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ORIGINAL ARTICLE

Subgrouping of facilitatory or inhibitory conditioned pain modulation responses in patients with chronic knee pain. Explorative analysis from a multicentre trial

J. B. Larsen[1] | **P. Madeleine**[2] | **L. B. Sørensen**[1] | **J. Sachau**[3] | **J. C. Otto**[4] | **R. Baron**[3] | **L. Arendt-Nielsen**[5,6,7]

[1]Musculoskeltal Health and Implementation, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[2]Sport Sciences – Performance and Technology, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[3]Division of Neurological Pain Research and Therapy, Department of Neurology, University Hospital Schleswig-Holstein, Kiel, Germany

[4]Ameos Clinic Eutin, Eutin, Germany

[5]Center for Neuroplasticity and Pain, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark

[6]Department of Gastroenterology and Hepatology, Mech-Sense, Aalborg University Hospital, Aalborg, Denmark

[7]Steno Diabetes Center North Denmark, Clinical Institute, Aalborg University Hospital, Aalborg, Denmark

Correspondence
J. B. Larsen, Musculoskeletal Health and Implementation, Department of Health Science and Technology, Aalborg University, Selma Lagerløfs Vej 249, 9260 Gistrup, Denmark.
Email: jbl@hst.aau.dk

Abstract

Background: Facilitatory and inhibitory conditioned pain modulation (CPM) responses are observed in healthy volunteers and chronic pain patients, but the clinical implications for phenotyping are unknown. This study aimed to subgroup and compare chronic knee pain patients according to their CPM responses.

Methods: This explorative, cross-sectional study included 127 patients with chronic knee pain (osteoarthritis or following total knee arthroplasty). Individual CPM responses were categorized as facilitatory (test stimuli pain intensity increased when conditioning stimuli were applied), as inhibitory (test stimuli pain intensity decreased) or as no change (defined as less than 5.3% change in pain intensity). Outcomes were clinical pain intensities, temporal summation, widespread pain, self-reported physical function, PainDETECT questionnaire and Pain Quality Assessment Scale. Data were analysed as comparisons between the inhibitory and the facilitatory groups and using multivariate linear regression models.

Results: Fifty-four patients had facilitatory CPM responses, 49 had inhibitory CPM responses, and 24 showed no change in CPM response. A between-group difference was observed for self-reported physical function, with the facilitatory CPM group reporting better function (54.4 vs. 46.0, $p=0.028$) and the facilitatory CPM group reported more deep pain sensations (3.2 vs. 2.0, $p=0.021$). The remaining outcomes showed no between-group differences. Higher clinical pain intensity and facilitated temporal summation were associated in the facilitated CPM group but not in the inhibitory CPM group.

Conclusion: These explorative findings indicated that quantitative clinical and experimental differences exist between facilitatory or inhibitory CPM responses in a chronic knee pain patient population. Differences in patients' CPM responses should be further investigated to unravel possible clinical importance.

Significance: Our findings confirm that conditioned pain modulation consist of inhibitory and facilitatory responders among a patient population with chronic knee pain. This explorative study indicates that patients with either facilitatory or inhibitory conditioned pain modulation could exhibit differences in pain outcomes. Subgrouping of chronic pain patients depending on individual conditioned pain modulation responses could be considered in phenotyping patients prior to inclusion in clinical trials or used for personalizing the management regime.

1 | BACKGROUND

Descending pain modulation is one of the central nervous system mechanisms to inhibit or facilitate incoming nociceptive signals to the dorsal horn. It can be assessed by various proxies in both human experimental and clinical studies (Arendt-Nielsen & Graven-Nielsen, 2011; Yarnitsky et al., 2010), such as conditioned pain modulation (CPM) (Arendt-Nielsen & Graven-Nielsen, 2011; Kennedy et al., 2016). Impaired CPM is considered a possible mechanism for the development and maintenance of chronic pain (Fernandes et al., 2019; Hackett et al., 2019). Conditioned pain modulation (termed diffuse noxious inhibitory control in animals) has been shown to be impaired in studies of animals with chronic pain (de Resende et al., 2011) and across studies on patients with chronic pain (Graven-Nielsen & Arendt-Nielsen, 2010; Lewis et al., 2012; Petersen et al., 2016; Teixeira et al., 2020). In human volunteer studies, the CPM effect depends on different test paradigms, for example using heat, cold, electrical or pressure as test and conditioning stimuli (Fernandes et al., 2019; Vaegter et al., 2018). Substantial variations have been found within and across studies (Arendt-Nielsen et al., 2020; Bie Larsen et al., 2020; Cummins et al., 2020; Hermans et al., 2016; Kennedy et al., 2016; Schliessbach et al., 2019).

Studies have shown that the CPM potency is highly variable and that chronic pain populations consist of patients with both facilitatory and inhibitory CPM responses (Bie Larsen et al., 2020; Teixeira et al., 2020; Teles et al., 2019). At present, the possible information provided by the CPM variation is not fully understood, despite the effort to investigate, for instance, CPM responders and non-responders (Potvin & Marchand, 2016) using different stimulation paradigms (Oono et al., 2011). It has been demonstrated that when both facilitatory and inhibitory CPM responses are present, these responses can level each other out when an average-group mean is calculated (Cummins et al., 2020; Larsen et al., 2019), thereby leaving no information on the individual patients showing signs of facilitatory or inhibitory CPM responses. Therefore, we argue that individual CPM responses should be the basis for analysis in future CPM studies. Similarly, it has been scrutinized what constitutes a meaningful CPM response (Cummins et al., 2020; Kennedy et al., 2020). Some studies interpret the presence of any improvement in, for example pain intensity or pressure pain threshold as a sign of CPM effect (Carlesso et al., 2022; Corrêa et al., 2015; Fingleton et al., 2017; Ibancos-Losada et al., 2020; Mertens et al., 2021), some specify a certain change as a cut-off as an indicator for CPM effect (Locke et al., 2014; O'Neill et al., 2021), and some reliability studies use the standard error of measurement as an indicator of a meaningful CPM effect (Cummins et al., 2020; Kennedy et al., 2020). Currently, no universally accepted meaningful CPM effect has been established. Since most CPM studies use a group-average approach and specifies any improvement in pain intensity or pressure pain thresholds as a CPM effect, valuable information could be overlooked regarding the individual facilitatory or inhibitory CPM responses. Therefore, subgrouping of chronic knee pain patients based on their individual CPM responses could lead to further insights into the descending pain modulation and the association of these mechanisms with pain outcomes and therapeutic modalities.

The aims of this explorative study, based on data from a multicentre trial (Sachau et al., 2022) were to (1) subgroup and compare chronic knee pain patients according to CPM responses (facilitatory or inhibitory) and (2) to evaluate the associations between pain intensity, movement-evoked pain, temporal summation, neuropathic-like symptoms and self-reported physical function in chronic knee pain patients subgrouped into facilitatory or inhibitory CPM responders.

2 | METHODS

2.1 | Study design

This cross-sectional study was explorative and presented secondary analysis from a multicentre trial. The primary

analysis aimed to develop a bedside toolkit for assessing sensitization, which is reported elsewhere (Sachau et al., 2022). Patients with chronic knee pain due to either knee OA or following total knee arthroplasty (TKA) were recruited from two study centres at Aalborg University Hospital, Denmark, and Kiel University Hospital, Germany. At Aalborg University Hospital, patients were recruited using medical charts to identify eligible patients, who were then contacted by mail and phone. At Kiel University Hospital, patients were recruited through personal contact when referred to the Department of Orthopedics and Trauma Surgery and with notice listings at general practitioners. The study period ran from May 2018 to June 2019.

The study followed the STROBE guidelines (von Elm et al., 2007). The study was approved by the local ethics committee in North Denmark Region (N-20170088) and the local ethics committee of the University Hospital of Kiel (AZ D403/18). All patients signed informed consent before participation, and the study was conducted in accordance with the Helsinki Declaration.

2.2 | Participants

Patients with long-term, moderate-to-severe pain were targeted because these aspects, present in both knee OA or TKA patients, could indicate signs of sensitization (Lluch et al., 2017).

The following inclusion criteria applied:

- Moderate-to-severe pain (average numerical rating scale (NRS) during last week ≥4/10) (Gerbershagen et al., 2011)
- Knee OA diagnosis according to the American College of Rheumatology criteria (Altman et al., 1986) and based on clinical and radiographic evidence of grade I, II or III at the index knee or primary TKA
- Duration of pain >6 months
- Aged 40–80 years
- Body mass index (BMI) between 19–40 kg/m^2.

Patients were allowed to continue using their regular analgesic medications.

Exclusion criteria were:

- Secondary causes of arthritis to the knee, such as rheumatoid arthritis or sequelae from previous accidents
- Surgery (including arthroscopy) of the index knee within 3 months prior to visit
- History of injury to the index knee within 12 months prior to visit
- Acute pain, other than in the index knee, affecting the lower limb and/or trunk at the time of participation
- Skin lesions in the test areas
- Pregnancy
- Drug and alcohol abuse
- Rheumatoid arthritis, neurologic illnesses or primary pain areas other than the knee (e.g. low back pain or upper extremity pain). Knee pain should be the predominant pain area.
- Use of lower extremity assistive devices other than a knee brace or 'shoe lift' (use of a cane in the hand opposite to the index knee was acceptable)
- Lack of ability to adhere to protocol.

2.3 | Outcomes

2.3.1 | Protocol

The patients participated in one session. Initially, demographic variables, including age, sex, BMI and duration of pain, were retrieved before the outcome assessment. The sequence of the assessment was questions related to pain intensities and painful sites, sensory testing including assessment of temporal summation and CPM. Lastly, patients were asked to fill out the questionnaires.

Based on the explorative design and the purpose of evaluating associations, no primary outcome was chosen. However, several outcomes of interest were included, possibly characterizing different traits of chronic pain from knee OA or following TKA (Bie Larsen et al., 2020). The outcomes of interest were CPM, pain intensity, movement-evoked pain intensity, temporal summation, widespread pain, self-reported physical function, presence of neuropathic pain, pain interference and pain qualities.

2.3.2 | Clinical pain outcomes

Pain intensity

Clinical pain was assessed as the average pain intensity in the knee over the last week prior to the visit using a numerical rating scale (NRS) in which '0' represented 'no pain' and '10' represented 'worst pain imaginable'.

Movement-evoked pain was assessed as the pain intensity experienced in the knee when climbing stairs, using an NRS in which '0' represented 'no pain' and '10' represented 'worst pain imaginable'.

Painful sites

The number of painful sites was registered using a pain mannequin with front and back. Patients were asked to

mark areas where their habitual painful sites were located. Pain locations were divided into 12 regions: knee, foot, shin, thigh, hip, back, shoulder, elbow, underarm/hand, stomach, chest and head (Holden et al., 2021). The presence of multiple painful sites has been suggested to imply widespread pain and widespread sensitization (Kittelson et al., 2021; Lluch et al., 2017; Riddle & Stratford, 2014).

2.3.3 | Experimental pain outcomes

Conditioned pain modulation

Test stimuli during CPM can be applied both heterotopic (remote location) and homotopic (painful region) (Ramaswamy & Wodehouse, 2020) and we chose the muscle belly of the tibialis anterior muscle as frequently used in CPM studies (e.g. (Skovbjerg et al., 2017). Further, it is recommended to include upper and lower limb testing areas (Yarnitsky et al., 2015); therefore, the earlobes were used as site for inducing conditioning stimuli. This led to the development of a bedside method, which was used for conditioning pain modulation in the present study and has previously been methodologically described (Larsen et al., 2019). In short, the test stimulus was applied with a standardized pressure algometer applying a pressure of approx. 590 kPa for 10 s to the tibialis anterior muscle, on the contralateral side of the index knee. Following application, the patient rated the experienced pain intensity, using a visual analogue scale (VAS). The patients rated the pain intensity in an analogue manner, using a slider to mark the pain anchored between '0: no pain' and '10: worst pain imaginable'. As the conditioning stimulus, a clamp applying a pressure of approx. 128 kPa was attached to the ipsilateral earlobe for 60 s. Following the 60 s of conditioning stimulus, the test stimulus was re-applied for 10 s in a parallel design with the conditioning stimulus being applied simultaneously. This was followed by a VAS rating of the experienced pain intensity from the test stimulus during the conditioning stimulus. The CPM effect was determined as the difference in pain intensity between the pain ratings with and without conditioning stimuli. A positive difference indicated a facilitatory CPM response (i.e. increased perceived pain during conditioned stimulus). In contrast, a negative difference indicated an inhibitory CPM response (i.e. decreased perceived pain during conditioning stimulus) (Yarnitsky et al., 2015).

Mechanical temporal summation

A pinprick using a CMS nylon filament of 0.7 mm (Chicago Medical Supplies, Chicago, USA) was applied as a single stimulus perpendicularly to the skin, followed by the patients rating the pain intensity on an NRS. Thereafter, the nylon filament was re-applied for the stimuli of 10 repeated pinpricks within an area of 1 cm^2 with a repetition rate of 1/second, followed by the patients rating the pain intensity of the last stimulus on an NRS. Temporal summation was calculated as the pain rating from the single stimulus subtracted from the pain rating of the last stimulus of the series. Temporal summation is believed to reflect sensitization (the 'wind-up' process) and can be tested both localized (painful area) and extrasegmentally (non-painful area) to evaluate signs of local and peripheral sensitization in, for example osteoarthritis (Arendt-Nielsen & Graven-Nielsen, 2011). The test was conducted localized in the most affected (index) knee, adjacent to the knee (10 cm above the knee, ventral thigh) and extrasegmentally on the medial side of the forearm (muscle belly of flexor digitorum superficialis).

2.3.4 | Patient-reported outcome measures

Knee injury and osteoarthritis outcome score

From the knee injury and osteoarthritis outcome score (KOOS), we used the domain KOOS activities of daily living (ADL) to determine self-reported physical function. The KOOS ADL subscale consists of multiple items to be scored on a 5-point Likert scale from 0 (none) to 4 (extreme). The KOOS ranges from 0 (worst) to 100 (best) (Roos et al., 1998). Knee injury and osteoarthritis outcome score is a patient self-reported outcome measure consisting of 42 questions, which has been found valid and reliable during short-term and long-term follow-up in patients with TKA (Collins et al., 2011; Gandek et al., 2017). For the KOOS, a difference of at least 10 points has been suggested as a minimally clinically important difference (Roos & Lohmander, 2003).

PainDETECT questionnaire

The painDETECT questionnaire was developed as a screening tool for detecting neuropathic symptoms in low back pain patients (Freynhagen et al., 2006) and has been applied to other chronic pain areas, for example OA and TKA (Arendt-Nielsen et al., 2016; Wylde et al., 2022). Furthermore, it has been suggested that sensitization characteristics in chronic musculoskeletal pain such as chronic low back pain and osteoarthritis can, to some degree, be captured (Freynhagen et al., 2006; Hochman et al., 2013). The questionnaire is comprised of three major components: general pain intensity, pain course pattern and radiating pain, as well as the graduation of pain. The pain graduation section consists of seven questions evaluating typical neuropathic symptoms on a 6-point Likert scale (0 = never, 5 = very strongly). A sum score, ranging

from −1 to 38, can be calculated by adding the patient's responses. Sum scores can be interpreted as ≤12, indicating that a neuropathic pain component is unlikely, scores of ≥19, indicating that a neuropathic pain component is likely, and scores of 13–18 are unclear (Freynhagen et al., 2006).

Brief pain inventory

The brief pain inventory (BPI) is a questionnaire that measures the severity of pain and the interference of pain with function (Cleeland & Ryan, 1994; Tan et al., 2004). Only the interference score was used for this study since pain intensities were already assessed as previously described using NRS. The interference scores range from 0 (no interference) to 10 (interferes completely). The interference of pain in the past 24 h for general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life was assessed through seven questions (Cleeland, 2009).

Pain quality assessment scale

The pain quality assessment scale (PQAS) evaluates the sensations and pain qualities experienced by the patient. The patient is asked to rate 20 pain domains on an 11-point NRS (0 = no sensation/item, 10 = the most pain sensation imaginable) as the average over the last week (Jensen et al., 2006). The items can be categorized into three subgroups representing paroxysmal pain (shooting, sharp, electric, hot, radiating), surface pain (itchy, cold, numb, sensitive, tingling) and deep pain (aching, heavy, dull, cramping, throbbing) (Victor et al., 2008). A mean score for each of the subgroups was calculated. Description of pain qualities have been shown to differ between patient populations (Vriezekolk et al., 2022) and was, therefore, included to investigate whether it could differ between the same pain population, subgrouped by their CPM responses.

2.4 | Statistical analysis

2.4.1 | Sample size

A sample size calculation was made for the primary analysis of the multicentre trial (Sachau et al., 2022), for which the cohort was sampled. The present secondary analyses are explorative and were not part of the sample size calculation for the primary analysis. A post hoc power calculation was performed to evaluate the statistical power. The analysis revealed that the study had a power of 58% (alpha = 0.05) to detect a significant between-group difference for the outcome of temporal summation at the knee.

2.4.2 | Subgrouping of conditioned pain modulation responses

The individual CPM effect was calculated as the absolute and relative difference in test stimulus pain. Most previous CPM studies have used a group-average approach (e.g. (Larsen et al., 2019; Mertens et al., 2021), but facilitatory and inhibitory CPM responses may cancel each other out when averaging the responses. The averaging approach, therefore, remove important individual patient/volunteer phenotype information. Therefore, we split patients into facilitatory, inhibitory and no-changes groups to be able to focus on those showing the most markedly signs of either facilitatory or inhibitory CPM changes. The group with no-changes is not of interest in this study because of the lack of signs of either facilitatory or inhibitory CPM responses. Several methods to determine a meaningful change for CPM have been proposed but they are all based on data from healthy subjects (Cummins et al., 2020; Kennedy et al., 2020; Locke et al., 2014). Therefore, it is uncertain if these approaches are meaningful for chronic pain populations (Locke et al., 2014). Despite this uncertainty, it was deemed necessary to include a cut-off to determine a meaningful CPM effect to avoid labelling anything but zero as a CPM effect. Considering the lack of golden standard, we adapted the findings from Locke et al., which proposed a relative increase of 5.3% in pressure pain thresholds, as a meaningful CPM effect in the present study (Locke et al., 2014). This approach has previously been adopted in CPM studies (Mertens et al., 2021). Consequently, the individual CPM response was categorized as inhibitory if pain intensity from the test stimulus was 5.3% lower during conditioning stimulus (i.e. CPM responder) and facilitatory if pain intensity from the test stimulus was 5.3% higher during conditioning stimulus (i.e. CPM non-responder) (see Figure 1 for graphical illustration). Patients with a relative change in pain rating below 5.3% were classified as having no change in CPM response.

Calculation of relative change of the CPM effect was performed using the formula proposed by Firouzian et al. (2020):

$$\text{Relative change in CPM effect} = \left(\left(\text{Pain rating for test stimulus}_{\text{with conditioning stimulus}} - \text{Pain rating for test stimulus}_{\text{without conditioning stimulus}}\right)/\text{Pain rating for test stimulus}_{\text{without conditioning stimulus}}\right) \times 100\%.$$

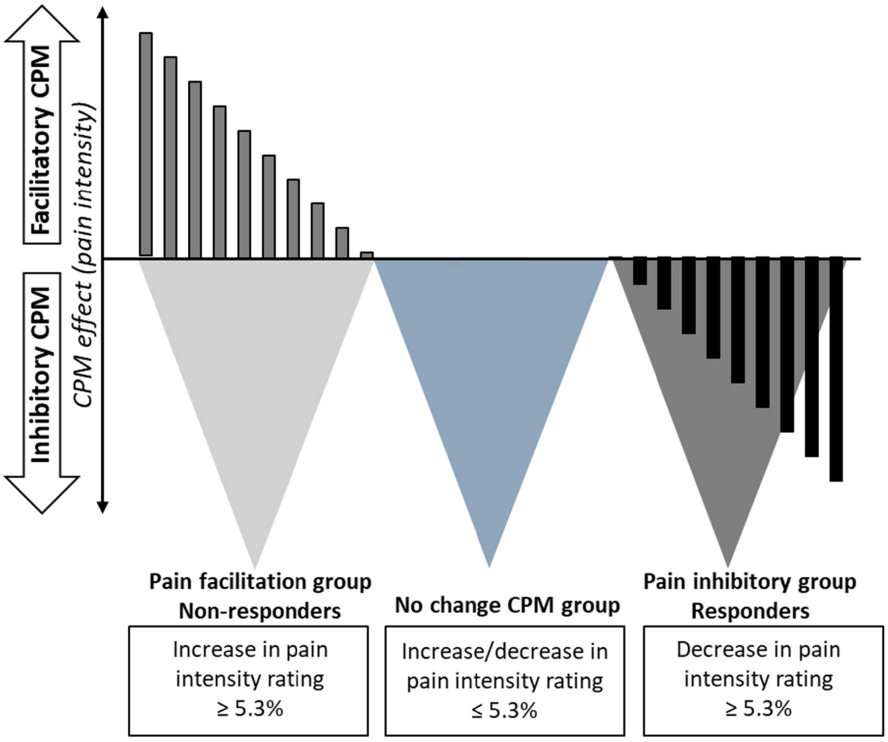

FIGURE 1 Graphical illustration of classifying conditioned pain modulation (CPM) as facilitatory, inhibitory or no-change response. Bars illustrate possible variations in CPM responses. The graphical illustration is not based on real data.

2.5 | Data analysis

Our analysis compared the groups with facilitatory and inhibitory CPM responses as this was the aim of the approved exploratory study. Hence, we also defined a no-changes group with a small variation around zero, which was left purposely out of the comparisons. Demographic data are reported as mean (SD). Outcome data were checked for normality by assessing the frequency in histograms, Q–Q plots and Shapiro–Wilk tests. For the variables, movement-evoked pain and KOOS ADL, the data were approximately normally distributed, and therefore, data are presented as mean (SD). For the remaining variables, data were not normally distributed and presented as median (interquartile range). Exploratory group-based comparisons were conducted using independent samples *t*-tests for the normally distributed data and the Mann–Whitney U test for the non-normally distributed data. Effect sizes were calculated as Cohen's d for between-group differences. Effect sizes quantify the differences between the groups and were interpreted as <0.2 = 'very small', 0.2 = 'small', 0.5 = 'medium', 0.8 = 'large', 1.2 = 'very large' and 2.0 = 'huge' as suggested by Sawilowsky (Sawilowsky, 2009) and Cohen (Cohen, 1988).

Numbers and percentages are calculated and reported for the outcomes of painful sites and painDETECT questionnaire to illustrate the proportion of patients with 1, 2 or 3 or more painful sites and painDETECT questionnaire categorization as 'neuropathic pain component unlikely', 'unclear' or 'neuropathic pain component likely'.

A multivariate linear regression model was conducted to analyse associations based on the enter method with an adjustment for age, sex and BMI. The assumption of linearity was checked by visually inspecting scatterplots, and the assumption of homoscedasticity was checked by visual inspection of scatterplots of the predicted values against the residuals. The assumption of no multicollinearity was checked by inspection of collinearity coefficients. Finally, the assumption of normality of the residuals was checked by visual inspection of histogram and Q–Q plots.

Associations were analysed for clinical pain (dependent variable) and movement-evoked pain (i.e. pain when climbing stairs), temporal summation, presence of widespread pain, self-reported physical function (KOOS ADL) and presence of a neuropathic pain component (independent variables). Associations were analysed separately for the groups, that is the facilitatory CPM, inhibitory CPM and no-change CPM groups. The β-coefficients indicate how strongly the independent variables influence the dependent variable. The R^2 values indicate the ratio of variability explained by the independent variable or the overall adjusted regression model.

The significance level was set to 0.05, and exact *p*-values and 95% confidence intervals (CI) are reported due to the explorative design of the study. All analyses were

conducted using the statistical software SPSS, Version 27 (SPSS Inc.).

3 | RESULTS

3.1 | Patient characteristics

One hundred thirty-eight patients were recruited, and 11 patients were excluded, leaving a total of 127 (mean age; 64.6 years, SD; 9.1, females 54%) patients with knee OA or following TKA available for the analysis. The 11 patients were excluded from the analysis because they exhibited floor or ceiling CPM effects. They reported either a pain intensity rating of VAS 10 out of 10 ($n = 10$) or VAS 0 out of 10 ($n = 1$) during, both with and without the conditioning stimulus, thereby making it impossible to investigate whether they experienced an increase or decrease in pain intensity, respectively. There were no statistically significant differences in patient characteristics between the three groups (Table 1). Patient characteristics for each of the two study centres can be seen in Supplementary Material S1.

The changes in test stimulus pain intensity ratings assessed with and without the application of conditioning stimuli revealed an increase of VAS 1.5 (SD 1.0), equalling a relative change of 27.3% in the facilitatory CPM group (CPM non-responders). For the inhibitory CPM group (CPM responders), a decrease in pain intensity of VAS 1.6 (SD 1.2), equalling a relative change of 27.6%, was observed. The distribution of individual CPM responses can be seen in Figure 2. The mean pain intensity experienced for the conditioning stimulus was 6.7 (SD 2.4) in the facilitatory CPM group, 5.9 (SD 2.4) in the inhibitory CPM group and 5.2 (SD 2.3) in the no-change CPM group. Raw pain intensities for the measurement of conditioned

TABLE 1 Patient characteristics. Values are mean (SD) unless otherwise stated.

Mean	Facilitatory CPM ($n = 54$)	Inhibitory CPM ($n = 49$)	No-change CPM ($n = 24$)
Age (years)	65.7 (8.0)	65.1 (9.1)	61.2 (11.0)
BMI (kg/m^2)	27.9 (4.7)	28.0 (4.7)	30.2 (4.6)
Sex (females, %)	30 (56%)	23 (47%)	16 (67%)
Pain duration (years)[a]	11.1 (8.9)	10.4 (10.3)	12.3 (11.3)
Clinical pain (NRS)[b]	5.6 (1.8)	5.5 (1.3)	4.8 (1.2)

Note: No significant differences were observed between groups (ANOVA and Chi^2 tests). 'Facilitatory CPM' is defined as a CPM non-responder and 'inhibitory CPM' as a CPM responder.

Abbreviations: BMI, body mass index; CPM, conditioned pain modulation; NRS, numerical rating scale.

[a]Self-reported number of years with pain in the index knee.

[b]Average daily pain intensity in the index knee over the last week.

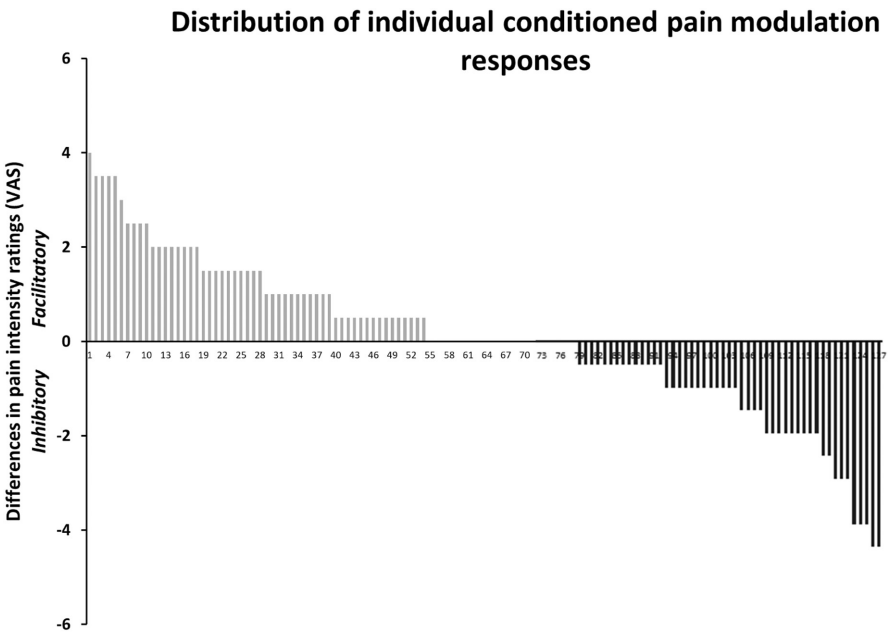

FIGURE 2 The distribution of ranked individual conditioned pain modulation (CPM) responses. The X-axis represents each individual patient and Y-axis illustrates the CPM responses. See text for information on how CPM responses were calculated. VAS, visual analogue scale.

	Facilitatory CPM ($n=54$)	Inhibitory CPM ($n=49$)	No-change CPM ($n=24$)
Test stimulus pain intensity without conditioning stimulus (VAS)	5.5 (2.2)	5.8 (2.5)	4.4 (2.5)
Test stimulus pain intensity during conditioning stimulus (VAS)	7.0 (2.1)	4.2 (2.5)	4.4 (2.5)
Pain intensity for 1 pinprick at the index knee (NRS)	1.1 (1.3)	1.4 (1.5)	1.0 (1.1)
Pain intensity for 10 pinpricks at the index knee (NRS)	3.0 (2.1)	2.6 (1.7)	2.0 (1.7)
Pain intensity for 1 pinprick extrasegmentally (NRS)	1.5 (1.7)	1.4 (1.3)	0.9 (1.2)
Pain intensity for 10 pinpricks extrasegmentally (NRS)	2.6 (2.2)	2.8 (1.8)	1.9 (1.8)

Abbreviations: NRS, Numerical rating scale; VAS, Visual analogue scale.

TABLE 2 Raw pain intensities for the measurement of conditioned pain modulation (CPM) and temporal summation. Values are mean (SD). 'Facilitatory CPM' is defined as a CPM non-responder and 'inhibitory CPM' as a CPM responder.

TABLE 3 Between-group comparison of chronic pain patients subgrouped by facilitatory or inhibitory conditioned pain modulation (CPM) responses. Values are presented as median and interquartile range unless otherwise stated.

	Facilitatory CPM ($n=54$)	Inhibitory CPM ($n=49$)	Effect size	*p*-value
Pain intensity when climbing stairs (NRS, mean, SD)[a]	6.0 (1.9)	5.8 (2.3)	0.01	0.655
Painful sites (numbers)[b]	2.0 (1)	2.0 (2)	0.05	0.976
Temporal summation at index knee (NRS)[b]	2.0 (2)	1.0 (1.5)	0.42	0.063
Temporal summation extrasegmentally (NRS)[b]	1.0 (2)	1.0 (1)	0.27	0.182
KOOS ADL (mean, SD)[a]	54.5 (16.7)	46.0 (22.0)	0.44	**0.028***
PainDETECT questionnaire[b]	10.0 (8)	9.0 (8)	0.06	0.662
Brief pain inventory – Interference[b]	3.1 (2.8)	3.0 (2.7)	0.08	0.874
Pain quality assessment scale				
Paroxysmal pain score[b]	3.5 (2.1)	3.2 (3.2)	0.27	0.151
Surface pain score[b]	1.5 (1.5)	1.2 (2.4)	0.21	0.300
Deep pain score[b]	3.2 (3.3)	2.0 (2.7)	0.41	**0.021***

Abbreviations: ADL, Activities of daily living; NRS, Numerical rating scale; KOOS, Knee injury and Osteoarthritis Outcome Score.

[a]An independent samples *t*-test was used for analysing normally distributed data.

[b]The Mann–Whitney U test was used for analysing non-normally distributed data.

*p-value <0.05.

pain modulation and temporal summation can be seen in Table 2. Individual test and conditioning stimuli pain intensity can be seen in Supplementary Material S2.

3.2 | Between-group differences

Overall, patients with either facilitatory or inhibitory CPM responses exhibited similar outcomes regarding movement-evoked pain, temporal summation, number of painful sites, painDETECT questionnaire, BPI interference score and PQAS paroxysmal pain and surface pain score (Table 3).

A significant difference in KOOS ADL was observed in favour of the facilitatory CPM group ($p=0.028$), indicating better self-reported physical function in this group compared to the inhibitory CPM group. The observed difference of 8.5 points is lower than the cut-off, indicating a minimally clinically important difference (Table 3).

A significant between-group difference was observed for the PQAS deep pain score. The facilitatory CPM group reported a higher level of deep pain, that is experiencing an aching, heavy, dull, cramping, throbbing sensation ($p=0.021$) (Table 3).

The proportion of patients with 1, 2 or 3 or more painful sites was similar between the groups. For the facilitatory CPM group, 13 patients (24%) reported one painful site (i.e., the knee), 17 patients (22%) reported two painful sites, and 24 patients (44%) reported three or more painful sites. For the inhibitory CPM group, 13 patients (27%) reported one painful site (i.e., the knee), 13 patients (27%) reported two painful sites, and 23 patients (46%) reported three or more painful sites.

For the painDETECT questionnaire categories, no significant between-group differences were found. For the facilitatory CPM group, 35 patients (65%) were classified as 'neuropathic pain component unlikely', 12 patients (22%) were classified as 'unclear', and 7 patients (13%) were classified as 'neuropathic component likely'. For the inhibitory CPM group, 37 patients (76%) were classified as 'neuropathic pain component unlikely', 6 patients (12%) were classified as 'unclear', and 6 patients (12%) were classified as 'neuropathic component likely'.

3.3 | Associations

The findings from the regression analysis are presented in Tables 4 and 5. In the facilitatory CPM group, pain intensity during stair climb, facilitated temporal summation at the index knee, and extrasegmentally were significantly ($p = 0.001$, 0.017 and 0.022, respectively) associated with clinical pain (R^2: 0.189, 0.100 and 0.092, respectively).

The β-coefficients indicate that when movement-evoked pain and facilitated temporal summation increases, this is associated with increases in clinical pain.

For the inhibitory CPM group, pain intensity during stair climb and KOOS ADL were significantly ($p = 0.0002$ and 0.019, respectively) associated with clinical pain (R^2: 0.251 and 0.110, respectively).

The β-coefficients indicate that when movement-evoked pain and KOOS ADL increase, this is associated with increases in clinical pain.

4 | DISCUSSION

This explorative multicentre study subgrouped patients with either facilitatory or inhibitory CPM responses to explore underlying clinical and experimental pain features, which could be associated with CPM responses in a population of patients with chronic knee OA pain or chronic pain after TKA.

A between-group difference was observed for self-reported physical function, with the facilitatory CPM group reporting better function (KOOS ADL). The facilitatory CPM group reported more deep pain sensations

TABLE 4 Associations between clinical pain and movement-evoked pain, temporal summation, presence of widespread pain, self-reported physical function and presence of a neuropathic pain component for the facilitatory conditioned pain modulation group.

Dependent variables	Independent variables	β	95% CI	R^2 change	R^2 for all independent variables
Clinical pain[a]	Pain intensity when climbing stairs	**0.472***	0.209 to 0.736	0.189	0.284
	Facilitated temporal summation at index knee	**0.347***	0.064 to 0.631	0.100	0.194
	Facilitated temporal summation extrasegmentally	**0.512***	0.075 to 0.948	0.092	0.187
	Painful sites	0.097	−0.183 to 0.378	0.009	0.103
	KOOS ADL	−0.017	−0.047 to 0.012	0.026	0.120
	PainDETECT questionnaire	0.026	−0.057 to 0.108	0.007	0.102

Abbreviations: ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score.

[a]Statistical analysis adjusted for age, body mass index and sex.

*Significant associations are in bold (p-value <0.05).

TABLE 5 Associations between clinical pain and movement-evoked pain, temporal summation, presence of widespread pain, self-reported physical function and presence of a neuropathic pain component for the inhibitory conditioned pain modulation group.

Dependent variables	Independent variables	β	95% CI	R^2 change	R^2 for all independent variables
Clinical pain[a]	Pain intensity when climbing stairs	**0.293***	0.147 to 0.439	0.251	0.324
	Facilitated temporal summation at index knee	0.043	−0.293 to 0.378	0.001	0.074
	Facilitated temporal summation extrasegmentally	−0.292	−0.658 to 0.074	0.051	0.124
	Painful sites	0.191	−0.001 to 0.383	0.078	0.151
	KOOS ADL	**0.021***	0.004 to 0.038	0.110	0.183
	PainDETECT questionnaire	0.057	−0.005 to 0.118	0.067	0.140

Abbreviations: ADL, activities of daily living; KOOS, Knee injury and Osteoarthritis Outcome Score.
[a]Statistical analysis adjusted for age, body mass index and sex.
*Significant associations are in bold (p-value <0.05).

than the inhibitory CPM group. Higher clinical pain intensity and facilitated temporal summation were associated in the facilitated CPM group, but not in the inhibitory CPM group. Considering the explorative nature and the limitations of the data, the findings are considered as hypothesis-generating.

4.1 | Subgrouping of facilitatory or inhibitory conditioned pain modulation responses

This study included a population consisting of patients with chronic pain due to knee OA or chronic pain following TKA. Patients with chronic pain because of knee OA or following TKA have been shown to have an impaired averaged CPM response in some studies (Arendt-Nielsen et al., 2010; Kosek & Ordeberg, 2000; Skou et al., 2013), contrary to findings in another study (Fingleton et al., 2017). Likewise, a systematic review (Fernandes et al., 2019) did not consistently find significant correlations between CPM and clinical pain in studies of patients with knee OA. Therefore, we suggest that the calculation of averaged CPM responses may not adequately and in sufficient details, utilize the individual CPM variation in the subgrouping of patients and healthy volunteers (Arendt-Nielsen et al., 2020; Bie Larsen et al., 2020). The relevance is reflected in studies of healthy subjects, showing proportions of both facilitatory and inhibitory CPM responses (Cummins et al., 2020; Firouzian et al., 2020; Mertens et al., 2021), illustrating the necessity of analysing subgroups to avoid losing individual variations.

4.1.1 | Clinical pain outcomes

Similar clinical and movement-evoked pain intensities were observed between the groups with both groups reporting moderate-to-high pain intensities during stair climbing. Similar results were observed in a population of patients with low back pain, where subgrouping patients into CPM responders and non-responders did not reveal differences in clinical pain (O'Neill et al., 2021). Although exploratory, these findings could indicate that CPM effect might not have a substantial impact on the clinical pain. The numbers of self-reported painful sites were similar between the groups. A large distribution of patients (44% in the facilitatory CPM group and 46% in the inhibitory CPM group) reported three or more painful sites. This reflects that widespread pain is a frequent finding in patients with chronic pain because of knee OA or following TKA (Skou et al., 2014).

4.1.2 | Experimental pain outcomes

Temporal summation, assessed localized at the knee and extrasegmentally at the forearm, was similar for the groups with a non-significant tendency of more localized facilitated temporal summation in the facilitatory CPM group. Effects sizes for localized temporal summation was 0.42 and for extrasegmentally temporal summation it was 0.27. Post hoc analysis revealed a power of 58% for detecting a between-group difference for temporal summation, possibly explaining the lack of significant differences between the groups. Signs of facilitated temporal summation was associated with higher clinical pain intensity in the facilitated CPM group, but not in the inhibitory CPM group, suggest that differences in the underlying pain mechanisms might exist in patients with chronic knee pain. Impaired CPM and facilitated temporal summation are thought to be important drivers of chronic pain (Fernandes et al., 2019; Hackett et al., 2019) and have been associated with developing chronic pain after TKA surgery (Petersen et al., 2015) and non-response after physiotherapy treatment in knee OA patients (O'Leary et al., 2018). The clinical implications for the subgroup of chronic knee pain patients, exhibiting both facilitated temporal summation and facilitatory CMP, should be considered when evaluating further treatments, as these underlying pain mechanisms could provide insight concerning the ability to obtain adequate treatment effects.

4.1.3 | Patient-reported outcomes

A difference in self-reported physical function (KOOS ADL) was observed with the facilitatory CPM group reporting better function. However, the difference of 8.5 points between the groups was lower than what has been proposed as a minimal clinically important difference (Roos & Lohmander, 2003) and exhibited a relatively small effect size of 0.44. Since an efficient CPM response may be protective for developing chronic pain (Ossipov et al., 2014), it could be expected that an efficient CPM effect would be associated with better outcomes, for example better self-reported physical function, which was not supported by our study. In line with this surprising finding, Carlesso et al., (2022) observed that adequate CPM effect was associated with higher likelihood of experiencing constant pain instead of intermittent pain. A constant pain experience could indicate the presence of ongoing pain mechanisms such as sensitization and/or impaired CPM effect. Although novel, this finding highlights the lack of complete understanding of CPM and chronic pain. The present explorative finding should be further investigated to unravel if or how the descending inhibitory modulation may be associated with physical function. Future studies should include objective assessments of physical function and not solely rely on self-reported physical function as physical function remain as important as pain for knee OA patients (de Rooij et al., 2016; Fransen et al., 2015).

When subgrouping patients according to their CPM responses, a difference in the deep pain score from the PQAS was found between the groups with the facilitatory CPM group experiencing a more pronounced sense of deep pain. Further, a relatively small effect size of 0.41 was observed. The deep pain domain is characterized by the pain being experienced as aching, heavy, dull, cramping or throbbing (Victor et al., 2008). Likewise, patients with knee OA have been shown to describe their pain using continuous pain descriptors such as aching, heavy and tender (Vriezekolk et al., 2022). Our explorative data suggests that chronic pain patients with facilitatory CPM responses experience pain sensations different from those perceived by the patients with inhibitory CPM responses. Description of pain qualities could be of clinical relevance, and it should be investigated whether these pain qualities could be associated with specific pain mechanisms.

A similar outcome was observed for BPI interference, which assesses how much the experienced pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. The findings indicate that the groups experience the same level of pain interference. Both groups showed similar outcomes regarding painDETECT questionnaire. For the facilitatory CPM group, 13% were classified as 'neuropathic component likely' and for the inhibitory CPM group, 12% were classified as 'neuropathic component likely'. These findings are similar to some studies including patients with knee pain (Arendt-Nielsen et al., 2016; Fernandes et al., 2018), while other studies using patients with hip and knee OA have reported higher proportions of patients exhibiting a possible neuropathic component (Berthelot et al., 2019; Zolio et al., 2021). Presence of a neuropathic pain component has been shown to have implications for pain management outcomes (Arendt-Nielsen et al., 2016).

4.2 | Associations

The findings of associations between clinical pain intensity and temporal summation in the facilitatory CPM group, but not in the inhibitory CPM group, are novel. Conditioned pain modulation and temporal summation have been proposed to be part of central pain amplification processes related to pain sensitization (Arendt-Nielsen et al., 2010), possibly explaining the observed association in the facilitatory CPM group (Fingleton

et al., 2015). Other studies have failed to find associations between CPM, sensitization and pain outcomes (Cardoso et al., 2016; Carlesso et al., 2022). However, these studies did not take the individual variation in CPM responses into account as suggested necessary in our recent studies (Arendt-Nielsen et al., 2020; Bie Larsen et al., 2020; Sachau et al., 2022). Our findings illustrate that subgrouping of patients according to their CPM responses can be essential to gain an insight into a chronic knee pain population with considerable variation in CPM responses (Bie Larsen et al., 2020). Evidently, these findings are explorative and should undergo further investigation.

Despite the lack of association between clinical pain and temporal summation in the inhibitory CPM group, this group experienced similar pain intensities as the facilitatory CPM group. This underlines our limited understanding of the factors that are the most important for chronic pain in knee OA or following TKA (Eitner et al., 2017; Fu et al., 2018). The quantitative profiling of pain mechanisms may form the basis for future personalized medicine approach (Petersen, 2021) together with other factors such as psychosocial features (Edwards et al., 2016; Fu et al., 2018; Martinez-Calderon et al., 2020).

The independent variables explained only small amounts of variation for the facilitatory and the inhibitory CPM groups. The adjusted variables, that is age, sex and BMI, explained similar or larger levels of variation, underlining the influence of these characteristics on pain intensity outcomes as in line with previous findings (Burgess et al., 2020).

4.3 | Limitations

Firstly, the explorative design of the analysis should be acknowledged and as previously mentioned, the lack of study power could lead to possible type 2 errors for the group comparisons. Secondly, because of the exploratory study that was designed and approved as a hypothesis-generating study, no statistical correction was made for the between-group comparisons. Third, since no control group was included in the study, we cannot conclude if observed changes reflect actual changes and not random variations in pain intensities. However, when comparing the current findings with our previous data on healthy subjects (Larsen et al., 2019), using the same CPM paradigm, we observe similar changes in test stimuli pain intensity ratings with and without the presence of conditioning stimuli for the facilitatory, inhibitory and no-change groups (Supplementary Material S3), indicating that changes could reflect real changes. Fourth, since the patients experienced chronic pain, they were allowed to continue using their regular pain medication up to and on the day of the assessment, reflecting the real-life settings. Fifth, to subgroup patients according to their CPM responses it was necessary to determine a cut-off for what denotes a meaningful CPM effect. No gold standard exists for establishing a meaningful CPM effect, and the available data are based on healthy subjects (Cummins et al., 2020; Kennedy et al., 2020; Locke et al., 2014). This introduces a potential classification bias of patients as CPM responders or non-responders. Future studies addressing this issue related to CPM cut-off values are warranted. It should be acknowledged that outcomes from CPM assessment are dependent on the paradigms used, that is the test stimulus and the conditioning stimulus (Horn-Hofmann et al., 2018; Kennedy et al., 2016; Vaegter et al., 2018), which further challenge the definition of a meaningful CPM effect. Variations in CPM responses have been observed in the same individual and depend on the CPM paradigm being used (Oono et al., 2011; Vaegter et al., 2018), reflecting the complicated aspect of establishing normative values for CPM effect. Recently, based on studies on healthy subjects, it was proposed that CPM could be switching between facilitatory and inhibitory responses (Cummins et al., 2020; Oono et al., 2022), highlighting shortcomings when measuring CPM responses. It remains unknown whether similar shifts between facilitatory and inhibitory CPM responses are present in patients with chronic pain. Some studies evaluate the CPM responses based on whether a CPM effect is present or not (Firouzian et al., 2020; Teixeira et al., 2020) and thereby, does not consider the magnitude of the CPM effect or possible measurement error. To specify a meaningful CPM effect, we used a cut-off of a change of 5.3% to determine CPM as facilitatory or inhibitory. This was based on the work from Locke et al. (Locke et al., 2014). To evaluate the impact of different cut-off values, we examined the proportions when the cut-off was set to either a 4% or 6% change in test stimulus pain intensity rating. Changing the cut-off, showed that no changes in proportions would occur at 4% and that two patients from the facilitatory CPM group and two patients from the inhibitory CPM group would have been categorized as no-change CPM response when a 6% cut-off was applied. We also conducted a sensitivity analysis using the two cut-off values (4% and 6%) and found no changes in between-group comparisons and statistical significance (data are not shown). This illustrates the relative robustness of the chosen cut-off value and that between-groups changes can be bidirectional. However, unravelling a meaningful CPM effect remains challenging (Cummins et al., 2020), and the inclusion of cut-off values cannot guarantee that an actual CPM effect is present.

5 | CONCLUSIONS

This hypothesis-generating, explorative study subgrouped patients with chronic knee OA pain or chronic pain following TKA according to their facilitatory or inhibitory CPM responses. A between-group difference for self-reported physical function was observed, with the facilitatory CPM group reporting better function. Further, the facilitatory CPM group reported more deep pain sensations than the inhibitory CPM group. These exploratory findings should be subject to further investigation. An association between higher clinical pain intensity and facilitated temporal summation was observed in the facilitatory CPM group, but not in the inhibitory CPM group. This study highlights that the individual variation in CPM responses and the distribution in chronic knee pain patients may provide complementary information on underlying individual pain phenotypes and could be considered in phenotyping patients prior to inclusion in clinical trials or used for personalizing the management regime.

AUTHOR CONTRIBUTIONS

JBL, PM, LBS, JS, JCO, RB and LAN made substantial contributions to the conception and design of the study. JBL, JS and JCO conducted the data collection and JBL the data analysis. All authors have read, discussed and provided critical feedback on the intellectual content and approved the final manuscript. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

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ORCID

J. B. Larsen https://orcid.org/0000-0003-3077-7913

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