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Original experimental

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Abstract

Background and aims: Psychological traits such as pain catastrophizing may play a role in the development of chronic pelvic pain (CPP). Pain catastrophizing is the tendency to amplify negative cognitive and emotional pain processes. The Pain Catastrophizing Scale (PCS) assesses elements of pain catastrophizing divided into three subgroups of factors (rumination, helplessness and magnification). Previous studies have shown associations between CPP and increased pain sensitivity, widespread generalized hyperalgesia, and decreased pain thresholds, but the relation between pain catastrophizing and specific pain thresholds has not yet been widely examined in this patient group. The aims of this study were (a) to determine if catastrophizing is increased in women with CPP compared with pain-free women, (b) to assess the importance of pain catastrophizing, psychological distress variables, and subjective pain sensitivity for pain thresholds of heat, cold and pressure in these two groups, and (c) to determine whether psychological variables or pain thresholds best contribute to the differentiation between CPP and controls.

Methods: Thirty-seven women with chronic pelvic pain who underwent diagnostic laparoscopy on the suspicion of endometriosis participated along with 55 healthy and pain-free controls. All underwent quantitative sensory testing on six locations on the body to determine heat (HPT), cold (CPT) and pressure (PPT) pain thresholds. The PCS, the Pain Sensitivity Questionnaire (PSQ), the Hospital Anxiety Depression Scale, (HADS) demographics and clinical data were collected prospectively. Principal component analysis and orthogonal partial least square regressions were used to assess the associations between PCS scores and pain thresholds.

Results: The women with CPP scored significantly higher on PCS than the healthy controls. PCS-helplessness, PCS-rumination and HADS-depression were significantly associated with pain thresholds for the whole group. In the CPP group, PCS-rumination, body mass index and PSQ were significant regressors for HPT and CPT. The PCS and the HADS subscales were strongly intercorrelated in women with CPP and were stronger regressors of group membership than the three pain thresholds. In the group of healthy control women, no relationships were found to be significant. The psychological variables were somewhat stronger significant regressors than pain thresholds (also significant) for group membership.

Conclusions: Women with CPP have significantly higher pain catastrophizing scores than women without CPP. The pain catastrophizing rumination factor is significantly associated with pain thresholds of heat and cold in CPP women. PCS and HADS are strongly intercorrelated and PSQ correlates positively with these variables. It seems that the psychological variables are important for group differentiation.

Implications: The results clearly indicate the need for a multimodal assessment (bio-psycho-social) of CPP patients including psychological symptoms such as catastrophizing, anxiety and depression. The registration of semi-objective pain thresholds captures both specific pain

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sensitivity information (mechanical pressure, cold or heat) and the degree of wide spread pain hypersensitivity. There is a need for future larger studies investigating whether certain profiles in the clinical presentations (including pain thresholds and psychological variables) are associated with outcomes after different types of interventions.

Keywords: chronic pelvic pain; catastrophizing; PCS; pain thresholds.

1 Introduction

Chronic pelvic pain (CPP) is common in women of reproductive age [1]. It often originates from multifactorial mechanisms and can manifest as dysmenorrhoea or endometriosis [2]. Chronic pain can lead to widespread reduced pain thresholds, i.e. generalized pain hypersensitivity. By definition, pain hypersensitivity as presented by reduced pain thresholds represents an abnormal state of responsiveness in the nociceptive pain system [3]. Pain hypersensitivity can be assessed with Quantitative Sensory Testing (QST), a set of psychophysical tools to assess mechanistically the status of the nociceptive and non-nociceptive pathways. The tests commonly include cold, heat and pressure thresholds, pain detection thresholds or pain tolerance thresholds [4]. QST has been used to investigate pain sensitivity in women with CPP and has shown increased and/or widespread hyperalgesia, elevated sensory thresholds and myofascial trigger points [5–10]. These results may indicate that CPP may be defined as nociplastic pain, the recently defined new type of pain mechanism defined by the International Association of the Study of Pain [11].

The perception of pain is integrated with psychological traits and pain coping behaviour and interacts with QST assessments [12]. Increased anxiety, depression and perceived pain sensitivity correlate with reduced pain thresholds [13–16]. Emotional dysregulation has been implicated as a transdiagnostic risk factor for pain severity and mood aspects [17, 18]. Emotion regulation, e.g. catastrophizing, is a trans-diagnostic process that ties pain and depression/emotion [19–21]. Pain catastrophizing is the tendency to amplify negative cognitive and emotional processes related to pain. It influences the sensation of pain [12] and may be a risk factor for the development of chronic pain after surgery [22]. Pain catastrophizing may act as a predictor of chronic pain among women with CPP [23–25] or endometriosis [26, 27] and in young women with menstrual pain [28]. Moreover, catastrophizing is one of several contributors to the severity of CPP [29] and to reduced quality of life [24]. CPP patients with high catastrophizing showed worse outcomes after different treatments compared with those with low catastrophizing [25].

The relationship between pain catastrophizing and pain thresholds in various chronic pain conditions has not been definitively established [30]. A deeper understanding of how pain mechanisms are related to psychological factors is essential for the planning and management of effective care for women with CPP. We have reported that women with CPP had alterations in pain thresholds indicating widespread hypersensitivity, and a time-dependent correlation between pain thresholds and duration of the CPP. In addition, the pain thresholds were significantly correlated with pain sensitivity [10, 16].

The aims of this study were (a) to determine if catastrophizing is increased in women with CPP compared with pain-free women, (b) to assess the importance of pain catastrophizing, psychological distress variables, and subjective pain sensitivity for pain thresholds of heat, cold and pressure in these two groups, and (c) to determine whether psychological variables or pain thresholds best contribute to the differentiation between CPP and controls.

2 Methods

2.1 Study design and sample

This is a secondary analysis of the data from a cross-sectional observational comparative study that was conducted between December 2013 and June 2016 at the Department of Obstetrics and Gynaecology at a central hospital and a university hospital in southeast Sweden [10]. The study was approved by the Regional Ethics Board of Linköping University (Reg.no. 2013/19-3).

In summary, pain thresholds for heat, cold and pressure were prospectively measured in 37 women with CPP referred for diagnostic laparoscopy due to symptoms that could indicate endometriosis, and in 55 healthy women without CPP. All participants filled in the PCS form, the Pain Sensitivity Questionnaire (PSQ) and the Hospital Anxiety and Depression Scale (HADS) form. A detailed description of the study is presented in the original study [10].

2.2 Measurements

2.2.1 Pain Catastrophizing Scale (PCS)

The PCS is a self-administered questionnaire consisting of 13 items divided into three domains: helplessness, magnification, and rumination. The questions cover the

patient's thoughts and feelings in different painful situations and include information on both intensity and frequency. The items are answered on a five point Likert-type scale using the phrases: *not at all (0), to a slight degree (1), to a moderate degree (2), to a great degree (3),* and *all the time (4)*. The scores for the three domains are summarised by different items: magnification relates to items 6, 7 and 13, rumination to items 8–11, and helplessness to items 1–5 and 12 [31]. Higher scores indicate a greater tendency for catastrophizing. The Swedish version of the PCS has been validated [32].

2.2.2 Pain Sensitivity Questionnaire (PSQ)

In the PSQ [14] the patient grades the imagined painfulness of 14 described painful everyday situations, where the situations include different pain types such as blunt, cold, hot and sharp, and are divided into different intensities and body sites. Three items serve as non-painful sensory references. The average rating is the PSQ total score, which is calculated from all painful items. A higher PSQ score indicates higher perceived pain sensitivity [14].

2.2.3 Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-rating test assessing symptoms of anxiety and depression using 14 items divided into two, seven items subscales (anxiety subscale and depression subscale) [33]. The subscale scores range between 0 and 21 points, with higher scores indicating more symptoms of anxiety or depression. The Swedish version has been validated [34].

2.2.4 Quantitative Sensory Testing (QST)

Pain thresholds for heat, cold and pressure were measured on six body sites using QST [35] according to the guidelines proposed by the German Research Network on Neuropathic Pain, with minor deviations [36]. The body sites were: the abdominal wall, seven cm lateral to the umbilicus on both sides, the abdominal wall just above the symphysis pubis, five cm lateral to the midline on both sides, the medial plane of the low back just below the fifth lumbar vertebra, and on the dominant leg, four cm distally from the tuberositas tibiae (the control area).

Heat (HCP) and cold (CPT) pain thresholds were measured with The Medoc TSA II NeuroSensory Analyzer (Medoc Ltd. 1 Ha'dekel St. Ramat Yishai 30095 Israel) using a 3×3 cm^2 computer-controlled thermode. The temperature dropped or increased from 32 °C at a rate of 1.5 °C/s to a maximum of 50 °C, or a minimum of 0 °C. The participant stopped the stimulation when first detecting a painful stimulus.

Pressure pain threshold (PPT) measurements were performed using a hand-held electronic algometer (Sometic AB, Hornby, Sweden) with a pressure surface area of 1 cm^2. Pressure was applied at a rate of approximately 40 kPa/s and was discontinued on the first sensation of pain.

Three measurements of each stimulus were performed on each body site and the arithmetic average was presented as the pain threshold [35]. The testing order of both body sites and stimuli was altered randomly. The majority of the measurements were performed by the first author, and the rest by three research nurses experienced in QST.

2.3 Statistical analyses

Statistical analyses were conducted with the software Statistica v 13.1 (Dell Software, 5 Polaris Way, Aliso Viejo, CA 92656, USA) and the SIMCA-P software version 15 (Umetrics, Sartorius Stedim Biotech, Umeå, Sweden). Data are presented as median and interquartile range (IQR) or frequency (number and percent).

A between-group comparison of demographic characteristics, clinical characteristics, pain thresholds and questionnaire data was conducted using a Mann-Whitney *U*-test for continuous data and Pearson's chi-squared test or Fisher's exact test for nominal data. The level of statistical significance was set at $p < 0.05$ for two-sided tests.

Due to the risk of downplaying the interrelationship among factors and thus reaching incorrect conclusions when using classic statistical methods (for instance linear regression), and the obvious risk of multicollinearity problems when using psychological variables, we used advanced multivariate data analysis (MVDA) as elaborated more in detail elsewhere [16]. The MVDA in the present study consists of principal component analysis (PCA) to detect outliers, and orthogonal partial least square regressions (OPLS) for the multivariate regressions. OPLS discriminant analysis (OPLS-DA) is used to show which variables have the largest discriminatory power for group separation (i.e. CPP vs. controls). Methods such as multiple linear regression assumes that the independent variables (x-variables, regressors) are not strongly intercorrelated i.e. multicollinearity is not present. Based on previous research we had good reasons to suspect the presence of multicollinearity. OPLS is instead based upon

the assumption that the independent variables may be intercorrelated (in unknown ways) and takes advantage of this multicollinearity pattern.

The data is not required to be normally distributed when applying these methods of MVDA [37]. Basically, the MVDA R^2 describes the goodness of fit – the fraction of sum of squares of all the variables explained by a principal component. Q^2 describes the goodness of prediction – the fraction of the total variation of the variables that can be predicted by a principal component using cross-validation methods [38].

A check for outliers was conducted using score plots of the PCA in combination with Hotelling's T^2, and distance to model in X-space [38]. No extreme outliers were detected in the present study. PCA can be regarded as a multivariate correlation analysis. Instead of performing multiple bi-variate correlations a PCA analysis is performed and the risks associated with multiple testing is markedly reduced. Besides checking for multivariate outliers PCA's were made in order to understand the correlation pattern among the variables used as regressors (x-variables). Graphic presentations implemented in SIMCA-P software were used to facilitate the understanding of the correlation pattern.

OPLS was used to explore the relative roles of PCS subscales, HADS subscales and PSQ together with background data (age, BMI, and smoking) to explain the variations in the pain thresholds for each stimulus [38]. A variable influence on projection (VIP) ≥ 1.0 was considered significant if the VIP value had a 95% jack-knife uncertainty confidence interval non-equal to zero [38]. P(corr) depicts the loading of each variable scaled as a correlation coefficient, thus standardising the range from –1 to +1. An absolute p(corr) > 0.4–0.5 is generally considered significant [37]. VIP values are specific for a certain regression but can be compared within a regression i.e. between the x-variables (regressors). P(corr) is suitable for comparisons between regressions but require that the same dependent variable (Y-variable) is used. For each regression, we report the R^2, Q^2, and the result (i.e. p-value) of a cross-validated analysis of variance (CV-ANOVA). In the present study we required a significant CV-ANOVA for a regression to be significant. A certain variable was considered a significant variable when VIP > 1.0 and absolute p(corr) ≥ 0.50.

3 Results

The demographic and descriptive data and the scores of the psychometric instruments for the 37 CPP women and the 55 controls are presented in Table 1. The CPP women deviated significantly from the control women in all

Table 1: Demographics, clinical characteristics, pain thresholds for heat, cold and pressure, PCS subscales, HADS subscales and PSQ total scores of women with chronic pelvic pain and healthy controls.

Variable	Women with chronic pelvic pain (n = 37)	Control group of healthy women (n = 55)	*p*-value
Age (years)	25.0; 22–30	31.0; 25–35	0.002
BMI (kg/m²)	23.7; 20.8–26.8	23.9; 21.1–25.7	0.796
Nulli-parous (no. of women)	30 (81)	24 (44)	0.014
Currently smoking (no. of women)	9 (24)	2 (4)	0.006
Hormonal birth control medication (no. of women)	20 (54)	34 (62)	0.520
Duration of pelvic pain (months)	36.0; 16–78	–	
Heat pain threshold (°C)	44.6; 41.0–47.2	47.8; 46.6–49.1	<0.001
Cold pain threshold (°C)	10.5; 6.3–20.5	0.59; 0.0–6.9	<0.001
Pressure pain threshold (kPa)	290.8; 227.3–434.8	553.0;401.5–654.8	<0.001
PCS rumination	11.0; 10.0–12.8	4.0; 1.8–7.0	<0.001
PCS magnification	5.5; 4.0–8.0	2.0; 1.0–4.0	<0.001
PCS helplessness	13.5; 11.0–18.0	3.0; 1.0–5.3	<0.001
HADS anxiety	10.0; 7.0–12.0	4.0; 2.0–7.0	<0.001
HADS depression	8.0; 5.0–11.0	2.0; 1.0–3.0	<0.001
PSQ	4.6; 2.6–4.1	3.6; 3.4–5.3	<0.001

Furthest to the right is shown the between-group comparisons (*p*-value).

Figures denote median; 25th–75th interquartile range or number of women and (%).

BMI = Body Mass Index; PCS = Pain Catastrophizing Scale; PCS rumination = rumination scale of PCS; PCS magnification = magnification scale of PCS; PCS helplessness = helplessness scale of PCS; HADS = Hospital Anxiety and Depression Scale; HADS-Depression = depression scale of HADS; HADS-anxiety = anxiety scale of HADS; PSQ = Pain Sensitivity Questionnaire – total index.

variables accounted for except for BMI and use of hormonal birth control. The median duration of pelvic pain in the CPP women was 36 months (IQR 18–72 months). Likewise, and as reported earlier for these two cohorts [10, 16] the pain thresholds were significantly lower in the CPP group.

3.1 Catastrophizing – group comparisons

Catastrophizing scores were significantly higher in the CPP women than in the healthy control women according to the three aspects (subscales) captured by PCS (Table 1).

3.2 Regressions of pain thresholds

3.2.1 Regressions of pain thresholds – all subjects taken together

The associations between the three pain thresholds (y-variables) and the other variables (x-variables) were investigated in three regressions (Table 2). Highly significant regressions (R^2: 0.30–0.45; all CV-ANOVA $p < 0.001$) were obtained for the three pain thresholds. A mix of variables showed important associations with the three investigated thresholds. The three analyses presented in Table 2

had in common that PCS-helplessness, PCS-rumination and HADS-depression were significantly associated with the pain thresholds.

The three scales of PCS and the two scales of HADS were important regressors correlating negatively with PPT. Two PCS scales (i.e. helplessness and rumination) were the most important regressors. In summary, psychological distress and catastrophizing were associated with low PPT when analysing all subjects taken together.

Both scales of HADS, PSQ and the three PCS scales were positively associated with CPT (Table 2). Depressive symptoms according to HADS and PSQ followed by two PCS scales (i.e. helplessness and rumination) were the variables most strongly correlated with CPT.

For HPT, a negative association with PSQ, the depression subscale of HADS and two of the PCS scales (i.e. helplessness and rumination) were found (Table 2).

3.2.2 Regressions of pain thresholds in women with CPP

Among women with CPP, the regression of PPT did not reach significance according to the CV-ANOVA (Table 3). Two of the subscales of PCS together with PSQ tended to be most important for PPT.

Table 2: OPLS regressions of PPT, CPT and HPT in all subjects taken together (n = 92), i.e. women with CPP and healthy control women.

PPT – all subjects			CPT – all subjects			HPT – all subjects		
Variables	**VIP**	**p(corr)**	**Variables**	**VIP**	**p(corr)**	**Variables**	**VIP**	**p(corr)**
PCS-helplessness	**1.31**	**−0.88**	**HADS-depression**	**1.26**	**0.73**	**PSQ**	**1.39**	**−0.79**
PCS-rumination	**1.27**	**−0.85**	**PSQ**	**1.25**	**0.72**	**PCS-rumination**	**1.19**	**−0.67**
PCS-magnification	**1.22**	**−0.82**	**PCS-rumination**	**1.16**	**0.67**	**HADS-depression**	**1.14**	**−0.64**
HADS-anxiety	**1.19**	**−0.79**	**PCS-helplessness**	**1.12**	**0.65**	**PCS-helplessness**	**1.11**	**−0.63**
HADS-depression	**1.16**	**−0.78**	**HADS-anxiety**	**1.05**	**0.60**	PCS-magnification	0.98	−0.55
PSQ	0.91	−0.60	**PCS-magnification**	**1.02**	**0.59**	HADS-anxiety	0.96	−0.54
Age	0.64	0.43	BMI	0.89	0.52	BMI	0.88	−0.50
Smoking	0.39	−0.26	Smoking	0.52	0.30	Smoking	0.57	−0.32
BMI	0.07	−0.05	Age	0.22	−0.12	Age	0.34	0.19
R^2	0.30		R^2	0.45		R^2	0.43	
Q^2	0.27		Q^2	0.36		Q^2	0.35	
CV-ANOVA *p*-value	<0.001		CV-ANOVA *p*-value	<0.001		CV-ANOVA *p*-value	<0.001	
Number of subjects (n)	92		Number of subjects (n)	92		Number of subjects (n)	92	

Note that pain duration was not included in the regression since it defines the two groups of subjects.
Variables with VIP > 1.0 and absolute p(corr) > 0.50 are significant and shown in bold type. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; − = negative correlation). The four bottom rows of each regression report R^2, Q^2, *p*-value of the CV-ANOVA and number of subjects (n).
PPT = mean value of pressure pain thresholds; CPT = mean value of cold pain thresholds; HPT = mean value of heat pain thresholds; BMI = body mass index; Smoking = currently smoking (i.e. dummy variable: smoking = 1, non-smoking = 0); HADS = Hospital anxiety and depression scale; HADS-Depression = depression scale of HADS; HADS-anxiety = anxiety scale of HADS; PCS = Pain Catastrophizing Scale; PCS-helplessness = helplessness scale of PCS; PCS-rumination = rumination scale of PCS; PCS-magnification = magnification scale of PCS; PSQ = Pain Sensitivity questionnaire – total index.

Table 3: OPLS regressions of PPT, CPT and HPT in women with CPP (n = 37).

PPT – CPP women			CPT– CPP women			HPT– CPP women		
Variables	VIP	p(corr)	Variables	VIP	p(corr)	Variables	VIP	p(corr)
PCS-rumination	**1.45**	**−0.79**	**BMI**	**1.89**	**0.82**	**PSQ**	**1.96**	**−0.83**
PSQ	**1.41**	**−0.75**	**PSQ**	**1.76**	**0.77**	**BMI**	**1.83**	**−0.78**
PCS-magnification	**1.38**	**−0.74**	**PCS-rumination**	**1.19**	**0.52**	**PCS-rumination**	**1.01**	**−0.43**
PCS-helplessness	**1.14**	**−0.61**	HADS-depression	0.82	0.36	Pain duration	0.79	0.34
HADS-depression	**1.09**	**−0.58**	Age	0.66	0.29	Age	0.70	−0.30
HADS-anxiety	0.92	−0.49	PCS-magnification	0.63	0.28	PCS-magnification	0.59	−0.25
BMI	0.79	−0.42	Pain duration	0.52	−0.23	HADS-depression	0.48	−0.21
Smoking	0.19	0.10	PCS-helplessness	0.31	0.14	PCS-helplessness	0.23	−0.10
Pain duration	0.14	0.08	HADS-anxiety	0.15	0.07	Smoking	0.17	−0.07
Age	0.10	−0.05	Smoking	0.09	0.04	HADS-anxiety	0.12	−0.05
R^2	0.17		R^2	0.52		R^2	0.51	
Q^2	0.02		Q^2	0.28		Q^2	0.23	
CV-ANOVA p-value	0.702		CV-ANOVA p-value	0.029		CV-ANOVA p-value	0.049	
Number of subjects (n)	37		Number of subjects (n)	37		Number of subjects (n)	37	

Variables with VIP > 1.0 and absolute p(corr) > 0.50 are significant and shown in bold type. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; − = negative correlation). The four bottom rows of each regression report R^2, Q^2, p-value of the CV-ANOVA and number of subjects (n).
PPT = mean value of pressure pain thresholds; CPT = mean value of cold pain thresholds; HPT = mean value of heat pain thresholds; BMI = body mass index; Smoking = currently smoking (i.e. dummy variable: smoking = 1, non-smoking = 0); HADS = Hospital anxiety and depression scale; HADS-Depression = depression scale of HADS; HADS-anxiety = anxiety scale of HADS; Pain duration = pain duration in months; PCS = Pain Catastrophizing Scale; PCS-helplessness = helplessness scale of PCS; PCS-rumination = rumination scale of PCS; PCS-magnification = magnification scale of PCS; PSQ = Pain Sensitivity questionnaire – total index.

For the two significant regressions of the thermal pain thresholds (R^2: 0.51–0.52; CV-ANOVA p-value: 0.029–0.049) it was found that the same variables were significant regressors even though their relative importance differed somewhat (Table 3). Hence, BMI, PSQ and the rumination subscale of PCS were the three significant regressors; the three variables correlated positively with CPT and negatively with HPT. BMI and PSQ were relatively equally important while the PCS rumination scale in both analyses had less importance even though it was significant.

3.2.3 Regressions of pain thresholds in healthy control women

No significant regressions were found for any of the three pain thresholds in the healthy control women (data not shown).

3.2.4 Intercorrelations among the independent variables (the regressors)

We also investigated the intercorrelation pattern among the variables used as regressors (x-variables) in the regressions above (Tables 2 and 3). Bivariate correlation analyses both for all subjects together and separate for the two groups clearly indicated intercorrelations between the independent variables (Supplementary Table S1). However, the interpretations of these are complicated and therefore multivariate correlation analyses by means of PCA were performed to investigate whether the regressors represented one or several groups of variables (latent variables or components).

In all subjects taken together, the PCA resulted in one significant component ($R^2 = 0.45$; $Q^2 = 0.32$) (Fig. 1). Figure 1 shows the two HADS scales and the three PCS scales as highly positively intercorrelated (they had the same sign and had high p-values according to the first component [p1 = the horizontal axis]). PSQ also had a relatively high loading on p1 but was more distant to the six psychological variables and was less strongly correlated with them. Smoking, BMI, and age had low absolute loadings (<0.22) upon p1 and thus were not so important. Note that the second component p2 (vertical axis) in Fig. 1 was not significant. In Supplementary Figure S1 the three pain thresholds are included in the PCA.

Also, in the CPP (Fig. 2), PCA resulted in one significant component ($R^2 = 0.31$, $Q^2 = 0.11$). The pattern of variables was very similar to what is shown in Fig. 1. Hence,
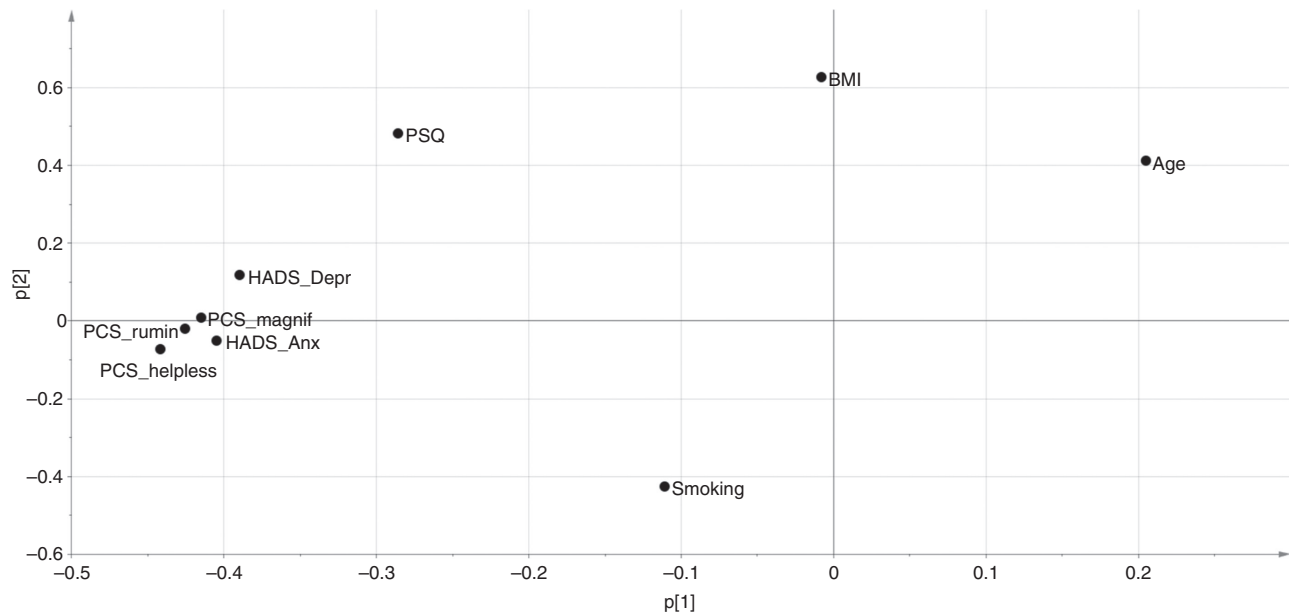
Fig. 1: PCA of the independent variables (X-variables) used in the regression of pain thresholds (cf. Table 2) in all subjects taken together (n = 92). Note that the second component p2 was not significant (only shown in order to improve interpretation). BMI = body mass index; Smoking = currently smoking (i.e. dummy variable: smoking = 1, non-smoking = 0); HADS-Depr = Hospital Anxiety and Depression Scale; =depression scale of HADS; HADS-Anx = anxiety scale of HADS; PCS = Pain Catastrophizing Scale; PCS-helpless = helplessness scale of PCS; PCS-rumin = rumination scale of PCS; PCS-magnif = magnification scale of PCS; PSQ = Pain Sensitivity questionnaire – total index
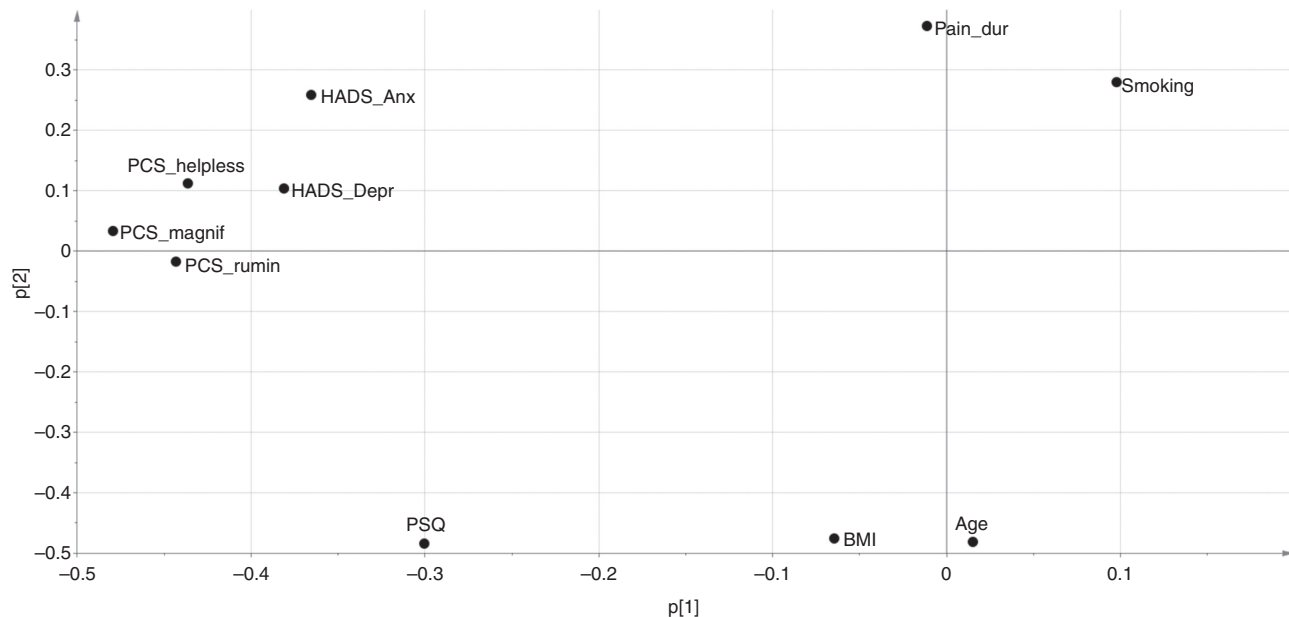

Fig. 2: PCA of the independent variables (X-variables) used in the regression of pain thresholds (cf. Table 3) in CPP (n = 37). Note that the second component p2 was not significant (only shown in order to improve interpretation). BMI = body mass index; Smoking = currently smoking (i.e. dummy variable: smoking = 1, non-smoking = 0); HADS-Depr = Hospital Anxiety and Depression Scale -depression scale; HADS-Anx = anxiety scale of HADS; Pain dur = pain duration; PCS = Pain Catastrophizing Scale; PCS-helpless = helplessness scale of PCS; PCS-rumin = rumination scale of PCS; PCS-magnif = magnification scale of PCS; PSQ = Pain Sensitivity questionnaire – total index.

in CPP the two HADS scales and the three PCS scales were highly intercorrelated (positively, i.e. they had the same sign and had high absolute p-values according to p1). The PSQ had a relatively high absolute loading on p1 but was more distant to the six psychological variables (not so strongly correlated with them). Smoking, BMI, and age

Table 4: OPLS-DA of group membership (i.e. healthy control women denoted 0 and women with CPP denoted 1) using psychological variables, pain thresholds and background variables as regressors (x-variables).

Variables	VIP	p(corr)
PCS-helplessness	1.27	0.84
PCS-rumination	1.22	0.81
PCS-magnification	1.15	0.77
HADS-anxiety	1.15	0.76
HADS-depression	1.13	0.75
CPT	1.12	0.74
HPT	1.09	−0.72
PPT	1.07	−0.71
PSQ	0.92	0.61
Age	0.57	−0.38
Smoking	0.45	0.30
BMI	0.14	0.09
R^2	0.64	
Q^2	0.62	
CV-ANOVA p-value	>0.001	
Number of subjects (n)	92	

Significant variables in bold type. Note that pain duration was not included in the regression since it defines the two groups of subjects.

VIP (VIP > 1.0 is significant) and p(corr) are reported for each regressor. The sign of p(corr) indicates the direction of the correlation with the dependent variable (+ = positive correlation; − = negative correlation). The four bottom rows of each regression report R^2, Q^2, and p-value of the CV-ANOVA and number of subjects included in the regression (n).
PPT = mean value of pressure pain thresholds; CPT = mean value of cold pain thresholds; HPT = mean value of heat pain thresholds; BMI = body mass index; Smoking = currently smoking (i.e. dummy variable: smoking = 1, non-smoking = 0); HADS = Hospital anxiety and depression scale; HADS-Depression = depression scale of HADS; HADS-anxiety = anxiety scale of HADS; PCS = Pain Catastrophizing Scale; PCS-helplessness = helplessness scale of PCS; PCS-rumination = rumination scale of PCS; PCS-magnification = magnification scale of PCS; PSQ = Pain Sensitivity questionnaire − total index.

had low absolute loadings (<0.15) upon p1. Note that the second component p2 is only shown to improve interpretation. It was not possible to obtain a significant PCA in the control group of healthy women. In Supplementary Figure S2 the three pain thresholds are included in the PCA.

To summarise both the analysis of all subjects and the separate analysis of the CPP group (Figs. 1 and 2) showed that scales of HADS and PCS were strongly intercorrelated and that PSQ correlated positively with these variables. Hence, we found no evidence that the regressors in Tables 2 and 3 represented several groups of variables.

3.3 Relative importance of psychological variables and pain thresholds for group differentiating

Group membership (y-variable) was regressed using the background variables, psychological variables, subjective pain sensitivity (PSQ) and pain thresholds as regressors (x-variables). From this significant OPLS-DA (Table 4) it can be concluded that the subscales of PCS and HADS were somewhat stronger regressors according to VIP and p(corr) than the three pain thresholds. PSQ, age, smoking and BMI were not significant regressors in this context (i.e. VIP < 1.0). Hence, the psychological variables contributed somewhat better than the pain thresholds to differentiating between CPP and healthy pain-free controls.

This conclusion was further demonstrated in two additional analyses. When only including the psychological variables including PSQ together with the background variables, a model with higher explained variation was achieved compared to when the pain thresholds together with background data and PSQ were used as regressors of group membership (R^2 = 0.62, Q^2 = 0.60, CV-ANOVA p-value < 0.001 versus R^2 = 0.43, Q^2 = 0.40, CV-ANOVA p-value < 0.001). Hence, these two analyses confirm the conclusion that the psychological variables were somewhat more important than pain thresholds for group differentiation.

4 Discussion

4.1 Summary of findings

Important results of the present study were:
- Women with CPP reported more catastrophizing than healthy pain-free women.
- In all subjects taken together, the three regressions of the pain thresholds had in common that PCS-helplessness, PCS-rumination and HADS-depression were significant regressors.
- In the group of women with CPP, the rumination subscale of PCS, BMI, and PSQ were significantly associated with HPT and CPT.
- The subscales of HADS and PCS were somewhat stronger regressors of group membership (control or CPP) than the three pain thresholds.

4.2 Interpretation of results in relation to current knowledge/literature

Our results conform with previous studies proposing high pain catastrophizing in populations with chronic pain [12, 22–24, 26, 27, 29, 30]. Catastrophizing is a significant variable for quality of life and treatment outcomes, where more catastrophizing leads to lower quality of life and less positive treatment outcomes. Furthermore, catastrophizing is a predictor for poor outcome after surgery [39]. The relationships show the importance of taking catastrophizing and other psychological aspects into account when treating people with chronic pain [24, 27, 29]. Also, the regression of group membership (Table 4) showed that catastrophizing aspects together with other psychological aspects were associated with the clinical presentation in CPP. However, the relationships between catastrophizing and pain thresholds is somewhat different in the literature and in the present study.

The OPLS regressions of CPT and HPT were significant, while the regression of PPT was not. The reasons for this need further evaluation. Meinits et al. [40] explored catastrophizing as a mediator for pain sensation in patients with chronic low back pain and found that PPT was inversely associated with pain catastrophizing [40]. Also, studies of chronic neck pain reported such a negative association between PPT and catastrophizing [41, 42]. Partly in contrast, Walton et al. [43] analysed the phenotypes of individuals with neck pain in five international registers and found the association between PPTs and pain characteristics, including catastrophizing, to be conflicting [43].

The psychological impact of the pain experience in CPP has been the focus of many studies, of which some are synthesised in the recent review by Till et al. [25]. There is convincing evidence for the theory of pain and emotion regulation as a trans-diagnostic process [21], where anxiety, depression and catastrophizing are highly collinear and together may influence the pain experience, and vice versa [25]. Martinez-Calderon et al. [44] recently reported that the diagnosis of depression had a stronger association with pain hypersensitivity than pain catastrophizing in patients with chronic shoulder pain [44]. In our results, the influence of PCS-rumination was significant for the regressions of the two thermal pain thresholds and a similar tendency was found in the non-significant regression of PPT in the CPP group. The fact that PCS-rumination was consistently significant while depression and anxiety were not in the CPP group is interesting and indicates the

important role of catastrophizing in the pain experience of CPP. The significance of the rumination scale of PCS may also suggest that rumination should be specifically targeted in the planning of new interventions. McPeak et al. [27] analysed the PCS subscales in relation to pain health-related quality of life. They found the strongest association between high helplessness and poor quality of life and suggested treatment strategies to manage pain catastrophizing [27]. The importance of taking a multi-disciplinary approach and thereby including these types of psychological aspects in the treatment and care of women with CPP has frequently been highlighted in the literature [19, 23, 25]. This conclusion is further supported by the results of the present study where emotional stress (i.e. symptoms of depression and anxiety) and catastrophizing aspects were increased in CPP and also constituted significant regressors for group membership. In order to understand the influence of psychological variables on the development of CPP, it may also be important to include pain catastrophizing.

Previous studies have shown an age-dependent factor in pain catastrophizing, where younger age was associated with higher pain catastrophizing intensity [22, 26]. We failed to demonstrate a significant age-dependent impact on pain catastrophizing. In contrast, BMI was a significant regressor for the two thermal pain thresholds but not for the pressure threshold. The scanty research on the influence of BMI upon pain sensitivity in women with CPP is ambiguous. Yosef et al. [29] found a positive association between high pain sensitivity and high BMI [29] while Gurian et al. [45] found higher pain thresholds among women with overweight compared with those with normal weight or with obesity [45]. This indicates that the influence of BMI upon pain thresholds merits further research.

The data pinpoints that the psychological variables i.e. symptoms of anxiety and depression and the three aspects of catastrophizing together with the three pain thresholds significantly explained group membership. Hence, both the psychological variables and the pain thresholds contribute to the understanding of the clinical presentation. Moreover, the five psychological variables were – according to VIP and p(corr) – somewhat more important than the three pain thresholds even though the three latter variables were also significant. From a clinical perspective, this information may be important since registration of pain thresholds is associated with short periods of pain and, moreover, is also considerably more time-consuming than filling out questionnaires on HADS and PCS. As

reported by us previously, PSQ is associated with the three pain thresholds and higher in women with CPP [16] but in the present study with a relatively comprehensive set up of variables, it can be concluded that PSQ was not significant in the regression (OPLS-DA) of group membership. PSQ captures the overall perceived pain sensitivity while the pain thresholds – semi-objective measures – capture both stimuli specific information (mechanical pressure, cold or heat) and the degree of spatial spreading [10].

4.3 Strengths and limitations

A strength of this study was the use of validated instruments and methods that provided information on different aspects of the subject. All women with pain had experienced pelvic pain for at least 4 months, a period which is often set as the minimum for considering the pain as chronic [46]. Another strength was the use of MVDA, which is designed to use the properties of the data set in an optimal way. This approach differs from classical statistical methods, such as multiple linear regression, which have a tendency to quantify the level of relations of individual factors and at the same time disregard interrelationships among different factors [47]. We also avoided the use of multiple linear regression due to the risk of multicollinearity problems in our data set. Although parity differed significantly between the groups it was not possible to include this variable in the MVDA since it did not fulfil the predetermined criteria (i.e. it had a VIP value with a 95% jack-knife uncertainty confidence interval including zero). Even though the number of participants in the study was sufficient to enable PCA and OPLS, the sample size may be considered small and thus may be a limitation of the study. Due to the very few studies published on the subject and consequently the lack of reliable information in the literature, no power analysis with sample size estimation was performed when planning the study. The sample size was intended to be at least the same as the studies previously published in the field. Another limitation may be that the women filled in the PCS after the QST, which may have influenced their scoring, even though the results of the QST were not disclosed. The cross-sectional design of the study and thus the direction of causality between catastrophizing and pain thresholds cannot be analysed. The relationship may be bidirectional.

5 Conclusions

This study showed that women with CPP, when measured by PCS, were more prone to exhibiting catastrophizing compared with healthy pain-free women. This was particularly evident in regard to the PCS subscale 'rumination' in the women with CPP. Although the pain thresholds (PPT, CPT and HPT) were all significantly associated with the PCS and HADS subscales they were weaker regressors of group membership. This underlines the importance of taking patients' psychological status and coping strategies, such as catastrophizing, into consideration when analysing the occurrence of pain hypersensitivity as a proxy for nociplastic pain in women with CPP.

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