulus.

*Conditioned pain modulation*

Brain-orchestrated nociceptive inhibition was evaluated using a parallel CPM paradigm for which electrical stimulation as test stimulus and a cold pressor task using water of 12°C as conditioning stimulus (VersaCoolTM, Thermo Scientific, Thermo Fisher Scientific Inc., Waltham, MA USA) were used. This temperature is sufficient to produce a painful response and is bearable for a few minutes. In the first phase, the participant received 20 electrical stimuli(39) at an intensity of 140% the individualized

EPT(40). After the last stimulation, the participant was instructed to rate the pain intensity of the electrical stimuli on a vNRS from 0 to 10 with 0 indicating “no pain” and 10 “worst pain imaginable”. In the second phase, the participant received the same test stimulus together with the conditioning stimulus. The participant was instructed to submerge the hand of the non-symptomatic side upto the wrist into the cold water. After the last electrical stimulation was provided, participants could withdraw their hand. Again, a vNRS pain intensity score was asked for the electrical stimuli. Stimuli were always provided with a variable inter-stimulus interval of 8 to 12 seconds. After testing the CPM paradigm at one location a rest interval of 3 minutes was taken into account. Next, the CPM protocol was repeated for the other test locations in the same randomized order as for the electrical threshold assessments. A higher pain intensity score for the test stimulus alone versus the test stimulus in combination with the conditioning stimulus, was considered to be an inhibitory CPM effect. A lower or equal pain intensity score for the test stimulus alone versus the test stimulus in combination with the conditioning stimulus, was considered to be a facilitatory CPM effect. Participants did not receive specific instructions regarding their attention, thus they were not instructed to pay specific attention to either the test stimuli or the conditioning stimulus.

Data analysis

Statistical analyses were performed in R Studio version 1.2.5019 (R version 3.6). Normality was checked with the Shapiro Wilk test and QQ-plots and equality of variances by Levene’s tests. Demographics were presented as means with corresponding standard deviations (SD) or medians with corresponding first and third quantiles (Q1-Q3), for normally and non-normally distributed data, respectively.

The magnitude of TS was determined by using two different calculation methods(41). The first method calculated the absolute difference in vNRS scores between the last ($20^{th}$ stimulus) and first pain rating by subtracting the pain score of the first rating from the last rating, here called “the absolute difference”. The second method consisted of calculating the percent change in pain scores between

the last and first pain intensity rating, here called “the relative difference”. For the percentage change, vNRS score from the last pain rating minus vNRS score from the first pain rating was divided by the vNRS score from the first pain rating. This value was multiplied by 100 to obtain the percent change. For both the absolute and relative difference, higher positive values are indicating higher levels of nociceptive facilitation.

Also for the analyses of CPM results, both absolute differences and percentage change were calculated(42). The absolute difference was calculated by subtracting the pain intensity before the application of the conditioning stimulus from the pain intensity during the application of the conditioning stimulus. For the relative difference, pain intensity during the conditioning stimulus minus pain intensity before the conditioning stimulus was divided by the pain intensity before the conditioning stimulus. This value was multiplied by 100 to obtain the percent change (i.e., the relative difference). For both the absolute and relative difference, negative values are indicating the presence of nociceptive inhibition during CPM testing(43). No difference in pain scores between the two conditions of the CPM paradigm, or a positive difference, is representing impaired functionality of the endogenous nociceptive inhibitory system.

First, Wilcoxon tests were used to evaluate whether a TS and CPM effect occurred across the sample by comparing the data for the first and last vNRS score for TS and the data for the pain intensity before and during the application of the conditioning stimulus for CPM. Secondly, correlation analyses were performed between QST outcomes (i.e., EDTs, EPTs, TS and CPM) on the one hand, and VAS for pain intensity and pain cognition scores (i.e., TSK, PCS_R, PCS_M, PCS_H and PVAQ) on the other hand, using Spearman correlations. A Bonferroni correction was applied to correct for multiple testing.

Finally, to further explore the relationship between QST measures and pain intensity and cognitions, multivariate linear regression analyses with QST outcomes as the dependent variable were performed. For TS the absolute difference was used as dependent variable. For CPM, the relative method was taken into account. For QST measures, ‘Tukey’s ladder of powers’ was used to obtain a more normally

distributed vector of values. All independent variables (pain cognitions and pain intensity) were included in multivariate linear regression analyses predicting QST outcomes. A combined forward and backward stepwise elimination procedure was used to select the final models. Assumptions were checked for the final multivariate models. Robust models were used in case of outlying observations. Significance level for the interpretation of the analyses was set at 0.05.

## Results

Demographics

In this study, data of 120 participants (62 males, 58 females) were included (Table 1). The participants had a median age of 49.16 (Q1-Q3: 37.3-57.43) years. Ninety participants (75%) were experiencing chronic pain, defined as pain present for 3 months or longer. The median average VAS score for back pain intensity was 45/100 (Q1-Q3: 16.5-66) and 55/100 (Q1-Q3: 32.75-77.25) for leg pain intensity.

Pain cognitions

The sample had a median score on the TSK of 43/68 (Q1-Q3: 39 - 47) with 106 (88.3%) participants presenting maladaptive levels of kinesiophobia. Pain catastrophizing was present to a maladaptive degree in 40 (33.3%) participants with a median score on the PCS of 25/52 (Q1-Q3: 18 -32.25). Median scores of 10 (Q1-Q3: 7 - 12), 4 (Q1-Q3: 3 - 6) and 11 (Q1-Q3: 8 - 16) were found for the PCS subscales rumination, magnification and helplessness, respectively. The median PVAQ score was 38/80 (Q1-Q3: 32-48).

Temporal summation

At the location of the Median nerve, vNRS scores on the first stimulus (median score: 4 (Q1-Q3: 3-5)) were significantly lower compared to vNRS scores on the $20^{th}$ stimulus (median score: 5.5 (Q1-Q3: 4-7)) (V statistic (V)=196.5, $p<0.001$) (Figure 1). At the Sural nerve on the symptomatic side, vNRS scores

increased significantly from 3 (Q1-Q3: 2-5) on the first stimulus to 6 (Q1-Q3: 4-8) on the 20$^{th}$ stimulus (V=147.5, p<0.001). For the test location at the Sural nerve on the non-symptomatic side, a significant increase (V=153, p<0.001) was found in vNRS scores between the first stimulus (3 (Q1-Q3: 2-5)) and 20$^{th}$ stimulus (5.05 (Q1-Q3: 5-7)). Absolute and relative differences for TS are presented in Table 1.

Conditioned Pain Modulation

At the three test locations, pain scores for the electrical stimuli were significantly lower when the conditioning stimulus (cold water) was applied compared to the pain scores for the electrical stimulation without conditioning stimulus (Median nerve V=1925.5, p<0.001; Sural nerve symptomatic side V=2127.5, p<0.001; Sural nerve non-symptomatic side V=2746, p<0.001) (Figure 1). When combining all test locations, 10 participants showed impaired endogenous nociceptive inhibition as measured by the CPM paradigm, while 32 patients did present an inhibitory response during the CPM paradigm at all locations. Absolute differences and percentage changes for CPM are presented in Table 1.

Correlations between QST outcomes and pain cognitions/pain intensity

Correlation analyses between QST outcomes and pain cognitions showed 1 significant association. The total score on the TSK was negatively correlated with the EPT at the Sural nerve on the non-symptomatic side (r=-0.26; p=0.006), presenting a weak correlation coefficient.

Also, 2 significant correlations were found between QST results and self-reported pain intensity levels. The EPT for the Sural nerve at the symptomatic (r=-0.23; p=0.01) and non-symptomatic side (r=-0.22; p=0.02) showed a weak negative correlation with the VAS score for leg pain.

No other significant correlations were found. Correlation matrices between QST outcomes and pain intensity and cognitions can be found in Figure 2.

Multivariate regression predicting QST outcomes with pain intensity and cognitions as independent variables

Two multivariate models were significantly better than a model with only an intercept, namely, a model for the EPT on the Sural nerve at the symptomatic side ($F(2,106)=6.316$, $p=0.003$) and a model for the EPT on the Sural nerve at the non-symptomatic side ($F(2,106)=5.96$, $p=0.004$). In the model for the EPT on the Sural nerve at the symptomatic side, TSK ($\beta=-0.002$; $p=0.02$) and VAS leg ($\beta=-0.0004$; $p=0.03$) remained statistically significant. This model had an adjusted $R^2$ of 8.96%. For the EPT on the Sural nerve at the non-symptomatic side, TSK ($\beta=-0.004$; $p=0.02$) and VAS leg ($\beta=-0.001$; $p=0.04$) remained statistically significant. This model had an adjusted $R^2$ of 8.41%. Full details of both models can be found in Table 2. Both models presented satisfying results concerning normality of error terms, independence of error terms, linearity and homoscedasticity.

## Discussion

This cross-sectional study aimed to provide more insight in the presence of maladaptive nociceptive processing and pain cognitions and investigated the association between QST outcomes versus self-reported pain intensity and pain cognitions in people scheduled for surgery for lumbar radiculopathy. The presence of an impaired inhibitory response to nociceptive stimuli could be confirmed in a subgroup of the sample, however, no clear characterization of this sample was possible. This sample (N=10) consisted of 6 males and 4 females of which 4 patients had pain less than 3 months with median scores for leg pain of 56 (Q1-Q3: 46.25 – 82.75) and back pain of 38.5 (Q1-Q3: 19 – 50). All patients in this sample presented with kinesiophobia to a maladaptive degree, while pain catastrophizing was only pronounced in 4 patients. The majority of the participants in this study presented kinesiophobia to a maladaptive degree, while pain catastrophizing and hypervigilance levels were less pronounced. Leg pain intensity and kinesiophobia levels showed a weak but significant association with pain thresholds in both the symptomatic and non-symptomatic leg. No significant associations between self-reported pain intensity and cognitions and the remaining QST outcomes (i.e., EDTs, TS and CPM) could be confirmed.

Our findings concerning a potential association between QST outcomes and self-reported pain intensity are in line with the available literature concerning this relationship in a variety of populations experiencing pain. In accordance with the results of the present study, a systematic review by Hübscher et al. (2013) found only weak negative correlations between pain thresholds and pain severity in people with chronic spinal pain(14). For the remaining correlates of endogenous nociceptive processing (i.e., TS and CPM), no significant associations with pain intensity could be confirmed in the present sample. In line with this, the systematic review by McPhee et al. (2020) did not find a relationship between worse pain severity and more facilitation in people with low back pain(44). Also in the meta-analysis of Hübscher et al. (2013) only a weak to non-existent positive association between pain intensity and TS measures in people with chronic spinal pain was found(14). Concerning the relationship between correlates of endogenous nociceptive inhibition (i.e., CPM) and pain intensity, the former systematic review by McPhee et al. (2020) found that pain severity was impacting the degree of impairment in CPM(44), which is in contrast with the findings of the present study. A systematic review by Fernandes et al. (2019), on the other hand, found that the majority (62%) of studies investigating the relationship between CPM and pain intensity in a variety of populations with chronic pain, reported no significant associations between these variables(45).

Taken together, it can be stated that the available research regarding a potential relationship between pain intensity and QST measures, including the results of the present study in a population consisting of 75% chronic pain patients, is rather inconclusive. Especially for correlates of endogenous nociceptive facilitation (TS) and inhibition (CPM) there seems to be no firm evidence for a relationship in a variety of pain populations. For pain thresholds, it can be concluded that our findings of a significant but weak negative association with pain severity are in line with the available literature.

Given the fact that QST is deemed to be a measure for endogenous nociceptive processing, it was expected to find at least a fair relationship between QST measures and pain intensity, but this hypothesis was not confirmed by the present study in people scheduled for surgery for lumbar

radiculopathy. A potential explanation for this absence of a relationship might be the fact that QST was initially developed to assess central and/or peripheral sensitization, implying impaired endogenous nociceptive processing towards decreased inhibition and increased facilitation of nociceptive stimuli(46, 47). However, such impaired neurophysiological processing was only present in a subgroup of the present sample (N=10, as described above), which might indicate that pain experience in this sample was not predominantly determined by impaired nociceptive processing, potentially diminishing the association between QST measures and pain intensity(14). It was previously suggested that patients with chronic low back pain present themselves within a spectrum ranging from healthy persons towards patients with fibromyalgia, the latter being a group in which abnormal pain processing has previously been reported(48). Based on the currently obtained results, it might be possible that patients with lumbar radiculopathy present themselves more towards the side of healthy persons. Additionally, there might be a difference between evoked pain experience and clinical pain. Apparently, brain areas associated with emotions, i.e., the prefrontal limbic areas, are engaged during clinical pain, but not during evoked pain(14, 49). This might explain the limited relationship between QST measures in which evoked pain is used, such as TS and CPM, and clinical pain intensity.

The relationship between pain cognitions and QST measures, has been investigated before in different populations with pain, including people with chronic low back pain(50, 51). Overall these studies showed inconsistent results, comprising either weak significant associations or no evidence for an association between pain cognitions and QST outcomes, which is confirming our findings in people with lumbar radiculopathy. In accordance with our findings for a relationship between kinesiophobia levels and EPTs in people with radiculopathy, earlier studies also found associations between fear of movement and pain thresholds in people with chronic low back(52) and neck(53) pain, using thermal(52) and mechanical stimuli(53), respectively. On the other hand, a study on people with chronic musculoskeletal pain was not able to confirm a significant relationship between kinesiophobia and pressure pain thresholds(54). The present study was not able to confirm an association between kinesiophobia and TS which is in line with the results of a study in people with chronic low back

pain(52). On the contrary, another study in the latter population, did find evidence for a relationship between fear of movement and TS(55).

Concerning pain catastrophizing, the literature reports conflicting evidence for a potential relationship with pain thresholds, with some studies indicating a significant, often small, relationship(50, 56), while others could not confirm this association(51, 57) in a variety of pain populations. Although, in line with the results of Sullivan et al. (2009)(55), we did not find a significant relationship between pain catastrophizing and TS, other studies did report evidence for this association in people with chronic low back pain(52). Remarkably, in a 2016 meta-analysis pain catastrophizing was found to be the sole psychological factor related to CPM using electrical stimulation(58). This result could not be confirmed, potentially due to a different stimulation protocol that was used in the present study. For the PVAQ, significant associations have been found with pressure pain thresholds, but not with heat pain thresholds, again indicating a potential influence of the protocol used(59). The same study in people with knee osteoarthritis also found that higher pain vigilance levels were related with more nociceptive facilitation(59). In our study however, no significant relationship between QST measures and the PVAQ were shown. For CPM, this is in line with the results of the meta-analysis by Nahman-Averbuch et al. (2016)(58).

This inconsistency in the literature concerning relationships with QST measures can possibly be explained by the fact that a variety of testing protocols is used to assess correlates of endogenous nociceptive processing, highlighting the current absence of a universal gold standard protocol, despite extensive initiatives to create a standardized protocol such as the German Research Network on Neuropathic Pain (DFNS)(60). Moreover, the potential influence of different protocols on the eventual outcomes, or the fact whether different protocols (e.g., the use of mechanical, heat or electrical stimuli) can be correlates for different aspects of the neurophysiological processes that they are deemed to represent, is not yet entirely clarified(58). These uncertainties should be taken into account when comparing results concerning QST data across different studies.

Recommendations for future research

The variety in QST protocols and presumptions that different protocols might be measuring different neurophysiological processes, highlight the need for further research on differences between QST protocols, which could eventually lead to a gold standard, potentially condition-specific, testing protocol. In the meantime, studies assessing QST measures should consider to use different modalities for the correlates of endogenous nociceptive processing that they are aiming to measure, as has been suggested in QST guidelines before(43, 58). Furthermore, the results of this study together with the rationale behind a potential relationship between pain cognitions and measures of nociceptive processing, suggest that it could be interesting to further investigate these associations specifically in people presenting with maladaptive pain cognitions to a clinically relevant degree.

Limitations

First of all, this study reports the analysis of baseline data of a large randomized controlled trial (n=120), and although the character of the research question was primarily explorative, this might imply that the study was not sufficiently powered for the present research questions. Second, only one modality (i.e., electrical stimulation) was used for QST, while the available guidelines are recommending using different modalities(43, 58). This choice was made to not further increase the burden for the study participants, as the protocol for the randomized controlled trial was already asking for a high time investment. Potentially other significant relationships could have been identified when using different stimulation modalities (e.g., mechanical or thermal stimulation). Also, QST measurements were performed by 2 researchers, which may imply a risk of operator bias. However, stringent measures were taken to minimize the latter: both researchers were trained simultaneously by the same expert in QST; a standardized protocol was used, including predetermined participant instructions; and together, the researchers performed a pilot trial to optimize the standardized QST protocol and confirm its feasibility(61). Furthermore, patients were allowed to continue taking their pain medication to ensure validity of the results in the clinical setting. Nevertheless, this decision could

have influenced QST measures (62). Moreover, 75% of the patients presented with chronic pain (pain lasting ≥ 3 months) whereby 25% presented with pain lasting for less than 3 months. Potentially, this heterogeneity could have influenced the results of this study. Last, due to the cross-sectional design, no conclusions can be made on potential causal interactions between the predictor variables and QST measures.

## Conclusions

This study showed impaired nociceptive processing and maladaptive pain cognitions in subgroups of people scheduled for surgery for lumbar radiculopathy. Kinesiophobia was found to be present to a maladaptive degree in the majority of the participants. A significant association between EPTs and leg pain intensity and kinesiophobia levels was identified. Correlates for endogenous nociceptive facilitation and inhibition were not found to be related with any of the pain cognitions, nor with pain intensity, in people undergoing surgery for lumbar radiculopathy.

## Author contributions

Conception and design: JN, KP, MM, RB, KI, Acquisition of data: EH, LG, WVB, Analysis and interpretation of data: all authors, Drafting the article and revising it critically for important intellectual content: all authors. All authors approved the final version of the manuscript.

## References


1. Van der Heyden J, Charafeddine R. Gezondheidsenquête 2018: Chronische ziekten en aandoeningen. In: Van der Heyden J, Charafeddine R, eds. *Gezondheidsenquëte 2018*. Belgium: Sciensano, 2019.
2. Collaborators GBDDIIP. 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* 2018;**392**(10159)**:** 1789-858.

3. Koes BW, van Tulder MW, Peul WC. Diagnosis and treatment of sciatica. *BMJ* 2007;**334**(7607)**:** 1313-7.
4. Kreiner DS, Hwang SW, Easa JE, Resnick DK, Baisden JL, Bess S, Cho CH, DePalma MJ, Dougherty P, 2nd, Fernand R, Ghiselli G, Hanna AS, Lamer T, Lisi AJ, Mazanec DJ, Meagher RJ, Nucci RC, Patel RD, Sembrano JN, Sharma AK, Summers JT, Taleghani CK, Tontz WL, Jr., Toton JF, North American Spine S. An evidence-based clinical guideline for the diagnosis and treatment of lumbar disc herniation with radiculopathy. *Spine J* 2014;**14**(1)**:** 180-91.
5. Dohrmann GJ, Mansour N. Long-Term Results of Various Operations for Lumbar Disc Herniation: Analysis of over 39,000 Patients. *Med Princ Pract* 2015;**24**(3)**:** 285-90.
6. Rathod TN, Chandanwale A, Ladkat KM, Chavan S, Chavan A, Bhosale PB. High sensitive C-reactive protein-Effective tool in determining postoperative recovery in lumbar disc disease. *Indian J Orthop* 2014;**48**(4)**:** 354-9.
7. Liedgens H, Obradovic M, De Courcy J, Holbrook T, Jakubanis R. A burden of illness study for neuropathic pain in Europe. *ClinicoEconomics and outcomes research : CEOR* 2016;**8:** 113-26.
8. Anderson JT, Haas AR, Percy R, Woods ST, Ahn UM, Ahn NU. Clinical depression is a strong predictor of poor lumbar fusion outcomes among workers' compensation subjects. *Spine* 2015;**40**(10)**:** 748-56.
9. Fregoso G, Wang A, Tseng K, Wang J. Transition from Acute to Chronic Pain: Evaluating Risk for Chronic Postsurgical Pain. *Pain physician* 2019;**22**(5)**:** 479-88.
10. Klinger R, Geiger F, Schiltenwolf M. Can failed back surgery be prevented? Psychological risk factors for postoperative pain after back surgery. *Orthopade* 2008;**37**(10)**:** 1002-6.
11. Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. *Br J Surg* 1999;**86**(12)**:** 1528-31.
12. Nijs J, Leysen L, Vanlauwe J, Logghe T, Ickmans K, Polli A, Malfliet A, Coppieters I, Huysmans E. Treatment of central sensitization in patients with chronic pain: time for change? *Expert opinion on pharmacotherapy* 2019;**20**(16)**:** 1961-70.
13. Sangesland A, Støren C, Vaegter HB. Are preoperative experimental pain assessments correlated with clinical pain outcomes after surgery? A systematic review. *Scandinavian journal of pain* 2017;**15:** 44-52.
14. Hubscher M, Moloney N, Leaver A, Rebbeck T, McAuley JH, Refshauge KM. Relationship between quantitative sensory testing and pain or disability in people with spinal pain-a systematic review and meta-analysis. *Pain* 2013;**154**(9)**:** 1497-504.
15. Rabey M, Kendell M, Koren S, Silva I, Watts L, Wong C, Slater H, Smith A, Beales D. Do chronic low back pain subgroups derived from dynamic quantitative sensory testing exhibit differing multidimensional profiles? *Scandinavian journal of pain* 2021;**21**(3)**:** 474-84.
16. Overstreet DS, Michl AN, Penn TM, Rumble DD, Aroke EN, Sims AM, King AL, Hasan FN, Quinn TL, Long DL, Sorge RE, Goodin BR. Temporal summation of mechanical pain prospectively predicts movement-evoked pain severity in adults with chronic low back pain. *BMC musculoskeletal disorders* 2021;**22**(1)**:** 429.
17. Schreiber KL, Campbell C, Martel MO, Greenbaum S, Wasan AD, Borsook D, Jamison RN, Edwards RR. Distraction analgesia in chronic pain patients: the impact of catastrophizing. *Anesthesiology* 2014;**121**(6)**:** 1292-301.
18. Wiech K, Edwards R, Moseley GL, Berna C, Ploner M, Tracey I. Dissociable neural mechanisms underlying the modulation of pain and anxiety? An FMRI pilot study. *PloS one* 2014;**9**(12)**:** e110654.
19. Nahman-Averbuch H, Yarnitsky D, Sprecher E, Granovsky Y, Granot M. Relationship between Personality Traits and Endogenous Analgesia: The Role of Harm Avoidance. *Pain Pract* 2016;**16**(1)**:** 38-45.
20. Svensson GL, Lundberg M, Ostgaard HC, Wendt GK. High degree of kinesiophobia after lumbar disc herniation surgery: a cross-sectional study of 84 patients. *Acta Orthop* 2011;**82**(6)**:** 732-6.

21. Ostelo RW, de Vet HC, Berfelo MW, Kerckhoffs MR, Vlaeyen JW, Wolters PM, van den Brandt PA. Effectiveness of behavioral graded activity after first-time lumbar disc surgery: short term results of a randomized controlled trial. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2003;**12**(6)**:** 637-44.
22. Sullivan MJL. The Pain Catstrophizing Scale: User Manual. 2009: 36.
23. Deguchi N, Hirakawa Y, Izawa S, Yokoyama K, Muraki K, Oshibuti R, Higaki Y. Effects of pain neuroscience education in hospitalized patients with high tibial osteotomy: a quasi-experimental study using propensity score matching. *BMC musculoskeletal disorders* 2019;**20**(1)**:** 516-16.
24. Roelofs J, Goubert L, Peters ML, Vlaeyen JW, Crombez G. The Tampa Scale for Kinesiophobia: further examination of psychometric properties in patients with chronic low back pain and fibromyalgia. *European Journal of Pain* 2004;**8**(5)**:** 495-502.
25. Malfliet A, Kregel J, Coppieters I, De Pauw R, Meeus M, Roussel N, Cagnie B, Danneels L, Nijs J. Effect of Pain Neuroscience Education Combined With Cognition-Targeted Motor Control Training on Chronic Spinal Pain: A Randomized Clinical Trial. *JAMA Neurol* 2018;**75**(7)**:** 808-17.
26. Roelofs J, Peters ML, McCracken L, Vlaeyen JW. The pain vigilance and awareness questionnaire (PVAQ): further psychometric evaluation in fibromyalgia and other chronic pain syndromes. *Pain* 2003;**101**(3)**:** 299-306.
27. Ickmans K, Moens M, Putman K, Buyl R, Goudman L, Huysmans E, Diener I, Logghe T, Louw A, Nijs J. Back school or brain school for patients undergoing surgery for lumbar radiculopathy? Protocol for a randomised, controlled trial. *J Physiother* 2016;**62**(3)**:** 165.
28. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice ASC. Reliability of conditioned pain modulation: a systematic review. *Pain* 2016;**157**(11)**:** 2410-19.
29. Mertens MG, Hermans L, Crombez G, Goudman L, Calders P, Van Oosterwijck J, Meeus M. Comparison of five conditioned pain modulation paradigms and influencing personal factors in healthy adults. *European journal of pain (London, England)* 2021;**25**(1)**:** 243-56.
30. Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychol Assess* 1995;**7**(4)**:** 524-32.
31. Severeijns R, van den Hout MA, Vlaeyen JW, Picavet HS. Pain catastrophizing and general health status in a large Dutch community sample. *Pain* 2002;**99**(1-2)**:** 367-76.
32. Van Damme S, Crombez G, Bijttebier P, Goubert L, Van Houdenhove B. A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. *Pain* 2002;**96**(3)**:** 319-24.
33. Swinkels-Meewisse EJ, Swinkels RA, Verbeek AL, Vlaeyen JW, Oostendorp RA. Psychometric properties of the Tampa Scale for kinesiophobia and the fear-avoidance beliefs questionnaire in acute low back pain. *Man Ther* 2003;**8**(1)**:** 29-36.
34. Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain* 1995;**62**(3)**:** 363-72.
35. Jurth C, Rehberg B, von Dincklage F. Reliability of subjective pain ratings and nociceptive flexion reflex responses as measures of conditioned pain modulation. *Pain Res Manag* 2014;**19**(2)**:** 93-6.
36. Motohashi K, Umino M. Heterotopic painful stimulation decreases the late component of somatosensory evoked potentials induced by electrical tooth stimulation. *Brain research Cognitive brain research* 2001;**11**(1)**:** 39-46.
37. Vuilleumier PH, Biurrun Manresa JA, Ghamri Y, Mlekusch S, Siegenthaler A, Arendt-Nielsen L, Curatolo M. Reliability of Quantitative Sensory Tests in a Low Back Pain Population. *Reg Anesth Pain Med* 2015;**40**(6)**:** 665-73.
38. Vuilleumier PH, Besson M, Desmeules J, Arendt-Nielsen L, Curatolo M. Evaluation of Anti-Hyperalgesic and Analgesic Effects of Two Benzodiazepines in Human Experimental Pain: A Randomized Placebo-Controlled Study. *PloS one* 2013;**8**(3)**:** e43896.

39. Piché M, Watanabe N, Sakata M, Oda K, Toyohara J, Ishii K, Ishiwata K, Hotta H. Basal μ-opioid receptor availability in the amygdala predicts the inhibition of pain-related brain activity during heterotopic noxious counter-stimulation. *Neuroscience research* 2014;**81-82:** 78-84.
40. Fujii-Abe K, Oono Y, Motohashi K, Fukayama H, Umino M. Heterotopic CO2 laser stimulation inhibits tooth-related somatosensory evoked potentials. *Pain medicine (Malden, Mass)* 2010;**11**(6)**:** 825-33.
41. Granot M, Granovsky Y, Sprecher E, Nir RR, Yarnitsky D. Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. *Pain* 2006;**122**(3)**:** 295-305.
42. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, Hansson P, Lautenbacher S, Marchand S, Wilder-Smith O. Recommendations on terminology and practice of psychophysical DNIC testing. *European journal of pain (London, England)* 2010;**14**(4)**:** 339.
43. 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* 2014.
44. McPhee ME, Vaegter HB, Graven-Nielsen T. Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis. *Pain* 2020;**161**(3)**:** 464-75.
45. Fernandes C, Pidal-Miranda M, Samartin-Veiga N, Carrillo-de-la-Pena MT. Conditioned pain modulation as a biomarker of chronic pain: a systematic review of its concurrent validity. *Pain* 2019;**160**(12)**:** 2679-90.
46. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *The journal of pain : official journal of the American Pain Society* 2009;**10**(6)**:** 556-72.
47. Yarnitsky D, Granot M. Quantitative Sensory Testing. In: Cervero F, Jensen T, eds. Handb Clin Neurol. Amsterdam: Elsevier; 2006: 397-409.
48. Goubert D, Danneels L, Graven-Nielsen T, Descheemaeker F, Meeus M. Differences in Pain Processing Between Patients with Chronic Low Back Pain, Recurrent Low Back Pain, and Fibromyalgia. *Pain physician* 2017;**20**(4)**:** 307-18.
49. Parks EL, Geha PY, Baliki MN, Katz J, Schnitzer TJ, Apkarian AV. Brain activity for chronic knee osteoarthritis: dissociating evoked pain from spontaneous pain. *European journal of pain (London, England)* 2011;**15**(8)**:** 843 e1-14.
50. Meints SM, Mawla I, Napadow V, Kong J, Gerber J, Chan ST, Wasan AD, Kaptchuk TJ, McDonnell C, Carriere J, Rosen B, Gollub RL, Edwards RR. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain. *Pain* 2019;**160**(4)**:** 833-43.
51. Curatolo M, Muller M, Ashraf A, Neziri AY, Streitberger K, Andersen OK, Arendt-Nielsen L. Pain hypersensitivity and spinal nociceptive hypersensitivity in chronic pain: prevalence and associated factors. *Pain* 2015;**156**(11)**:** 2373-82.
52. George SZ, Wittmer VT, Fillingim RB, Robinson ME. Sex and pain-related psychological variables are associated with thermal pain sensitivity for patients with chronic low back pain. *The journal of pain : official journal of the American Pain Society* 2007;**8**(1)**:** 2-10.
53. Walton DM, Levesque L, Payne M, Schick J. Clinical pressure pain threshold testing in neck pain: comparing protocols, responsiveness, and association with psychological variables. *Phys Ther* 2014;**94**(6)**:** 827-37.
54. Vaegter HB, Madsen AB, Handberg G, Graven-Nielsen T. Kinesiophobia is associated with pain intensity but not pain sensitivity before and after exercise: an explorative analysis. *Physiotherapy* 2018;**104**(2)**:** 187-93.

55. Sullivan MJ, Thibault P, Andrikonyte J, Butler H, Catchlove R, Lariviere C. Psychological influences on repetition-induced summation of activity-related pain in patients with chronic low back pain. *Pain* 2009;**141**(1-2)**:** 70-8.
56. Terry MJ, Moeschler SM, Hoelzer BC, Hooten WM. Pain Catastrophizing and Anxiety are Associated With Heat Pain Perception in a Community Sample of Adults With Chronic Pain. *Clin J Pain* 2016;**32**(10)**:** 875-81.
57. Martinez-Calderon J, Meeus M, Struyf F, Diaz-Cerrillo JL, Clavero-Cano S, Morales-Asencio JM, Luque-Suarez A. Psychological factors are associated with local and generalized pressure pain hypersensitivity, pain intensity, and function in people with chronic shoulder pain: A cross-sectional study. *Musculoskelet Sci Pract* 2019;**44:** 102064.
58. Nahman-Averbuch H, Nir RR, Sprecher E, Yarnitsky D. Psychological Factors and Conditioned Pain Modulation: A Meta-Analysis. *Clin J Pain* 2016;**32**(6)**:** 541-54.
59. Herbert MS, Goodin BR, Pero STt, Schmidt JK, Sotolongo A, Bulls HW, Glover TL, King CD, Sibille KT, Cruz-Almeida Y, Staud R, Fessler BJ, Bradley LA, Fillingim RB. Pain hypervigilance is associated with greater clinical pain severity and enhanced experimental pain sensitivity among adults with symptomatic knee osteoarthritis. *Ann Behav Med* 2014;**48**(1)**:** 50-60.
60. Rolke R, Baron R, Maier C, Tolle TR, Treede DR, 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* 2006;**123**(3)**:** 231-43.
61. Goudman L, Huysmans E, Coppieters I, Ickmans K, Nijs J, Buyl R, Putman K, Moens M. Electrical (Pain) Thresholds and Conditioned Pain Modulation in Patients with Low Back-Related Leg Pain and Patients with Failed Back Surgery Syndrome: A Cross-Sectional Pilot Study. *Pain medicine (Malden, Mass)* 2020;**21**(3)**:** 538-47.
62. Lelic D, Olesen AE, Grønlund D, Jure FA, Drewes AM. Opioid Specific Effects on Central Processing of Sensation and Pain: A Randomized, Cross-Over, Placebo-Controlled Study. *The journal of pain : official journal of the American Pain Society* 2021;**22**(11)**:** 1477-96.

## Tables

**Table 1**: Demographics and outcome measurements for all patients.

| Topic | Variables (n) | Patients[1] | Patients with pain < 3 months (N=30) | Patients with pain ≥3 months (N=90) |
|---|---|---|---|---|
| **Demographics** | Sex | 62 (51.67%) males<br>58 (48.33%) females | 18 (60%) males<br>12 (40%) females | 44 (48.89%) males<br>46 (51.11%) females |
| | Age (years) | 49.16 (Q1-Q3: 37.3-57.43) | 51.25 (Q1-Q3: 44.37-56.45) | 47.84 (Q1-Q3: 36.45-57.87) |
| | n (%) with chronic pain (≥3 months) | 90 (75%) | | |
| **Pain** | Mean VAS back (/100) (n=120) | 45 (Q1-Q3: 16.5-66) | 15 (Q1-Q3: 11.25-36) | 50 (Q1-Q3: 34-69) |
| | Mean VAS leg (/100) (n=120) | 55 (Q1-Q3: 32.75-77.25) | 49.5 (Q1-Q3: 24.25-75) | 55.5 (Q1-Q3: 33.75-77.75) |
| **Pain cognitions** | Total score TSK (/68) (n=120)<br>n (%) TSK score ≥37/68 (n=120) | 43 (Q1-Q3: 39 - 47)<br>106 (88.3%) | 41 (Q1-Q3: 38.25 – 46.75)<br>24 (80%) | 43.5 (Q1-Q3: 39.25 - 47)<br>82 (91.1%) |
| | Total score PCS (/52) (n=120)<br>n (%) PCS score ≥30/52 (n=120)<br>Subscore rumination (/16)<br>Subscore magnification (/12) | 25 (Q1-Q3: 18 -32.25)<br>40 (33.3%)<br>10 (Q1-Q3: 7 - 12)<br>4 (Q1-Q3: 3 - 6) | 19 (Q1-Q3: 16 -25.75)<br>6 (20%)<br>8 (Q1-Q3: 6 - 10)<br>4 (Q1-Q3: 3 - 5) | 26 (Q1-Q3: 20.25 -37)<br>34 (37.8%)<br>10 (Q1-Q3: 7 - 13)<br>4 (Q1-Q3: 3 - 7) |

| | | | | | |
|---|---|---|---|---|---|
| | | Subscore helpnessness (/24) | 11 (Q1-Q3: 8 - 16) | 9.5 (Q1-Q3: 6.25 - 11) | 12 (Q1-Q3: 9 – 17.75) |
| | | Total score PVAQ (/80) (n=120) | 38 (Q1-Q3: 32-48) | 36.5 (Q1-Q3: 29.25-42.75) | 38.5 (Q1-Q3: 33.25-48.75) |
| **QST** | EDT (mA) | Median nerve (n=110) | 1.5 (Q1-Q3: 1-1.83) | 1.33 (Q1-Q3: 1-1.67) | 1.5 (Q1-Q3: 1-1.83) |
| | | Symptomatic Sural nerve (n=109) | 2.33 (Q1-Q3: 1.83-3) | 2.33 (Q1-Q3: 1.83-3) | 2.33 (Q1-Q3: 1.83-2.83) |
| | | Non-symptomatic Sural nerve (n=109) | 2.17 (Q1-Q3: 1.67-2.67) | 2.17 (Q1-Q3: 2-2.67) | 2.17 (Q1-Q3: 1.67-2.71) |
| | EPT (mA) | Median nerve (n=110) | 4.17 (Q1-Q3: 3-6.4) | 4 (Q1-Q3: 2.5-5.17) | 4.17 (Q1-Q3: 3-6.5) |
| | | Symptomatic Sural nerve (n=109) | 7 (Q1-Q3: 5.17-10) | 7.67 (Q1-Q3: 5-9.83) | 6.92 (Q1-Q3: 5.29-10.04) |
| | | Non-symptomatic Sural nerve (n=109) | 7 (Q1-Q3: 5.33-10.33) | 7.33 (Q1-Q3: 5.5-10.83) | 6.75 (Q1-Q3: 4.83-9.71) |
| | TS absolute[2] | Median nerve (n=110) | 1 (Q1-Q3: 0-3) | 1 (Q1-Q3: 0-3) | 1 (Q1-Q3: 0-3) |
| | | Symptomatic Sural nerve (n=109) | 2 (Q1-Q3: 0-4) | 2 (Q1-Q3: 0-4) | 2 (Q1-Q3: 0-4) |
| | | Non-symptomatic Sural nerve (n=108) | 2 (Q1-Q3: 0-3.25) | 1 (Q1-Q3: 0-3) | 2 (Q1-Q3: 0-4) |
| | TS relative[3] | Median nerve (n=110) | 25 (Q1-Q3: 0-100) | 16.67 (Q1-Q3: 0-75) | 28.57 (Q1-Q3: 0-100) |
| | | Symptomatic Sural nerve (n=109) | 50 (Q1-Q3: 0-133.3) | 50 (Q1-Q3: 0-133.3) | 55 (Q1-Q3: 0-133.3) |
| | | Non-symptomatic Sural nerve (n=108) | 50 (Q1-Q3: 0-150) | 33.33 (Q1-Q3: 0-100) | 50 (Q1-Q3: 0-150) |
| | CPM absolute[4] | Median nerve (n=98) | -1 (Q1-Q3: -1 – 0) | 0 (Q1-Q3: -1 – 0) | -1 (Q1-Q3: -2 – 0) |
| | | n (%) with impaired nociceptive inhibition | 42 (43.86%) | 13 (52%) | 29 (39.73%) |

| | | | | |
|---|---|---|---|---|
| | Symptomatic Sural nerve (n=99) | -1 (Q1-Q3: -1 – 0) | -0.25 (Q1-Q3: -1 – 0) | -1 (Q1-Q3: -2 – 0) |
| | n (%) with impaired nociceptive inhibition | 42 (42.42%) | 13 (50%) | 29 (39.73%) |
| | Non-symptomatic Sural nerve (n=101) | -1 (Q1-Q3: -2 – 0) | -1 (Q1-Q3: -1.75 – 0) | -1 (Q1-Q3: -2 – 0) |
| | n (%) with impaired nociceptive inhibition | 33 (32.67%) | 10 (38.46%) | 23 (30.67%) |
| CPM relative[5] | Median nerve (n=98) | -16.67 (Q1-Q3: -33.33 – 0) | 0 (Q1-Q3: -25 – 0) | -20 (Q1-Q3: -33.33 – 0) |
| | Symptomatic Sural nerve (n=99) | -14.29 (Q1-Q3: -33.33 – 0) | -7.14 (Q1-Q3: -32.14 – 0) | -16.67 (Q1-Q3: -33.33 – 0) |
| | Non-symptomatic Sural nerve (n=101) | -20 (Q1-Q3: -40 – 0) | -18.33 (Q1-Q3: -33.33 – 0) | -25 (Q1-Q3: -40 – 0) |

N: sample size; Q: quartile; VAS: Visual Analogue Scale; TSK: Tampa Scale for Kinesiophobia; SD: standard deviation; PCS: Pain Catastrophizing Scale; QST: quantitative sensory testing; EDT: electrical detection threshold; mA: milliamps; EPT: electrical pain threshold; TS: temporal summation; CPM: conditioned pain modulation

[1]Demographics were presented as means with corresponding standard deviations (SD) or medians with corresponding first and third quantiles (Q1-Q3), for normally and non-normally distributed data, respectively.

[2]TS absolute difference = vNRS for the last ($20^{th}$) stimulus – vNRS for the first stimulus

[3]TS relative difference = ((vNRS for the last ($20^{th}$) stimulus – vNRS for the first stimulus)/vNRS for the first stimulus)*100 (percentage change)

[4]CPM absolute difference = vNRS during conditioning stimulus – vNRS before conditioning stimulus

[5]CPM relative difference = ((vNRS during conditioning stimulus – vNRS before conditioning stimulus)/vNRS before conditioning stimulus)*100 (percentage change)

**Table 2:** Coefficients of the multivariate linear regression analyses predicting QST outcomes with pain intensity/cognitions as independent factors.

| Outcome | Predictor | Estimate | SE | t-value | p-value | 95% CI | Adj. $R^2$ model |
|---|---|---|---|---|---|---|---|
| **EPT symptomatic Sural nerve[a]** | *Intercept* | 1.33 | 0.038 | 3. | <0.001 | 1.257 to 1.408 | 8.96% |
| | TSK | -0.002 | 0.001 | -2.47 | 0.02 | -0.0004 to -0.004 | |
| | VAS leg | -0.000 | 0.000 | -2.16 | 0.03 | -0.00004 to -0.0008 | |
| **EPT non-symptomatic Sural nerve[b]** | *Intercept* | 1.62 | 0.07 | 22.69 | <0.001 | 1.483 to 1.767 | 8.41% |
| | TSK | -0.004 | 0.002 | -2.42 | 0.02 | -0.0007 to -0.007 | |
| | VAS leg | -0.001 | 0.000 | -2.08 | 0.04 | -0.00004 to -0.001 | |

The following transformations were applied to the independent variable x, wherefore model interpretation is on this level: [a] $x^{0.1}$, [b] $x^{0.175}$. Abbreviations: adj: adjusted; CI: confidence interval; EPT: electrical pain threshold; SE: standard error; TSK: Tampa Scale for Kinesiophobia; VAS: Visual Analogue Scale.

## Figures

**Figure 1:** vNRS pain intensity reportings during temporal summation (left; TS) and conditioned pain modulation (right; CPM) protocol on the three test locations. For TS, vNRS scores on the first and 20$^{th}$ stimulus are presented. For CPM, vNRS reportings for the electrical stimuli (stim) and electrical stimuli in combination with the conditioning stimulus (stim+water) are presented. The orange bars represent the measurements on the Median nerve, the blue bars represent the measurements on the symptomatic Sural nerve and the red bars represent the measurements on the non-symptomatic Sural nerve. Abbreviations: CPM: conditioned pain modulation; TS: temporal summation; Stim: stimulus. *: $p<0.05$.

**Figure 2**: Correlation plots between experimental pain measurements and pain intensity/pain cognitions at the Median nerve (left), Sural nerve at the symptomatic side (middle) and Sural nerve at the non-symptomatic side (right). Correlation coefficients are ranging from -1 (red) to +1 (blue). The strength of the correlation is represented in the size of the circles. Abbreviations: EDT: electrical detection threshold; EPT: electrical pain threshold; TS: temporal summation; abs: absolute difference; rel: relative difference; CPM: conditioned pain modulation; VAS: visual analogue scale; TSK: Tampa Scale for Kinesiophobia; PCS_H: Pain Catastrophizing Scale subscore helplessness; PCS_M: Pain Catastrophizing Scale subscore magnification; PCS_R: Pain Catastrophizing Scale subscore rumination; PVAQ: Pain Vigilance and Awareness Questionnaire.