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Petersen, Kristian Kjær; Simonsen, Ole; Laursen, Mogens Berg; Arendt-Nielsen, Lars

Published in:
The Clinical Journal of Pain

DOI (link to publication from Publisher):
10.1097/AJP.0000000000000528

Publication date:
2018

Document Version
Accepted author manuscript, peer reviewed version

The Clinical Journal of Pain Publish Ahead of Print
DOI:10.1097/AJP.0000000000000528

The Role of Preoperative Radiological Severity, Sensory Testing, and Temporal Summation on Chronic Postoperative Pain following Total Knee Arthroplasty

Authors: Kristian Kjær Petersen[1], Ole Simonsen[2], Mogens Berg Laursen[2], Lars Arendt-Nielsen[1*]

Affiliations:

(1) SMI, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

(2) Aalborg University Hospital, Orthopaedic Surgery Research Unit, Aalborg, Denmark

Keywords: Thermal testing, radiological osteoarthritis, temporal summation, chronic postoperative pain

***Corresponding Author:**

Prof. Lars Arendt-Nielsen, Ph.D., DMSc.

SMI

Department of Health Science and Technology

Faculty of Medicine, Aalborg University

Fredrik Bajers Vej 7 D3, DK-9220 Aalborg, Denmark

Phone:+45 9940 8831, Fax:+45 9815 4008, E-mail: LAN@HST.AAU.DK

The authors declare no conflict of interest

Abstract

Objectives: Knee osteoarthritis (KOA) can be associated with local and central sensitization. As an indicator of the central gain, facilitated temporal summation of pain (TSP) has been found in KOA patients. This facilitation is predictive of the development of chronic postoperative pain after total knee arthroplasty (TKA). Other studies have suggested hypoesthesia/hypoalgesia to thermal stimuli as a feature in KOA. This study investigated associations between preoperative TSP, thermal sensitivity and radiological severity for the development of chronic postoperative pain after TKA.

Methods: Radiological KOA (Kellgren & Lawrence, KL), TSP, and thermal stimuli were collected preoperatively. Clinical knee pain intensity (VAS 0-10) was assessed before and 12 months following TKA. Subjects were categorized into a chronic postoperative pain group if they experienced less than 30% pain reduction of the initial pain after 12 months.

Results: 19% of the subjects were categorized as chronic pain subjects and presented facilitated preoperative TSP ($P<0.05$) and a trend towards increased heat pain threshold ($P=0.077$) compared with subjects with normal recovery. Pearson correlations found that preoperative TSP ($R=0.193$, $P=0.013$), KL ($R=-0.168$, $P=0.027$), warm detection threshold ($R=0.195$, $P=0.012$), and heat pain threshold ($R=0.196$, $P=0.012$) were associated with pain intensity 12 months after TKA where TSP was identified as an independent factor.

Discussion: This study showed that preoperatively facilitated TSP in KOA patients was predictive of the development of chronic postoperative pain following TKA. Furthermore, this study is the first to find an association between preoperative hypoalgesia to heat and the development of chronic postoperative pain following TKA.

Introduction

Total joint arthroplasty surgery is considered an effective intervention to improve function and reduce pain in the end-stage of knee osteoarthritis (KOA). In the United States alone, the number of total knee arthroplasties (TKA) has increased from 31.2 per 100,000 person years in the period 1971-1976 to 220.9 in the period 2005-2008[1]. By 2030, the incidence of TKA is expected to be increased by approx. 700% [2]. Prosthesis-related outcomes such as radiographic appearance of the prosthesis, implant survival, or surgeon-assessed outcomes are highly successful after TKA; and while most patients experience pain relief after TKA, approx. 20% of the TKA patients continue to suffer from chronic postoperative pain [3].

Understanding pain is complex and a single preoperative measure cannot predict chronic postoperative pain. However, several risk factors have been identified[4] including preoperative pain sensitization[5–11]. Further, joint pain is highly individual and nociceptors have been identified in, e.g. the fat pad, subchondral bone, periosteum, and the synovium but not in normal cartilage[12]. This could partly explain why cartilage features have not demonstrated robust associations with the pain manifestations[13]. Recent studies have even demonstrated that low structural damage (low KL) before surgery is associated with a high risk of poor postoperative outcomes[8,14].

The role of pain amplification in the development of chronic postoperative pain has been identified in patients undergoing total hip arthroplasty (THA)[7,11] and TKA[5,6,8]. Quantitative sensory testing (QST) is used for mechanistic profiling of the underlying features of KOA pain[15]. Patients with chronic pain, e.g. OA[16,17], fibromyalgia[18], or low back pain[19] show facilitated pain responses to repeated painful stimulation (temporal summation of pain, TSP) compared with healthy controls. This suggests that the central gain is facilitated. Recent studies have found facilitated preoperative TSP to be associated with

the development of chronic postoperative pain following TKA using both cutaneous, modified Von Frey filaments[6] and targeting of deep muscle structures using cuff algometry[5]. Further, these associations have also been found for total hip arthroplasty (THA)[11] and acute postoperative pain in patients undergoing thoracotomy[20] and are suggested to be a precursor for the development of chronic postoperative pain[21].

Recently, thermal cutaneous hypoesthesia and hypoalgesia have been reported for knee OA pain[22,23]. A similar loss of function has been seen in patients with, e.g. neuropathic pain[24] whereas patients with knee OA generally report gain of function of the central nervous system to stimulation of musculoskeletal structures [25,26].

The current study aimed to investigate and compare the predictive values of preoperative radiological knee OA and quantitative sensory testing (cutaneous thermal testing and temporal summation of pain) for the development of chronic postoperative pain 12 months after TKA surgery.

Materials and Methods

Patients

KOA patients (N=200) scheduled for unilateral TKA from the Outpatient Clinic, Orthopaedic Department Frederikshavn, Aalborg University Hospital, Denmark, were invited to join the study. The radiological KOA progression was evaluated using the Kellgren & Lawrence (KL) score[27]. Patients with other diagnosed pain problems (e.g. hip OA, rheumatoid arthritis, fibromyalgia, neuropathic pain) or mental impairments were excluded from the study. The study was approved by The North Denmark Region Committee on Health Research Ethics (N-20120015) and conducted in accordance with the Helsinki Declaration. All patients signed an informed consent. The patients recruited were part of a

large study aiming at linking preoperative factors to postoperative outcomes. A subsample of this cohort has previously been included in another scientific publication[5].

Protocol

The peak pain intensity within the last 24 hours (0-10, visual analogue scale, VAS), demographics and thermal detection and pain thresholds and temporal summation of pain ratings (TSP) were collected before TKA. Thermal thresholds were recorded using the Medoc Pathway system (Medoc ltd., Ramat Yishai, Israel) with an ATS probe (30 x 30 mm). TSP was collected using a modified von Frey stimulator with a weighted load (Aalborg University, Denmark) as previously used in other KOA studies[6,28,29]. The subjects were not allowed to take any analgesic medication 24 hours prior to the examination. Moreover, the subjects were contacted 12 months after surgery to collect the VAS score of the peak pain intensity within the last 24 hours (VAS). The subjects were divided into two groups: subjects with more than 30% reduction in pain (normal recovery group) and subjects with less than 30% reduction in pain (chronic pain group) as compared with the initial preoperative pain ratings.

Thermal Stimuli

Cold detection thresholds (CDTs) and warm detection thresholds (WDTs) were measured followed by cold pain thresholds (CPTs) and heat pain thresholds (HPTs) as previously described[30]. The mean threshold temperature of three consecutive measurements was calculated. All thresholds were obtained with ramp stimuli (1ºC/sec). The stimuli were terminated when the subject pressed a button. Pre-defined cut-off temperatures from the Medoc Pathway system were 0 and 50ºC. Baseline temperature for all measurements was 32ºC.The subjects were not able to watch the computer screen during the experiment. All assessments were performed on the tibialis anterior muscle. High WDT and low CDT indicated thermal hypoesthesia and high HPT and CPT indicated thermal hypoalgesia.

Temporal Summation of Pain

A modified von Frey stimulator (tip area 0.2 mm2) with a weighted load (Aalborg University, Denmark) was used to induce TSP as previously conducted in other KOA studies[6,28,29]. A force of 25.6g was applied once over the tibialis anterior muscle and the subject was asked to rate the pain intensity on the VAS (0-10). Then ten consecutive stimuli were applied (1 sec interval between consecutive stimuli) to the same site and the subject was asked to rate the pain intensity of the last stimulation on the VAS. TSP was calculated as the difference in the pain intensity between the first and the last stimulation. High TSP scores indicated facilitated temporal summation.

Statistics

The data are presented as means and standard errors (SE) unless otherwise stated. An independent sample t-test was used to compare pre-operative data between the two groups. Pearson correlations were used for correlation analysis between preoperative measures and postoperative pain levels. Linear regression on significant parameters from the Pearson correlations was used to categorize independent parameters. $P<0.05$ was considered significant.

Results

Sixty subjects were excluded from the data analysis due to technical issues with the Medoc Pathway system and 10 subjects were excluded due to misunderstanding of the procedure or lack of preoperative or postoperative VAS scores. The subjects excluded were not different with regard to postoperative pain levels (P=0.259), pain relief (P=0.701), and KL (P=0.659) but showed a trend towards lower preoperative pain levels (P=0.072) compared with the subjects included in the analysis.

Of the remaining 130 subjects, 25 subjects (19%) were categorised into the chronic pain group and 105 (81%) were categorised into the normal recovery group. Preoperative demographics are shown in table 1.

Thermal Thresholds

Preoperative CDT, WDT, CPT and HPT from both groups are shown in figure 1. No differences were found between the groups for the detection thresholds (CDT: P>0.632, WDT: P>0.365).

Thirteen subjects (52%) in the chronic pain group and 50 subjects (48%) in the normal recovery group did not reach the CPT before the system terminated the stimuli (pre-defined at 0ºC). No differences were found between the groups for CPT (P>0.667) but a trend towards significantly increased HPT was found in the chronic pain group (P=0.077).

Temporal Summation of Pain

Preoperative TSP from both groups is shown in figure 2. Preoperative TSP was facilitated by 4.19 (SEM: 0.46) VAS points in the chronic pain group compared with the recovery group with 3.13 (SEM: 0.23) VAS points (P<0.05).

Correlations

Significant correlations between preoperative pain intensity and preoperative TSP (R=0.192, P=0.017) and KL (R=-0.155, P=0.044) were found. No significant correlations were found between preoperative pain intensity and the other sensory tests.

Significant Pearson correlations between preoperative TSP (R=0.193, P=0.013), KL (R=-0.168, P=0.027), WDT (R=0.195, P=0.012) and HPT (R=0.196, P=0.012) were found to be associated with pain intensity ratings 12 months after TKA. Linear regression showed that only preoperative TSP was

an independent factor (table 2). No significant associations were found between CDT (R=0.025, P>0.05) and CPT (R=-0.002, P>0.05) and pain intensity rating 12 months after surgery.

Discussion

The current study confirmed that independently of radiological KOA and thermal test preoperative temporal summation of pain can predict KOA patients at risk of having chronic postoperative pain 12 months following TKA. Further, the current study is the first to find associations between preoperative hypoesthesia and hypoalgesia to heat and associated low radiological KOA with high postoperative pain intensity levels 12months after TKA.

Preoperative Measures of Central Pain Mechanisms

Accumulating evidence suggests that preoperative assessment of increased gain in the pain system is associated with the development of chronic postoperative pain. Widespread hyperalgesia, facilitated TSP, and impaired conditioned pain modulation (CPM) have been reported in KOA patients as compared with healthy controls and are signs of increased gain in the central nervous system[15]. Previously, preoperative widespread hyperalgesia has been associated with the development of chronic postoperative pain following TKA[5,8] and THA[7]. Further, impaired preoperative CPM has been associated with postoperative pain following abdominal surgery[10], thoracotomy[9] and TKA[5]. Finally, preoperative TSP has been associated with postoperative pain following thoracotomy[20], THA[11] and TKA[6] and preoperative TSP has been shown to be associated with chronic postoperative pain following TKA independently of the preoperative pain intensity[6]. The current study found that preoperative TSP was associated with chronic postoperative pain following TKA independently of KL, WDT and HPT.

Structural Damage and Knee Osteoarthritis

Radiological assessments focusing on cartilage, such as the Kellgren & Lawrence scale[27], have not shown robust associations with pain manifestations in KOA, neither in the individual patient's rating of the clinical pain [13] nor in experimental pain measures[31]. Finan et al., 2013[32] found that a subgroup of KOA patients characterized by high pain and low structural damage displayed widespread hyperalgesia, high pain during a cold pressor test and facilitated TSP. Arendt-Nielsen et al., 2015[31] supported that high pain level and low structural damage were associated with local and widespread pressure hyperalgesia, impaired CPM, and facilitated TSP. Riis et al., 2014[14] found that low structural damage was associated with low functional levels 12 months after TKA. Finally, Wylde et al., 2016[8] found that widespread hyperalgesia in combination with lower radiological assessments was associated with less pain relief after TKA. In summary, all studies mentioned indicate that low preoperative radiological assessments are associated with poor outcome following TKA. In line with previous studies, the current study found that low radiological assessment was associated with high preoperative pain intensities and was associated with high postoperative pain intensities but found that this association was not independent of TSP.

Thermal Testing in Knee Osteoarthritis

Kuni et al., 2014[33] found warmth hypoesthesia in the asymptomatic knee but not in the symptomatic knee in early KOA compared with healthy controls. Similarly, Izumi et al., 2016[11] showed the same in severe hip OA patients compared with healthy controls. King et al, 2013[22] found that heat pain threshold and tolerance thresholds were elevated in patients with severe symptomatic KOA but not in patients with less symptomatic KOA compared with healthy controls. Further, studies have found heat related hypoesthesia and hypoalgesia in patients with lateral epicondylalgia[34] and in patients with chronic neuralgia[35]. Üçeyler et al., 2013 [36] found that a subgroup of fibromyalgia patients displayed

increased thermal detection thresholds, and skin biopsies confirmed a loss of small thin cutaneous never fibers. Leinders et al., 2016[37] recently found that several systemic mirco-RNAs (miR), specifically miR-103, miR-151, and miR-let-7d, were downregulated in patients with fibromyalgia whereas cutaneous miR-let-7d was elevated in patients with reduced small nerve fiber density. miR-let-7d has previously been found to be associated with chronic pain in patients with complex regional pain syndrome[38] and to affect the endogenous opioid system[39], which is known to be impaired in, e.g. KOA[15] or fibromyalgia[40]. It is currently unknown if patients with KOA have reduced small nerve fiber density and what the underlying reason for this might be.

Experimentally, tactile hypoesthesia has been observed, e.g. outside an hyperalgesic area following a cutaneous capsaicin injection[41] and vibration thresholds have been found to increase during heat pain[42]. This phenomenon has been explained by a presynaptic inhibition by differentiated sensory inputs [41]. The current study was not able to determine if the strong peripheral drive from the musculoskeletal type II (joint) and type III (free nerve endings) mechanoreceptors may have an inhibitory effect on the cutaneous fibers, but it is the first KOA study to suggest that heat-related hypoesthesia and hypoalgesia could be possible predictors of the processes involved in the development of chronic postoperative pain following TKA. These findings should be further investigated in large, sufficiently powered studies.

Limitations

Sixty patients were excluded from the data analysis of this study due to technical issues and 48% of the patients included in the analysis did not reach the CPT before the equipment reached the pre-defined endpoint. The thermal stimulation device used had too many technical break-downs and more reliable devices should be used in future studies. This limits the current study and its conclusions.

The current study did not include a detailed pre- and acute postoperative medical history of the patients included. Use of analgesics have been found to vary among patients following TKA[43] and could be important for chronic pain following TKA, which should be studied in future studies.

Further, the study is limited by the small patient group developing chronic postoperative pain although it matches previous reports from TKA studies [5–8]. Thus, the results of the current study should be interpreted with care; especially the predictions of the pain intensity levels 12 months after TKA surgery.

Finally, this study was designed as an explorative study and as such no firm statistical plan was formulated à priori which further highlights the preliminary nature of the study. The findings should be replicated in future large cohort studies before the findings can be conclusive of diagnosis and treatment of patients before TKA.

Conclusion

The current study found preoperatively elevated temporal summation of pain and a trend towards heat hypoalgesia in patients who developed chronic postoperative pain following TKA. The study is the first to report an association between thermal hypoesthesia and hypoalgesia and the development of chronic postoperative pain. Preoperative temporal summation of pain levels correlated with the postoperative pain intensity and may be a preoperative mechanistic predictor of the development of chronic postoperative pain in OA patients after TKA.

Source of Funding

The Danish Rheumatism Association, The Innovation Fund Denmark (j.no. 136-2014-5), and The Shionogi Science Program are acknowledged for providing the opportunity to conduct the study. None of the funding sources played a role in the investigation.

Figure Legends

Figure 1: Mean (±SEM) (**A**) warm detection threshold (WDT) and heat pain threshold (HPT) and **(B)** cold detection threshold (CDT) and cold pain threshold (CPT) measured over the tibialis anterior muscle for patients with chronic postoperative pain (dark grey bars) and with recovery 12 months after total knee arthroplasty. No significant differences were found between groups.

Figure 2: Mean (±SEM) temporal summation of pain measured at the tibialis anterior muscle using a modified Von Frey Filament for patients with chronic postoperative pain and patients with recovery 12 months after total knee arthroplasty. * indicates $P<0.05$.

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Table 1

	Chronic pain	Normal recovery	p-value
Number of patients (percentage of total)	25 (19%)	105 (81%)	-
Preoperative pain intensity (0-10) (+/- SD)	6.46 (0.35)	6.67 (0.19)	0.5
Gender (percentage of females)	56%	57%	-
Age (+/-SD) [years]	69.17 (2.20)	68.92 (0.86)	0.7
BMI (+/-SD) [kg/m^2]	30.08 (1.01)	28.90 (0.46)	0.3
Radiological assessment			
KL 2	1 (2 %)	1 (1.3 %)	-
KL 3	11 (22 %)	14 (17.9 %)	-
KL 4	38 (76 %)	63 (80.8%)	-

Table 1 Demographic characteristics of the sub grouped knee OA patients. BMI: Body Mass Index. KL: Kellgren & Lawrence radiological scores are displayed as number of patients and percentage in relation to that group. No differences were found between groups.

Table 2

	Pearson correlation		Linear regression		
	R	P-value	Unstandardized coefficient	Standardized coefficient	P-value
TSP	0.200	0.010	0.217	0.194	0.023
KL	-0.159	0.032	-0.852	-0.151	0.074
WDT	0.195	0.012	0.058	0.089	0.368
HPT	0.196	0.012	0.182	0.178	0.075

Table 2: Pearson correlations and linear regressions to investigate associations between preoperative temporal summation of pain (TSP) ratings, Kellgren & Lawrence (KL), warm detection threshold (WDT) and heat pain threshold (HPT) and pain 12-months after total knee arthroplasty.

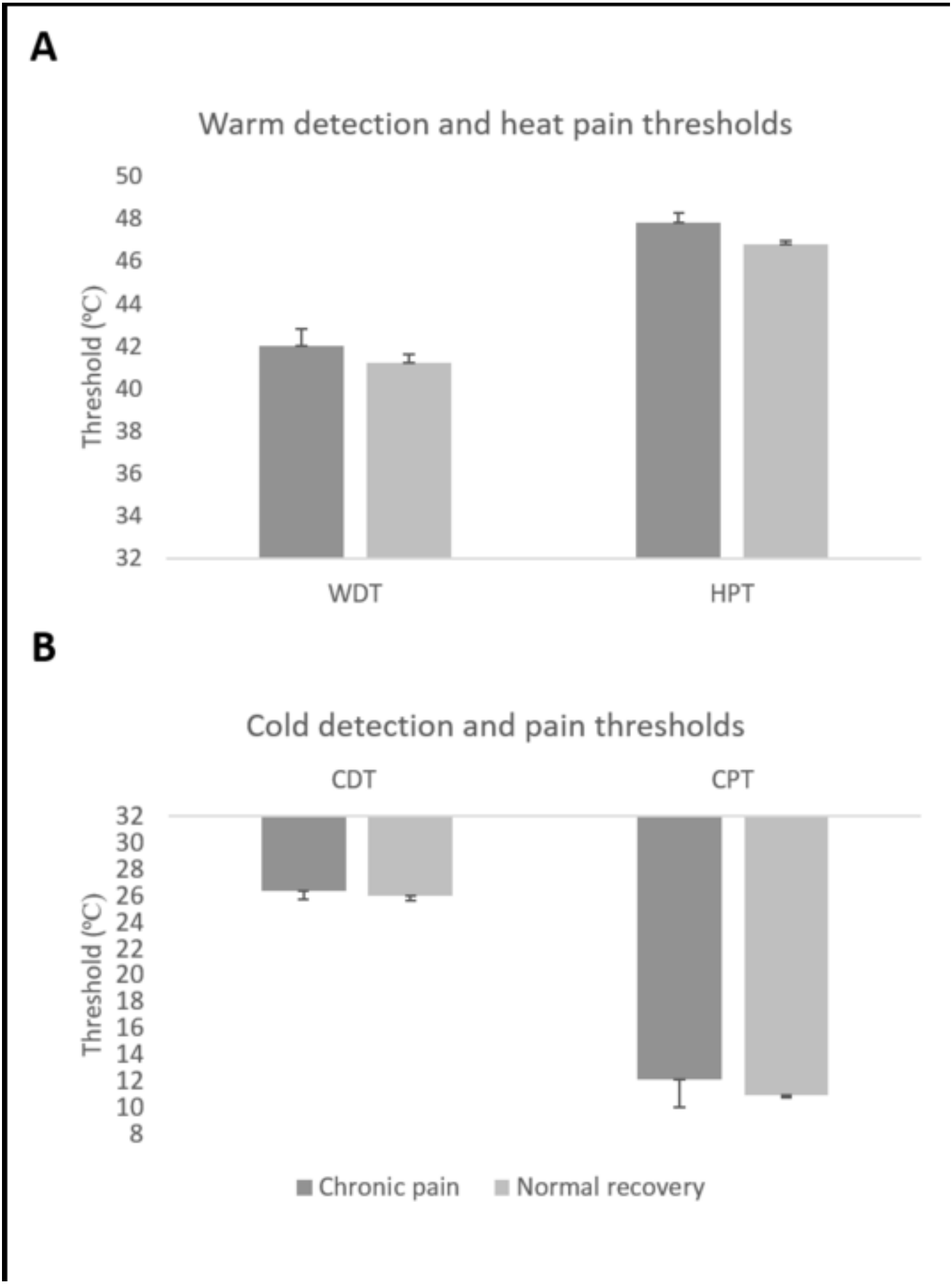

Figure 2