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Pain modulatory phenotypes differentiate subgroups with different clinical and experimental pain sensitivity

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PAIN MODULATORY PHENOTYPES DIFFERENTIATE SUBGROUPS WITH DIFFERENT CLINICAL AND EXPERIMENTAL PAIN SENSITIVITY

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ABSTRACT

Pain biomarkers are warranted for individualized pain management. Based on different pain modulatory phenotypes the objectives of this study were to explore the existence of subgroups within nonmalignant chronic pain patients and to investigate differences in clinical pain and pain hypersensitivity between subgroups. Cuff algometry was performed on lower legs in 400 chronic pain patients to assess pressure pain threshold (cPPT), pressure pain tolerance (cPTT), temporal summation of pain (TSP: increase in pain scores to ten repeated stimulations), and conditioned pain modulation (CPM: increase in cPPT during cuff pain conditioning on the contralateral leg). Heat detection (HDT) and heat pain thresholds (HPT) at clinical painful and non-painful body areas were assessed. Based on TSP and CPM four distinct groups were formed: Group 1 (n=85) had impaired CPM and facilitated TSP. Group 2 (n=148) had impaired CPM and normal TSP. Group 3 (n=45) had normal CPM and facilitated TSP. Group 4 (n=122) had normal CPM and normal TSP. Group 1 showed more pain regions compared with the other three groups (P<0.001) indicating that impaired CPM and facilitated TSP plays an important role in widespread pain. Group 1 and 2 compared with group 4 had lower HPT at non-painful areas and lower cPTT (P<0.02) indicating that CPM plays a role for widespread hyperalgesia. Moreover, group 1 demonstrated higher clinical pain scores compared with group 4 (P<0.05). Although not different between subgroups, patients were profiled on demographics, disability, pain catastrophizing, and fear of movement. Future research should investigate interventions tailored towards these subgroups.

Keywords: Chronic pain, temporal summation of pain, conditioned pain modulation, pain sensitivity, pain biomarkers, cuff algometry

1. INTRODUCTION

The pathophysiological understanding of pain has increased significantly over the past decades although chronic pain remains a significant clinical problem with few effective therapies [6]. Identification of pain biomarkers may be a step forward towards individualized pain medicine providing a basis for improved clinical management of pain [44]. Protocols for assessment of pain facilitation and pain inhibition has demonstrated some promise in predicting future pain status [16,27,41,43] and the efficacy of analgesics [7,21,24,45].

In chronic pain patients, several studies have demonstrated facilitated temporal summation of pain (TSP) [13,36] compared with asymptomatic controls. TSP is a dynamic psychophysical measure reflecting the degree of central integration of nociceptive input and when facilitated it is believed to represent features of sensitized central pain mechanisms. In humans, TSP can be reliably assessed by repetitive painful pressure [11], heat [14], or electrical [4] stimulations and is characterized by an increase in subjective pain ratings during repetitive stimulations with identical intensities. TSP assessed preoperatively was found to predict the pain intensity 12 months after total knee replacement [27]. Moreover, TSP predicted the efficacy of pregabalin, expected to reduce neuronal sensitization, in patients with chronic pancreatitis [24].

Reduced conditioned pain modulation (CPM) has been associated with several chronic pain conditions [19]. Assessment of CPM [41] is frequently demonstrated as an increase in pressure pain thresholds by a painful conditioning stimulus applied contralaterally [32,38]. The magnitude of the conditioned pain modulatory response assessed preoperatively predicted chronic pain in patients after thoracotomy [43] and abdominal surgery [41]. In addition, CPM predicted the effect of duloxetine [45] and tapentadol [23] in patients with painful diabetic neuropathy.

Coincidence of both facilitated TSP and impaired CPM has been demonstrated in patients with chronic musculoskeletal pain [39], cluster headache [25], and chronic post-mastectomy pain [8]. Although facilitated TSP and impaired CPM often co-occur, recent studies have demonstrated that the magnitude of TSP as well as the CPM response may differ between chronic pain patients [13,39]. Based on these findings and as hypothesized by Yarnitsky et al. [44] some patients present with both facilitated TSP and impaired CPM, some with either facilitated TSP or impaired CPM, and others with normal TSP and CPM. So far the relevance of such modulatory phenotype groups for the clinical profile of pain intensity, distribution, somatosensory sensitivity, and psychological characteristics have not been studied in a large cohort of chronic pain patients.

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The objectives of this study were to explore the existence of subgroups with different pain modulatory phenotypes in a cohort with mixed chronic pain conditions. It was hypothesized that the pain modulatory phenotype of chronic pain patients based on the degree of TSP and CPM could be used to form four unique subgroups demonstrating different degrees of clinical pain intensity, distribution, and widespread pain hypersensitivity associated with different psychological profiles.

2. MATERIALS AND METHODS

2.1 Subjects

Four-hundred chronic pain patients (mean age: 48.0±12.5 years [range: 18-97]; 263 women) referred to interdisciplinary pain treatment at a university hospital pain clinic in the period February 1st to November 13th 2015 were included in this cross-sectional study. Inclusion criteria were men and women at least 18 years old, chronic nonmalignant pain for minimum 6 months, and patients should speak and understand Danish to ensure they understood the information about the pain testing procedures. Exclusion criteria were pain primary in the genital area, and pregnancy. The study was conducted in accordance with the Declaration of Helsinki, approved by the local ethical committee (S-20140010), and all patients provided written informed consent.

2.2 Procedure

Prior to commencing treatment all patients were assessed in the laboratory of the pain clinic. Pain assessment was undertaken in the same order for all patients (Fig. 1). Patients were thoroughly introduced to the procedures by illustrations as well as verbal instructions. Patients underwent assessments of pressure pain threshold and pressure pain tolerance, a protocol for TSP, a protocol for CPM, as well as assessment of heat detection thresholds, and heat pain thresholds. All pain sensitivity assessments were performed with the patient seated on a plinth with both arms resting on the thighs. All assessments were performed by the same experienced male assessor and lasted 30 minutes. All patients tolerated and completed the pain sensitivity assessments and the CPM protocol. Prior to the appointment in the laboratory, data were collected via an electronic software system (PainData, Australia and Denmark) on age, gender, body mass index (BMI), pain duration, and use of opioids, antidepressants, anticonvulsants, and NSAIDs. The following pain related questionnaires were completed likewise online: Intensity of clinical peak pain, and clinical average pain on a 0-10 numerical rating scale (NRS) with 0 defined as "no pain" and 10 "as worst

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imaginable pain" during the previous 24 hours, Pain Catastrophizing Scale (PCS) [37], Pain Disability Index (PDI) [29], and Tampa Scale of Kinesiophobia (TSK) [15]. Furthermore, patients completed pain drawings indicating all areas with current pain and the total number of areas affected by pain was extracted as previously described [22]. Finally, patients were assessed by a pain specialist from the pain clinic and classified into the following pain conditions (Table 1): widespread pain (spinal pain + pain in all four extremities), multiple spinal areas (pain in more than one spinal area), low back pain (pain in the lower back without pain referral below the knees), sciatica (pain in the lower back + pain referral below the knee), extremity pain (pain localized to one or more extremities without pain in the truncus), cervicobrachialgia (pain in the neck + pain referral below the elbows), neck pain (pain in the neck without pain referral below the elbows), headache (pain localized in the face or head), abdominal pain (pain localized in the abdominal area), and others (1 with pain in one side of the body, 3 with pain in more than one spinal area and pain in more than one but less than four extremities). The majority of pain conditions were widespread or musculoskeletal in origin although patients with headache and abdominal pain, which may not be musculoskeletal in origin, were also included.

2.3 Assessment of pressure pain thresholds and tolerance

Pressure pain threshold (cPPT), and pressure pain tolerance (cPTT) were assessed by computer-controlled cuff algometry (Nocitech, Denmark and Aalborg University, Denmark) [28]. A 13-cm wide silicone tourniquet cuff (VBM, Sulz, Germany) with an equal-sized proximal and distal chamber was wrapped around the left lower leg. The cuff was mounted with a 5 cm distance between its upper rim and the tibial tuberosity. The cuff pressure was increased with a rate of 1 kPa/s in both chambers and the maximal pressure limit was 100 kPa. The maximal pressure limit was based on the maximum capacity of the system. Air was supplied from a 200 liters external air tank to avoid loud noises from the cuff system during assessment. Patients used an electronic visual analogue scale (VAS) to rate their pressure-induced pain intensity and a button to release the pressure. The electronic VAS was sampled at 10 Hz. Zero and 10 cm extremes on the VAS were defined as "no pain" and as "maximal pain", respectively. Patients were instructed to rate the pain intensity continuously on the electronic VAS from when the pressure was defined as first sensation of pain and to press the pressure release button when the pain was perceived as intolerable. The pressure value, when the patient rated the sensation of pain as 1 cm on the VAS was defined as the cuff pressure pain threshold, and when the patient terminated the pressure inflation, the pressure

value was defined as the cuff pressure pain tolerance. The VAS score of the pain intensity when cPTT was detected was extracted (VAScPTT). In case the maximum pressure stimulation was achieved before reaching the pain tolerance, 100 kPa was used for further analysis as a conservative estimate and for VAScPTT the VAS score at termination was used. Assessment of cPPT and cPTT were performed twice with a 3 min pause between assessments and the average of repetitions was used for further analysis. Test-retest reliability and sensitivity of computer-controlled cuff algometry for assessment of pain sensitivity and pain modulation has been demonstrated in patients with chronic pain [39] and healthy subjects [11].

2.4 Assessment of temporal summation of pressure pain

Assessment of temporal summation of pain (TSP) was performed approximately 1 min after the first assessment of cPPT and cPTT (trial 1; Fig. 1). Ten repeated cuff pressure stimulations (1 s duration and 1 s interval between stimuli) were delivered by inflation of the cuff with an intensity equivalent to the cPTT recorded during the immediately preceding assessment. Pressure with an intensity equivalent to the cPTT was chosen to ensure that the first stimulation was perceived as painful by patients although not extremely painful due to the short stimulation time. In the period between stimuli a constant non-painful pressure of 5 kPa was kept ensuring that the cuff did not move. Patients rated their pressure pain intensity continuously during the sequential stimulation on the electronic VAS without returning it to zero between the ten stimulations. The VAS score immediately after each stimulus was extracted and the mean VAS score was calculated after stimulation 1-4 (VAS-I), stimulations 5-7 (VAS-II), and stimulations 8-10 (VAS-III). The degree of TSP was calculated as the TSP-ratio between VAS-III and VAS-I, with positive values indicating an increase in VAS scores during the sequential stimulation. This method has previously demonstrated good reliability in patients with chronic pain [39] and in healthy subjects [11].

2.5 Assessment of conditioned pain modulation

Conditioned pain modulation (CPM) was assessed approximately 3 min after the second assessment of cPPT and cPTT. The conditioning stimulus was delivered by a 7.5 cm wide silicone tourniquet cuff (VBM, Sulz, Germany) with one chamber wrapped around the right lower leg (conditioning stimulus cuff). The cuff was mounted with 8 cm distance between its upper rim and the tibial tuberosity. The cuff was inflated to 30 kPa within 1 s and the pressure was kept constant throughout the CPM protocol (maximum of 100 sec). Intensity of 30 kPa was chosen to ensure that the

conditioning cuff was above cPPT and thus would be perceived as moderately painful as recommended [41]. A constant conditioning stimulus of 30 kPa for all patients were chosen as the intensity of perceived pain induced by a conditioning stimulus has been found uncorrelated with the magnitude of the CPM effect [40]. Five seconds after inflation of the conditioning stimulus cuff, the double chambered cuff on the left leg (test stimulus cuff) was inflated with a rate of 1 kPa/s and the cPPT and cPTT were reassessed as described above. Patients were instructed that the conditioning stimulus cuff would be moderately painful and that they should focus their attention on the test stimulus cuff on the left leg. The CPM-effect was defined as the percentage difference in cPPT recorded during conditioning and baseline assessments with positive values indicating hypoalgesia.

2.6 Assessment of heat detection and heat pain thresholds

Heat detection thresholds (HDT) and heat pain thresholds (HPT) were assessed by a computer-controlled contact thermal stimulator (MSA Thermal Stimulator, SENSELab, Somedic Sales AB, Hörby, Sweden) with a thermode covering a 25x50 mm skin area over the thenar eminence of the left hand (non-painful area) followed by assessment directly over the midpoint of the primary painful body area. If patients reported pain at the thenar of the left hand, HPT was assessed at the right thenar. The method of limit was used to establish the heat thresholds. The temperature started at a baseline of 32°C and increased by 1.0°C/s to a maximum of 50°C. As soon as a change in heat sensation was detected (HDT), the subjects were instructed to press a handheld switch. Following assessment of HDT, HPT was assessed. As soon as the heat sensation was defined as first sensation of pain, the subjects were instructed to press the handheld switch. The peak temperature was stored and the thermode instantly decreased its temperature (3.0°C/s) to the baseline of 32°C. Stimuli were repeated three times and the averages of HDT and HPT, respectively, were calculated. Furthermore, the difference between HPT at the non-painful hand and the painful area was calculated with positive values indicating local hyperalgesia (diffHPT). HDT and HPT were always assessed in the non-painful area first.

2.7 Subgrouping of patients

Subgrouping of patients into four distinct groups based on pain modulatory phenotype was performed using CPM (normal/impaired) and TSP (normal/facilitated) as categorical variables. Patients were classified as having facilitated TSP if the TSP-ratio was greater than 2.48 (mean + 1.96 · standard deviation of the TSP ratio recorded in healthy subjects) and normal TSP if the TSP-

ratio was equal to or less than 2.48. This cutoff was chosen based on a recent test-retest cuff algometry study in 136 healthy subjects demonstrating a ratio (between VAS-III and VAS-I) of 1.5±0.5 [11].

Currently, there is no consensus on a normal CPM effect. The current study used a method to categorize the CPM response as normal and impaired based on the within-subject coefficient of variation in cuff pressure pain thresholds (cPPT). Patients were classified as having impaired CPM if the CPM response was less than or equal to the normal within-subject coefficient of variation in cPPT between two repeated assessments without the conditioning cuff and normal CPM if the CPM response was greater than the normal variation plus the upper limit of the 95% confidence interval. The percentage variation and 95% confidence interval between the two cPPT assessments in the current study (trial 1 and trial 2) were 18.2% (16.3-20.0%) and patients were classified as having less efficient CPM if the CPM response was less than or equal to an increase of 20% of the baseline cPPT. The magnitude of CPM response used as cutoff in this study is similar to the magnitude demonstrated in previous studies using a tourniquet cuff as conditioning stimulus [33].

2.7 Statistics

All data are reported as mean and standard deviation (SD) in the text and as mean and standard error of the mean (SEM) in figures. Statistical analyses were run in SPSS Statistics (Version 21; IBM, Armonk, NY, USA). Initially, the effect of the CPM protocol on cPPT and cPTT was analyzed with paired t-test comparing the mean cPPT and cPTT values of cuff trial 1 and 2, respectively, with the cPPT and cPTT values during the conditioning cuff stimulation. Furthermore, the effect of 10 repeated pressure stimulations on pain ratings immediately after each of the 10 repeated stimulations were analyzed with a repeated measure analysis of variance (RM-ANOVA) with stimulations (1-10) as repeated measures.

Potential differences between men and women in clinical pain, experimental pain sensitivity and psychological variables were analyzed by Mann-Whitney U test. Distribution of gender, different pain diagnosis and use of analgesics between groups was analyzed by Chi-square and P-values determined based on adjusted standardized residuals. No significant difference in distribution of men and women between the four groups was found. However, due to the different gender-ratios between groups and the significant differences between men and women in several experimental and clinical pain parameters, all parameters were gender-adjusted by z-transformation by subtraction of the mean values divided by the standard deviation (SD) for men and women,

respectively. Differences in demographic parameters between groups were analyzed with one-way ANOVA for continuous variables. Potential differences in z-scores for clinical pain, experimental pain sensitivity, and psychological parameters were examined using analysis of variance (ANOVA). In case of significant factors or interactions, Bonferroni pairwise comparisons correcting for multiple comparisons were used. Finally, to assess potential sensitization or habituation effects due to repetitive pain assessments, intraclass correlations (ICCs) based on a single rating, consistency, 2-way mixed effect model (ICC3,1), and Bland–Altman methods were used for analysis of test-retest reliability of cPPT and cPTT. *P*-values less than 0.05 were considered significant.

3. RESULTS

3.1 Conditioned pain modulation

Including all patients, cPPT and cPTT were significantly increased during conditioning cuff stimulation (cPPT: 23.0 ± 14.3 kPa, cPPT: 46.1 ± 21.8 kPa) compared with before conditioning (cPPT: 20.0 ± 9.4 kPa, cPTT: 44.1 ± 19.4 kPa; Paired T-Test: $P < 0.001$).

3.2 Temporal summation of pressure pain

The RM-ANOVA of the VAS scores immediately after the 10 repeated cuff stimulations demonstrated a significant main effect of stimulations (Fig 2; $F(9,3582) = 788.1$, $P < 0.001$). Post-hoc test showed increased VAS scores after stimulation 10 compared with VAS scores after stimulations 1 to 9, and increased VAS scores after stimulation 5 compared with VAS scores after stimulations 1 to 4 ($P < 0.001$).

3.3 Subgrouping patients based on CPM and TSP profiles

Four groups, with different pain modulatory characteristics were derived based on the TSP-ratio and the CPM-effects (Fig. 3). Group 1 (21.2% of patients, n=85) was characterized by an impaired CPM response and facilitated TSP. Group 2 (37.0% of patients, n=148) was characterized by an impaired CPM response and normal TSP. Group 3 (11.2% of patients, n=45) was characterized by a normal CPM response and facilitated TSP. Group 4 (30.5% of patients, n=122) was characterized by normal CPM and normal TSP. All raw parameters are presented in Table 2 for women and men. Z-scores for all parameters pooled across gender were used for further analysis (Table 3).

Obviously the four groups differed in the degrees of CPM and TSP since these were used to subdivide the patients (Table 3). Within group 3 and 4 with normal CPM, the CPM was lower in the group with facilitated TSP compared with the group with normal TSP, but this difference was not significant ($P = 0.23$).

Group 1 had a significantly higher proportion of patients with widespread pain and group 4 had a significantly higher proportion of patients with localized neck pain compared with the other groups (Table 1; $X^{(27)} = 57.16$, $P < 0.001$). There was no significant difference in distribution of men and women or patients using opioids, antidepressants, anticonvulsants or NSAIDs between the four groups (Table 1 and 2; $X^{(3)} = 7.60$, $P = 0.06$, $X^{(3)} < 3.12$, $P > 0.37$, respectively) and the ANOVAs demonstrated no significant difference in age and BMI between groups ($F(3,396) = 2.24$, $P = 0.08$ and $F(3,396) = 0.78$, $P = 0.51$).

3.4 Clinical pain distribution and intensity

The ANOVAs demonstrated a significant group difference in number of pain areas (Table 3; $F(3,396) = 5.04$, $P = 0.002$) and average NRS pain scores ($F(3,396) = 2.60$, $P = 0.048$). Post-hoc test showed that group 1 had more pain areas compared with the other three groups ($P < 0.04$) and that group 1 had higher average NRS pain scores compared with group 4 ($P = 0.048$). The ANOVA of peak NRS pain scores approached significance ($F(3,396) = 2.23$, $P = 0.08$). There were no significant differences in pain duration between groups ($F(3,396) = 0.79$, $P = 0.50$).

3.5 Heat and cuff pressure hyperalgesia

There was a significant difference in the ANOVAs of HPT at the non-painful hand (Table 3; $F(3,396) = 5.27$, $P = 0.001$), cPTT ($F(3,396) = 7.91$, $P < 0.001$), and diffHPT ($F(3,396) = 2.79$, $P = 0.04$) between groups with post-hoc test showing reduced HPT and cPTT in group 1 and 2 compared with group 4, as well as increased diffHPT in group 4 compared with group 1 ($P < 0.04$). There were no significant differences between groups in HDT, HPT at the painful area, cPPT or VAScPTT (Table 3; $F(3,396) < 2.33$, $P > 0.08$).

3.6 Psychological parameters

ANOVAs demonstrated no significant differences between the four groups on Pain Disability Index, Pain Catastrophizing Scale or Tampa Scale of Kinesiophobia (Table 2; ($F(3,396) < 1.83$, $P > 0.14$).

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3.7 Test-retest reliability for cuff algometry

Repeatability between cPPT and cPTT assessments in trial 1 and 2 was high with ICCs > 0.85 and results from Bland–Altman analysis demonstrated no systematic bias between two cuff algometry assessments (Table 4).

4. DISCUSSION

This study is the first to explore the existence of distinct subgroups based on pain modulatory phenotypes in a large cohort of patients with different chronic pain conditions. Patients with facilitated temporal summation of pain and impaired conditioned pain modulation had significantly more pain areas, indicating that both less efficient CPM and facilitated TSP may be important biomarkers for widespread pain. Furthermore, patients with less efficient CPM, independent of TSP status, demonstrated higher clinical pain as well as increased pressure and heat pain sensitivity compared with patients with a normal CPM response, demonstrating that the descending pain control plays a potential role for widespread hyperalgesia. Pain modulatory phenotypes are important determinants of pain status in patients with chronic pain and appear to be heterogeneous across different pain diagnosis and identification of subgroups may inform individualized pain treatment.

4.1 Subgrouping based on CPM and TSP profiles

Based on CPM and TSP profiles four distinct and clinical relevant groups with different clinical pain distribution and intensity were formed. The present findings indicate differences in central pain modulation between patients with chronic pain across different pain conditions. In agreement with the proposal of a pro-nociceptive and anti-nociceptive spectrum [44], patients demonstrating impaired CPM and facilitated TSP expressed higher intensity of clinical pain and increased experimental pain sensitivity compared with patients demonstrating a normal CPM response and normal TSP. While subgroups based on pain modulatory phenotypes were identified, non-noxious perception (HDT), disability and psychological distress did not differ between subgroups. This indicates that changes of pain inhibitory and facilitatory pathways assessed with the protocol used in this study are related with the manifestation of widespread pain and hyperalgesia.

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Group 1 demonstrated facilitated TSP and it cannot be excluded that the impaired CPM response caused an imbalanced descending control manifested as a net facilitatory effect [43]. However, groups 2 and 3 were characterized by impaired CPM or facilitated TSP, suggesting that the central pain mechanisms may be affected independently. Furthermore, group 4 demonstrated a larger difference in HPT between the painful and non-painful assessment areas (diffHPT) suggesting that localized sensitization in the painful area is an important mechanism in a majority of patients in group 4, whereas more generalized central pain processes plays an important role in a majority of patients in group 1. This cross-sectional study does not reveal whether impaired pain inhibitory and facilitatory pathways and the presence of widespread pain and hyperalgesia are causative, and if so, which is primary to the other. However, a pro-nociceptive profile seems to be associated with widespread pain and hyperalgesia. These results indicate that more generalized central pain processes are involved in pain with increased spatial manifestations which is in agreement with a recent study demonstrating increased pain sensitivity in patients with chronic widespread pain (CWP) compared with more localized low back pain [9]. This is also in agreement with the different proportions of patients with localized neck pain and chronic widespread pain in this study. However, normal TSP and CPM were also demonstrated in a subgroup of patients with CWP, indicating that CWP is heterogeneous with respect to pain modulation.

4.2 Conditioned pain modulation

Including all patients, the paradigm used to assess CPM demonstrated robust increases in pressure pain threshold and tolerance compared with the control condition. The current study used a method to categorize the CPM response as normal and impaired based on the within-subject coefficient of variation in cPPT measurement over repeated assessments. This method provides a conservative approach for determining whether an individual exhibits a normal CPM response and it may be a useful method in clinical trials to identify individuals with impaired CPM. Using this method in the present large sample of patients with chronic pain, 58.3% of patients demonstrated an impaired CPM response. Although, impaired CPM has been demonstrated in several chronic pain conditions [19], the conditioned pain modulatory response may differ between patients with chronic pain [39]. The present study extends these findings by showing a reduced CPM response in a subgroup of patients but a normal response in other. A reduced CPM response was demonstrated across different pain diagnosis; the proportion of patients with widespread pain was however increased compared with patients with efficient CPM. This is in agreement with a previous study including 464 chronic

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pain patients demonstrating less than 20% increase in pressure pain threshold after cold pressor test in 60% of patients across different chronic pain conditions [34].

The present findings are in agreement with the concept of pro-nociceptive and anti-nociceptive pain modulation proposed recently [44]. In the current study, patients with impaired CPM demonstrated higher clinical pain intensity and increased pain sensitivity to pressure at the leg and heat pain at the non-painful hand, indicating the presence of widespread hyperalgesia. Widespread hyperalgesia may represent impairment in pain inhibition [2], accounting for the reduced heat pain threshold and pain tolerance as well as the increased clinical pain scores.

Subgrouping based on CPM may be important for understanding chronic pain and potentially improving treatment strategies and clinical decision-making. The CPM response is based on a spino-bulbar-spinal loop [17,18] that involves serotonergic [5] and noradrenergic [26] mechanisms in the descending pain inhibitory systems. Patients with impaired CPM could potentially benefit more from treatments like serotonin norepinephrine reuptake inhibitors than chronic pain patients with normal CPM [45].

4.3 Temporal summation of pain

This study demonstrated robust temporal summation of cuff induced pain in line with recent studies in healthy subjects [11] and chronic pain patients [35,39]. The repeated sequence of 10 pressure stimuli at the same intensity delivered to the leg produced a progressive increase in pain ratings, indicating that the paradigm for inducing temporal summation of pressure pain was successful. Although, facilitated TSP has been demonstrated in several chronic pain conditions [13,36] compared with asymptomatic controls, the response to repetitive painful stimulations may differ between patients with chronic pain [39]. The cutoff-value to determine whether patients demonstrated normal or facilitated TSP was based on asymptomatic healthy subjects although not sex or age matched, as the literature offers no normative data on a similar population. However, the TSP-ratio for cuff algometry has shown good test-retest reliability in 136 healthy subjects [11]. Similar to the method used for CPM, this method provides a relatively conservative approach for determining whether an individual exhibits facilitated TSP. Using this cutoff value for TSP in the large sample of patients with chronic pain, 32.5% of patients demonstrated facilitated TSP. This is somewhat lower than a previous study on women with fibromyalgia in which approximately 50% of patients demonstrated facilitated TSP [30].

Patients with facilitated TSP in addition to impaired CPM had significantly more pain areas compared with the other three groups, indicating that facilitated pro-nociceptive mechanisms in combination with impaired anti-nociceptive mechanisms plays a role in widespread pain. In addition to subgrouping based on CPM, further subgrouping based on TSP may improve treatment strategies, e.g. targeting a combination of different central pain mechanisms. NMDA-receptors are involved in TSP in humans [1] and several studies have demonstrated a reduction in TSP after application of NMDA-receptor antagonists like ketamine [3,10,12] and dextromethorphan [31]. Moreover, pain patients with facilitated TSP had more benefit from pain treatment with the NMDA-receptor antagonist pregabalin compared with patients with normal TSP [24].

4.4 Limitations

Subgroups were formed based on a dichotomous evaluation of TSP and CPM. An alternative statistical approach would be to perform cluster-analysis with TSP and CPM as continuous variable. However, the approach used in this study appears to be more clinical applicable. Although the pain modulatory phenotypes formed distinct and relevant subgroups, the clinical and experimental pain sensitivity could be influenced by other factors like genetics, which were not controlled for in this study. The cutoff for subgrouping into normal or impaired CPM was based on the with-subject coefficient of variation of the included patients. Similar to our method a recent study [20] proposed a method for calculating a normal CPM response based on an increase in manual pressure pain thresholds after the cold pressor test greater than the inherent error of measurement. However, no studies have yet determined reference values for the CPM response for cuff algometry with a tourniquet cuff as the conditioning stimulus and this is warranted. In addition, the effect of conditioning pain intensity on the CPM response warrants further investigation. Finally, there was no random order of the tests causing a risk of carry-over effects with the current design.

4.5 Conclusion

Patients with facilitated pro-nociceptive mechanisms and impaired anti-nociceptive mechanisms had significantly more pain regions. Furthermore, patients with impaired anti-nociceptive mechanisms, independent of pro-nociceptive status, demonstrated higher clinical pain intensity as well as increased pressure and heat pain sensitivity. These findings could have important clinical implications as the effect of management strategies, e.g. treatment strategies utilizing the pain inhibitory systems, may differ depending on the pain modulatory phenotype. Future studies should

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investigate prognostic and management outcomes based on identification of such phenotypes and interventions tailored towards these subgroups.

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Figure legends

Fig. 1: Experimental procedure. Cuff pressure pain threshold (cPPT), pressure pain tolerance (cPTT), temporal summation of pressure pain (TSP) and conditioned pain modulation (CPM) were assessed with cuff algometry on the left leg. Heat detection threshold (HDT) and heat pain threshold (HPT) were assessed on non-painful hand and primary painful body area.

Fig. 2: Mean (± SEM, N = 400) VAS scores immediately after each of the ten repeated cuff pressure stimulations delivered with an intensity at pressure pain tolerance level on the left lower leg. Significantly different compared with stimulation 1-9 (†, Bonferroni: $P < 0.05$) and compared with stimulation 1-4 (*, Bonferroni: $P < 0.05$).

Fig. 3: Scatterplot (N = 400) for women and men of TSP-ratios and CPM-effects. The TSP cutoff is illustrated by a solid line. The CPM cutoff is illustrated by a broken line. 'TSP': Temporal summation of pain. 'CPM': Conditioned pain modulation.

Summary

Subgrouping based on pro-nociceptive and anti-nociceptive mechanisms differentiate chronic pain patients with different clinical pain and experimental pain sensitivity.
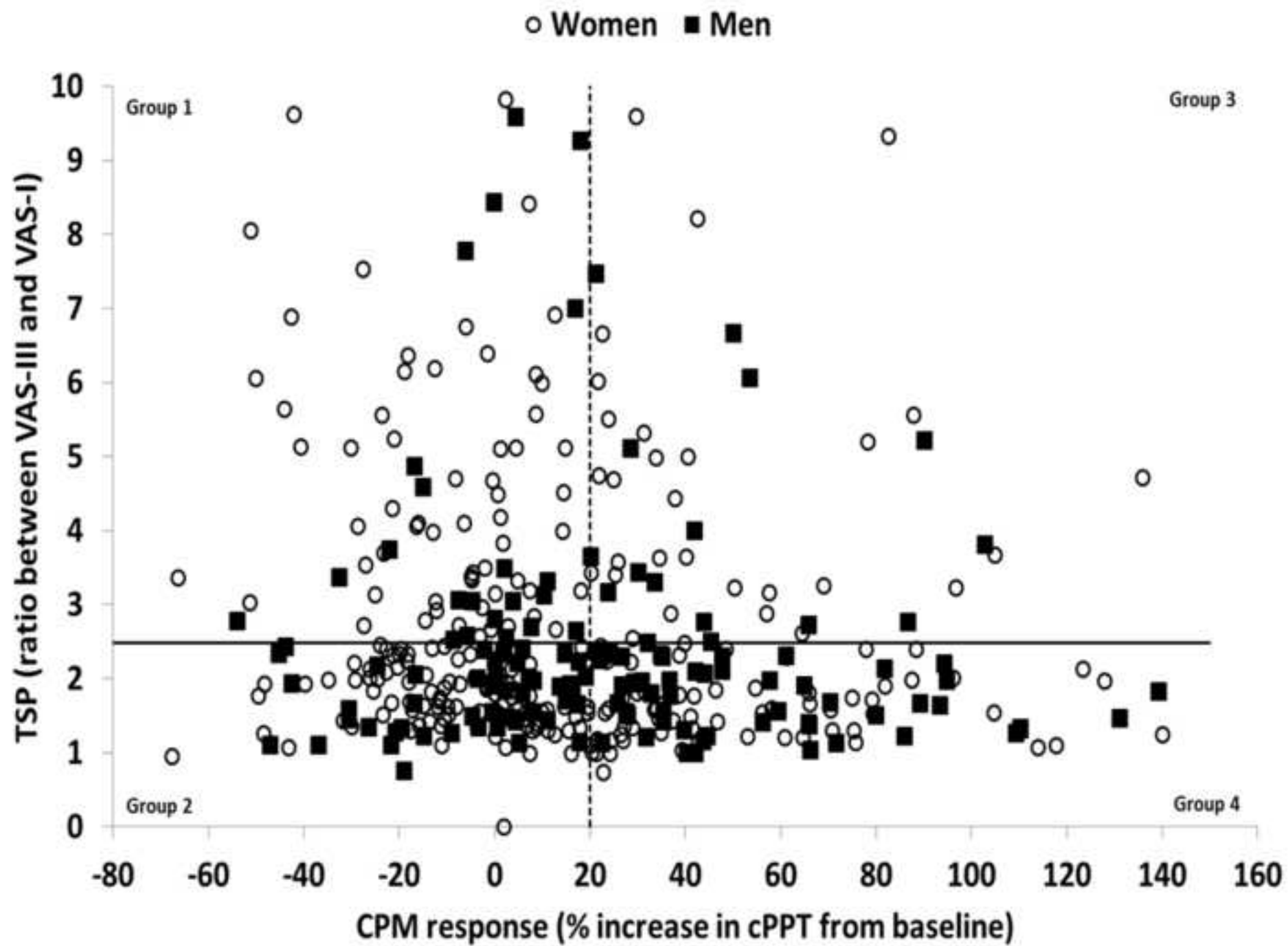
Figure1

Figure2

Figure3
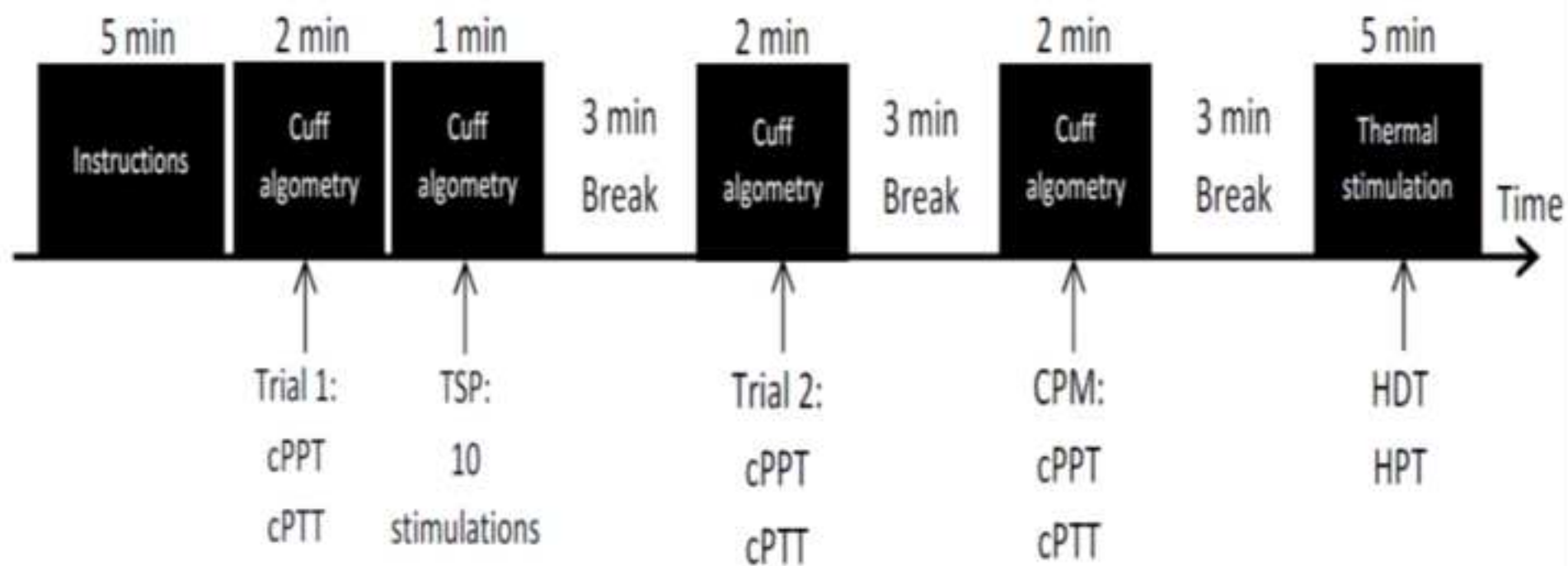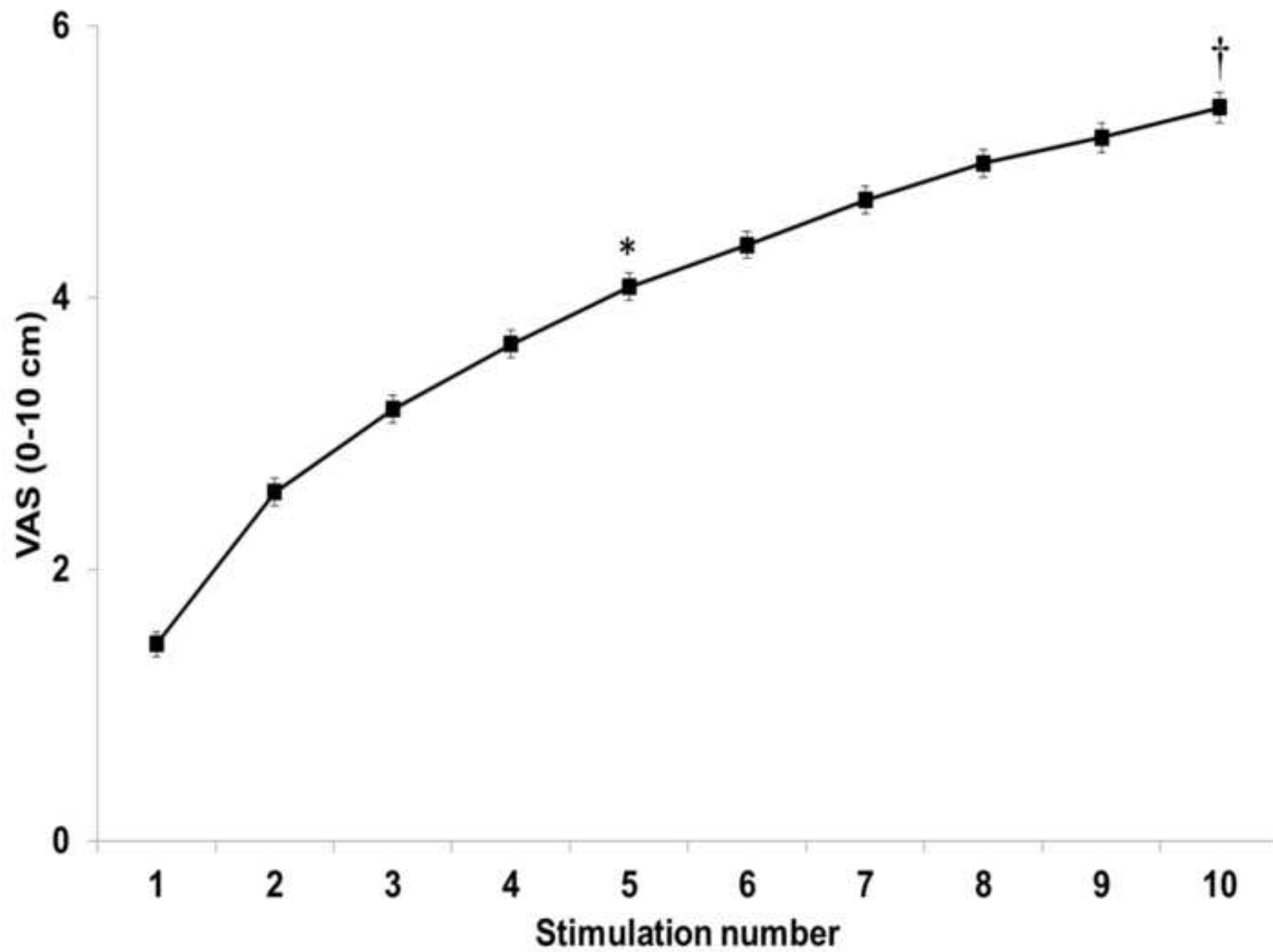
Table1

Table 1: Frequency of different pain conditions and use of analgesics across groups. Values presented as numbers and percentages.

	Variable	Group 1 (n=85)	Group 2 (n=148)	Group 3 (n=45)	Group 4 (n=122)	Total sample (n=400)
Pain diagnosis	Widespread Pain	31 (35.6%)	35 (23.6%)	7 (15.6%)	14 (11.5%)	87 (21.8%)
	>1 spinal areas	17 (20.0%)	33 (22.3%)	13 (28.9%)	21 (17.2%)	84 (21.0%)
	Low Back Pain	17 (20.0%)	21 (14.2%)	10 (22.2%)	27 (22.1%)	75 (18.8%)
	Sciatica	8 (9.4%)	17 (11.5%)	5 (11.1%)	20 (16.4%)	50 (12.5%)
	Extremity Pain	3 (3.5%)	18 (12.2%)	4 (8.9%)	12 (9.8%)	37 (9.3%)
	Cervicobrachialgia	5 (5.9%)	11 (7.4%)	4 (8.9%)	5 (4.1%)	25 (6.3%)
	Neck Pain	3 (3.5%)	3 (2.0%)	1 (2.2%)	15 (12.3%)	22 (5.5%)
	Headache	0 (0%)	4 (2.7%)	0 (0%)	3 (2.5%)	7 (1.8%)
	Abdominal	0 (0%)	3 (2.0%)	1 (2.2%)	2 (1.6%)	6 (1.5%)
	Other	1 (1.2%)	3 (2.0%)	0 (0%)	0 (0%)	4 (1.0%)
Analgesics	Opioids	62 (50.8%)	53 (47.7%)	35 (47.9%)	50 (53.2%)	200 (50%)
	Antidepressants	29 (23.4%)	21 (18.9%)	15 (20.5%)	23 (24.5%)	88 (22%)
	Anticonvulsants	20 (16.9%)	16 (15.0%)	8 (11.3%)	21 (23.1%)	65 (16.8%)
	NSAIDs	37 (31.4%)	28 (26.2%)	19 (26.8%)	23 (25.3%)	107 (27.6%)

Table2

Table 2: Demographic variables, clinical pain, experimental pain sensitivity, and psychological variables for the 4 groups based on pain modulatory phenotypes. Data presented as mean ± SD for women and men, respectively. 'TSP': Temporal summation of pressure pain. 'CPM': Conditioned pain modulation. 'BMI': Body Mass Index. 'NRS': Numerical Rating Scale. 'HDT': Heat Detection Threshold. 'HPT': Heat Pain Threshold. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance. 'VAScPTT': VAS score at cPTT. 'PDI': Pain Disability Index. 'PCS': Pain Catastrophizing Scale. 'TSK': Tampa Scale of Kinesiophobia. Significant difference between men and women (*, Mann Whitney U: $P < 0.05$).

		Women (n=263)					Men (n=137)				
		Group 1 n=63	Group 2 n=101	Group 3 n=30	Group 4 n=69	Total sample	Group 1 n=22	Group 2 n=47	Group 3 n=15	Group 4 n=53	Total sample
Pain modulation	TSP (ratio VAS-III/VAS-I)	4.8±1.9	1.7±0.4	4.6±1.9	1.6±0.4	2.8±1.9	4.4±2.4	1.7±0.4	4.2±1.6	1.7±0.4	2.4±1.6
	CPM (% change in cPPT)	-11.6±19.3	-8.3±17.7	48.9±29.2	57.7±35.6	14.7±40.2	-3.6±17.10	-5.6±18.9	49.2±26.3	56.9±31.9	24.9±39.3*
Demographic variables	Age (years)	50.5±12.0	46.8±12.9	47.1±12.5	47.1±14.9	47.8±13.2	52.1±9.5	46.4±11.6	51.3±8.9	47.5±11.6	48.4±11.1
	BMI (kg/m²)	27.4±5.7	27.1±5.7	26.5±3.6	25.6±5.5	26.7±6.8*	28.0±4.4	27.9±5.7	28.8±5.6	27.4±4.7	27.8±5.1*
Clinical pain	Duration of pain (years)	7.6±7.8	10.1±10.2	10.2±11.3	9.3±9.6	9.3±9.6	8.3±9.4	7.2±8.1	10.4±13.5	7.9±12.2	8.0±10.6
	Painful areas (1-45)	21.4±11.7	17.8±10.9	16.2±9.7	15.5±8.7	17.9±10.6*	17.6±11.7	13.3±8.2	13.1±8.9	11.5±7.7	13.6±9.1*
	Peak pain (NRS: 0-10)	8.7±1.4	8.4±1.2	8.5±1.3	8.1±1.5	8.4±1.3	8.5±1.4	8.3±1.1	8.1±2.2	8.0±1.5	8.2±1.4
	Average pain (NRS: 0-10)	7.2±1.8	7.0±1.6	6.8±1.5	6.3±1.7	6.9±1.7	7.1±1.3	6.7±1.5	6.8±1.8	6.4±1.9	6.8±1.6
Experimental pain	HDT Hand (°C)	34.7±1.3	34.7±1.1	34.8±1.7	34.5±1.1	34.7±1.2*	35.0±1.2	35.2±1.7	35.6±1.8	35.2±1.2	35.2±1.4*
	HDT Pain area (°C)	36.6±2.6	36.4±2.4	37.4±3.6	36.3±2.0	36.5±2.5*	38.6±4.0	37.0±2.9	36.7±2.9	36.5±2.2	37.0±2.9*
	HPT Hand (°C)	40.3±3.8	40.5±3.9	42.0±4.1	42.8±3.8	41.3±3.9*	42.4±3.9	43.0±4.1	42.9±3.1	43.7±3.6	43.2±3.8*
	HPT Pain area (°C)	41.0±3.7	39.9±3.8	42.0±4.2	42.2±4.1	41.0±4.0*	43.0±4.3	43.2±4.3	42.9±4.2	42.3±4.1	42.8±4.2*
	diffHPT (°C)	-0.5±3.6	0.5±3.6	-0.1±2.9	0.6±2.9	0.3±3.3	-0.6±3.4	-0.1±4.2	0.02±4.8	1.4±4.2	0.4±4.2
	cPPT (kPa)	17.6±7.8	17.0±7.9	18.9±8.1	17.5±6.9	17.5±7.6*	25.0±9.5	26.9±12.0	23.5±9.8	24.2±9.8	24.9±10.6*
	cPTT (kPa)	34.1±14.5	35.5±14.5	42.5±18.1	45.4±18.0	38.6±16.3*	49.3±21.0	52.0±18.6	53.9±21.2	58.8±21.3	54.7±20.4*
	VAScPTT (cm)	8.7±2.0	8.7±1.9	8.5±2.2	9.2±1.6	8.8±1.9	7.8±2.3	9.3±1.2	8.8±1.9	9.0±1.7	8.9±1.7
Psychological variables	Disability (PDI: 0-50)	37.4±9.0	34.9±8.8	35.0±9.4	33.6±9.9	35.2±9.3	37.1±7.1	36.0±7.3	35.9±7.2	36.0±7.8	36.1±7.4
	Catastrophizing (PCS: 0-52)	28.0±10.8	25.4±10.8	23.3±11.4	23.6±10.1	25.3±10.7	24.8±8.2	23.2±10.9	21.1±9.9	27.7±10.9	25.0±10.5
	Fear of movement (TSK: 17-68)	42.2±7.4	41.1±7.9	39.4±6.5	38.3±7.9	40.4±7.7*	43.6±6.7	42.0±8.4	43.5±6.9	43.6±9.3	43.0±8.2*

Table3

Table 3: Mean (± SD) Z-scores of pain modulation (TSP, CPM), clinical pain, experimental pain sensitivity and psychological variables for the 4 groups based on pain modulatory phenotypes. Negative Z-scores indicate reduced parameters compared with the group mean. 'HDT': Heat Detection Threshold. 'HPT': Heat Pain Threshold. 'DiffHPT': Difference between HPT at the non-painful hand and the painful area. 'cPPT': Cuff Pressure Pain Threshold. 'cPTT': Cuff Pressure Pain Tolerance. 'VAScPTT': VAS score at cPTT.

Domain	Variables	Group 1 (n=85)	Group 2 (n=148)	Group 3 (n=45)	Group 4 (n=122)	P-value
Pain modulation	TSP	1.10±1.3	-0.49±0.2	0.92±0.9	-0.51±0.2	**0.001** (1,3>2,4)
	CPM	-0.64±0.4	-0.61±0.4	0.69±0.6	0.93±1.0	**0.001** (3,4>1,2)
Clinical pain	Duration of pain	-0.13±0.8	0.03±1.0	0.14±1.2	-0.001±1.1	0.50
	Painful areas	0.36±1.1	-0.02±1.0	-0.18±0.9	-0.15±0.9	**0.002** (1>2,3,4)
	Peak pain intensity	0.20±1.0	0.02±0.8	0.006±1.2	-0.17±1.1	0.08
	Average pain intensity	0.23±1.0	0.05±0.9	-0.11±1.0	-0.16±1.1	**0.05** (1>4)
Experimental pain	HDT Hand	-0.02±1.0	0.01±1.0	0.16±1.3	-0.05±0.9	0.68
	HDT Pain area	0.16±1.1	-0.04±1.0	0.21±1.3	-0.13±0.8	0.10
	HPT Hand	-0.18±1.0	-0.14±1.0	0.08±1.0	0.27±1.0	**0.001** (4>1,2)
	HPT Pain area	0.01±0.9	-0.16±1.0	0.12±1.0	0.18±1.0	0.08
	DiffHPT	-0.24±1.0	0.03±1.0	-0.11±1.0	0.16±0.9	**0.04** (1<4)
	cPPT	0.02±1.0	0.02±1.1	-0.02±1.0	-0.03±0.9	0.97
	cPTT	-0.27±0.9	-0.14±0.9	0.10±1.1	0.32±1.1	**< 0.001** (4>1,2)
	VAScPTT	-0.19±1.1	0.03±0.9	-0.13±1.1	0.15±0.9	0.08
Psychological variables	Disability	0.22±1.0	-0.03±1.0	-0.02±1.0	-0.11±1.1	0.18
	Catastrophizing	0.19±1.0	-0.05±1.0	-0.24±1.1	0.02±1.0	0.14
	Fear of movement	0.20±0.9	0.02±1.0	-0.07±0.8	-0.13±1.1	0.20

Table4

Table 4: Test-retest reliability between two intra session assessments (n = 400) for cuff pressure pain threshold (cPPT) and tolerance (cPTT).

Pain sensitivity parameter	ICC			Bland and Altman			Intra CV
	1st Assessment Mean ± SD	2nd Assessment Mean ± SD	ICC$_{3,1}$ (95 % CI)	Mean difference (95 %CI)	SD diff (kPa)	95 % limits of agreement	% (95 % CI)
cPPT (kPa)	20.6 ± 8.7	20.1 ± 11.7	0.85 (0.81 – 0-88)	0.5 (-0.4 – 1.3)	7.4	-14.3 – 15.3	18.2 (16.3 – 20.0)
cPTT (kPa)	44.2 ± 18.8	44.7 ± 21.6	0.96 (0.94 – 0.97)	-0.5 (-1.5 – 0.4)	8.3	-17.1 – 16.1	9.7 (8.6 – 10.8)