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Temperament and character dimensions differ in chronic post-surgical neuropathic pain and cold pressure pain

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Abstract

Objectives: Psychobiological temperament and cognitive-evaluative character link to coping with chronic pain. The aim was to study possible independent role of temperament and character dimensions both in chronic and experimental pain in chronic post-surgical pain patients. This is a substudy of a previously published larger cohort of patients with intercostobrachial nerve injury after breast cancer surgery.

Methods: We recruited 241 women who had been treated for breast cancer 4–9 years before. They had a surgeon-verified intercostobrachial nerve injury with or without chronic post-surgical neuropathic pain (CPSNP). The patients filled in the Temperament and Character Inventory (TCI), Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale (HADS), and Brief Pain Inventory (BPI), and underwent the cold pressor test (CPT).

Results: 201 (83%) patients reported chronic pain and 135 (56%) met the criteria for CPSNP. Patients with CPSNP showed higher levels of Harm Avoidance (HA) temperament than non-CPSNP patients, which was associated with lower cold pain tolerance and greater increase of pain intensity during CPT. HA subscales Fear of Uncertainty and Fatigability contributed to a stronger pain experience. For character dimensions, CPSNP patients reported higher levels of Self-Transcendence (ST) and lower levels of Self-Directedness (SD) and Cooperativeness (CO) than non-CPSNP patients. Cold pain tolerance, intensity, or unpleasantness did not associate with character dimensions.

Conclusions: Psychobiological temperament, but not character, is independently from other psychological factors associated with primary pain processing in an experimental pain setting. Patients with and without CPSNP showed different profiles on both temperament and character dimensions suggesting a combination of heightened emotional vulnerability and lowered personality adaptability in CPSNP patients. Character dimensions associated with clinical but not experimental pain.

Ethical committee number: The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (reference number: 149/13/03/00/14).

Trial registry number: The study is registered in ClinicalTrials.gov (NCT 02487524).

Keywords: chronic pain; cold pressor test; neuropathic pain; pain sensitivity; temperament and character.

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Introduction

Psychological factors have an important role in evolving pain from acute to chronic and modulating experimental pain [1–3]. Individual differences in experimental pain sensitivity reflect the effect of various inherited and environmental contributions on the pain experience [4]. Several previous studies using the Temperament and Character Inventory (TCI) have shown a combination of high Harm Avoidance (HA) and low Self-Directedness

(SD) scores in chronic pain patients compared with healthy controls [5, 6]. This combination have also been associated with greater emotional distress and psychiatric comorbidities of chronic pain, e.g. mood and personality disorders [7].

The four dimensions of temperament, Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P) in Cloninger's psychobiological model of personality [8], reflect the mechanisms of behavioural activation, inhibition, and maintenance. Further, three character dimensions, Self-Directedness (SD), Cooperativeness (CO), and Self-Transcendence (ST), associate with level of maturation and adaptability of the personality.

According to Cloninger, there is a dynamic balance between temperament and character [8]. Temperament dimensions like HA are inherited and stable, reflecting responses to early emotions and related automatic responses to novel stimuli as well as neurochemical subsystems in the brain [9]. High HA scores suggest tendency for behaviour inhibition and intense responses to adverse stimuli. In contrast, character dimensions like SD, are learned during a lifespan and may fluctuate over time and define the significance and salience of different stimuli such as the experience of pain [8]. High SD scores are strongly associated with psychological well-being and successful adaptation in adverse situations.

Experimental pain sensitivity is known to be associated with the risk for acute postoperative pain [10], but the results of the association with the development of persisting post-surgical pain are conflicting [11, 12]. In previous experimental pain studies using heat stimulation, high levels of HA have correlated positively with amygdala activity [13] and with less efficient pain inhibition [14]. The cold pressor test (CPT) with high HA has shown low pain thresholds and tolerance [15, 16]. We previously showed that chronic post-surgical neuropathic pain (CPSNP) associates with increased experimental cold pain sensitivity [12]. As psychological factors affect the pain experience in many ways, here we aimed to study the role of temperament and character, in both clinical and experimental pain.

Patient with high HA scores may have an innate vulnerability factor that associates with specific personality characteristics, such as anxiety sensitivity, fear-avoidance response, and catastrophic thinking, that may contribute to the development of persistent pain [2, 5]. However, it is unclear whether HA is an independent from these psychobiological factors contributing to experimental and chronic pain responses.

We aimed to study the possible independent roles of temperament and character dimensions in experimental and chronic post-operative pain. The study cohort were women previously treated for breast cancer who had surgeon-verified intercostobrachial nerve injury, with or without CPSNP. We hypothesized that temperament and character have independent associations with experimental pain sensitivity. This is a substudy of a previously published larger cohort of breast cancer treated patients with CPSNP [12].

Methods

Patients and demographics

The current study is a substudy of a previous longitudinal cohort of 1000 breast cancer treated women recruited during 2006–2010 [17]. All patients had had either breast-conserving surgery (BCS) or mastectomy in combination with either sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND). Surgeon-verified intercostobrachial nerve injury (ICBN) status was available of 440 patients. These patients were invited for a new research visit 4–9 years after index surgery. Of these patients, the ones (N=251) with either total or partial ICBN resection, with or without pain, were eligible for this study. Chronic postsurgical pain was defined by the latest grading system for neuropathic pain (NP) [18]. Patient recruitment and eligibility have been described in detail elsewhere [12, 19].

The research visit was performed at the Pain Clinic of Helsinki University Hospital, where patients filled in several questionnaires and a neurologist performed a detailed clinical sensory examination. Data concerning previous surgery and breast cancer treatments were extracted from patient records [17]. Based on the sensory examination, the patients were classified into unlikely, possible, probable, and definite NP groups using the latest grading criteria for NP [12, 19]. Only definite NP was considered as CPSNP. General pain sensitivity and tolerance was assessed by the cold pressor test (CPT).

The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (reference number: 149/13/03/00/14) and registered in ClinicalTrials.gov (NCT 02487524). All patients provided a written informed consent.

Cold pressor test

Patients were instructed to immerse their contralateral (to previous breast cancer surgery) hand up to the wrist in circulating cold water (2–4 °C) bath (JULABO USA Inc., Allentown, PA, USA) for as long as they could tolerate it with a cut-off at 90 s. Withdrawal time, defined as the maximum time in seconds that the patient held her hand in cold water, was registered.

The patients were instructed to report pain intensity using the Numerical Rating Scale (NRS from 0 to 10, 0 indicating no pain and 10 the worst imaginable pain) every 15 s from the beginning of the CPT until the end of the test. Additionally, patients reported the unpleasantness, the affective component of experimental pain [20], by using NRS 0–10 immediately after the test. We used CPT withdrawal time, NRS values (0–10) during and at the end of CPT, and unpleasantness of the CPT procedure as measures for experimental cold pain sensitivity.

Temperament and Character Inventory (TCI)

We used the Finnish translation of the Temperament and Character Inventory (TCI) [8]. TCI consists of 240 items with true-false scaled questions assessing four temperament and three character dimensions. The psychometric properties of the Finnish translation have been tested and the results indicate good structural validity for temperament scales in the Finnish population [21].

TCI consists of four continuous temperament dimensions of Novelty Seeking (NS; range 0–40), Harm Avoidance (HA; range 0–35), Reward Dependence (RD; range 0–24), and Persistence (P; range 0–8) and three character dimensions of Self-Directedness (SD; range 0–44), Cooperativeness (CO; range 0–42), and Self-Transcendence (ST; range 0–33). All temperament and character dimensions are normally distributed, and they comprise a varying number of subscales (see Table S1). Descriptions of the temperament dimensions are presented in more detail elsewhere [8, 9].

Pain assessment and psychological questionnaires

For the assessment of the magnitude of CPSNP, we used Brief Pain Inventory (BPI) [22] to assess self-reported pain ("*worst pain during past week*") and pain interference ("*worst pain interference during past week*") in the operated area, including the breast, the axilla, and the upper arm. During the clinical sensory examination, patients were asked to rate possible evoked pain intensity for different sensory stimuli (light touch by cotton wool, sharp sensation by a cocktail stick, dynamic allodynia by a painter's brush, static allodynia by fingertip compression, cold and warm allodynia by metal roller) by using the NRS (0–10). In patients with CPSNP, we considered the highest rating of pain reported either during clinical examination or in BPI as a measure for "*intensity of worst CPSNP*" and used this for the analysis.

Additionally, patients were asked to rate other pains (apart from those in the operated area) with BPI ("*intensity of other chronic pains during the past week*"). The intensity of the worst of the other pains (NRS 0–10) was used as a covariate for the analyses. With all of these clinical pain variables (i.e. in the operated area and other pains), we considered NRS≥4/10 as moderate to severe pain [23].

Based on previous studies of psychological risk factors associated with chronic pain [1], we used Hospital Anxiety and Depression Scale (HADS) (scores varying from 0 to 21; cut-offs 8 to 10 for borderline and ≥11 for clinically significant anxiety and depression) to assess anxiety and depressive symptoms [24] and Pain Catastrophizing Scale (PCS) (scores varying from 0 to 52; cut-off ≥30 for clinically significant catastrophizing) to assess pain-related catastrophic thinking [25].

Statistical analysis

Descriptive statistics are presented as mean (standard deviation, SD), median (interquartile range, IQR), or number (percentage). We used univariate general linear model for comparison of temperament and character traits between patients with and without CPSNP. Pearson's correlation was used to assess correlations between continuous variables. Cronbach's alpha was used for reliability assessment for all psychological variables. We used Cohen's d for effect size estimate between-group comparisons.

Of the patients 212/241 (88%) had complete data. Missing values occurred in four measured variables: 26 in "*intensity of other chronic pains during the past week*", two in both anxiety and depression (HADS) scales, and four in Pain Catastrophizing Scale (PCS). The intensity of other chronic pains was included in the study protocol after the start of the study, and therefore, 26 patients (10.8%) lack data on this variable.

We used stepwise linear regression to study the association of TCI dimensions with experimental pain sensitivity. Covariates were selected based on significant correlations with dependent variables or significant intercorrelations with independent variables. All included variables in the regression models were centered to reduce multicollinearity.

To investigate the possible moderating role of CPSNP on the significant association between TCI dimensions and experimental pain, we performed separate regression analyses with the following interaction terms: (1) intensity of worst CPSNP × TCI dimension, and (2) dichotomized CPSNP (i.e. definite CPSNP) × TCI dimension. Interaction terms were included in fully adjusted models.

To study the association of TCI dimensions with NRS values during the CPT, we used linear mixed modelling for longitudinal data [26]. Both linear and quadratic components of time were included in the model to study whether there was a linear or a non-linear change in the NRS values over time. We used centered time variables to reduce collinearity between linear and quadratic time components in the model. The unstructured covariance matrix for the random effects was selected based on Bayesian Information Criteria (BIC). As an estimation method, we used restricted maximum likelihood. Age and CPT withdrawal time were added as independent predictors in all mixed models, as the duration of the painful stimulus varied between patients depending on their withdrawal time. For possible interaction between TCI dimensions and time variables, we used the following interaction terms in the mixed models: (1) TCI dimension × time and (2) TCI dimension × time^2.

Statistical analyses were performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA). For all statistical analyses, p-values under 0.05 were considered statistically significant.

Results

Patients

Altogether 241 patients had complete data on the main outcome variables (i.e. Temperament and Character Inventory and experimental pain test) and were included in the final analysis (Figure 1). Demographics, surgery- and treatment-related factors, clinical and experimental pain variables, and psychological variables including temperament traits (N=241) are presented in Table 1. Briefly, the majority of the patients had had mastectomy (57.7%), ALND (88.8%), had received chemotherapy (85.1%), radiotherapy (70.5%), and endocrine therapy (82.6%). In most patients, the ICBN had been partially resected (71.0%).

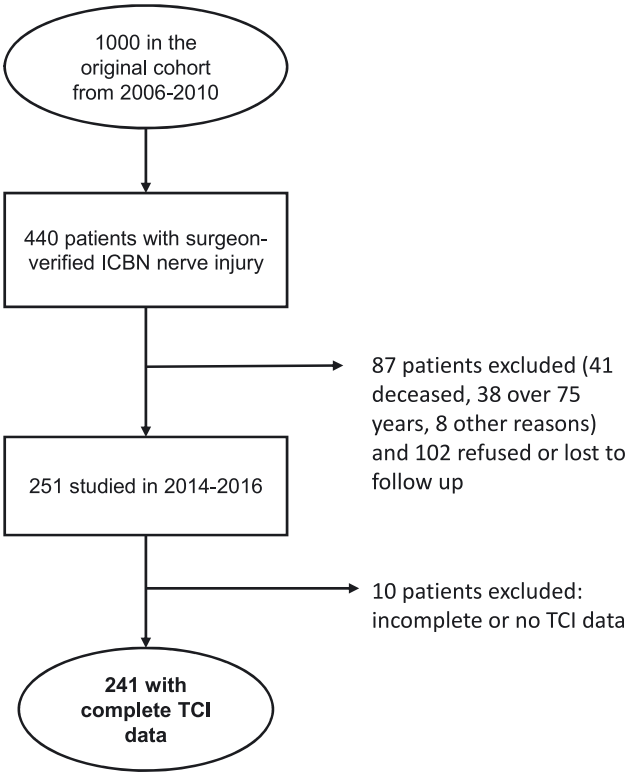

Figure 1: Flow chart of the patient recruitment.
ICBN, intercostobrachial nerve; TCI, temperament and character inventory.

Of all patients, 56.0% (135/241) met the criteria for definite CPSNP. Of the patients, 49.0% (99/241) reported moderate to severe pain (NRS≥4) at the previously operated area. However, only 10.8% (26/241) reported moderate to severe (NRS≥4) pain interference at the previously operated area.

CPT withdrawal time varied between 8 and 90 s, and 42.7% (103/241) of the patients held their hand in the cold water bath for the maximum of 90 s. Pain intensity (NRS) at the end of CPT varied between 0 and 10; two patients (0.8%) reported NRS 0 and 33.2% (80/241) reported the maximum intensity (NRS 10). Pain unpleasantness of the CPT procedure varied between 0 and 10; 3.7% (9/241) of the patients reported NRS 0 and 12.0% (29/241) NRS 10 at the end of the procedure.

When comparing CPSNP and non-CPSNP patients (after adjustment for age, anxiety, depressive symptoms, pain catastrophizing, and intensity of other pains), we found significant differences in the temperament dimension HA (14.6 vs. 12.8, p=0.010) (Cohen's d 0.26) and in character dimensions SD (33.6 vs. 35.3, p=0.001) (Cohen's d 0.29), CO (34.3 vs. 35.7, p<0.001) (Cohen's d 0.28), and ST (14.7 vs. 12.8, p<0.001) (Cohen's d 0.30) (Figure 2).

Table 1: Patient characteristics.

	Value
Demographics and clinical features	
Age, mean (SD), years	61.5 (8.2)
BMI, mean (SD), kg/m^2	25.7 (4.0)
Breast surgery type, number (%)	
BCS	102 (42.3)
Mastectomy	139 (57.7)
Axillary surgery type, number (%)	
SLNB	27 11.2)
ALND	214 (88.8)
Handling of ICBN, number (%)	
Partially resected	171 (71.0)
Totally resected	70 29.0)
Chemotherapy (yes), number (%)	205 (85.1)
Radiotherapy (yes), number (%)	170 (70.5)
Endocrine therapy (yes), number (%)	199 (82.6)
NP grading, number (%)	
Non-CPSNP	106 (44.0)
CPSNP	135 (56.0)
Pain variables	
Intensity of worst CPSNP[a], median (IQR), NRS 0–10	3 (0–6)
Intensity of other chronic pain during past week, mean (SD), NRS 0–10	2 (0–4)
Experimental pain variables	
Withdrawal time at CPT, median (IQR), seconds	69 (37–90)
Pain intensity at end of CPT, median (IQR), NRS 0-10	9 (8–10)
Pain unpleasantness at end of CPT, mean (SD), NRS 0–10	6.3 (2.8)
Other psychological variables	
Anxiety (HADS-A), mean (SD)	4.6 (3.1)
Depressive symptoms (HADS-D), mean (SD)	3.2 (3.5)
Pain catastrophizing (PCS), median (IQR)	4 (0–11)
TCI dimensions	
Novelty Seeking (NS), mean (SD)	17.4 (6.4)
Harm Avoidance (HA), mean (SD)	13.8 (6.9)
Reward Dependence (RD), mean (SD)	15.2 (3.9)
Persistence (P), mean (SD)	3.7 (1.9)
Self-Directedness (SD), mean (SD)	34.5 (5.7)
Cooperativeness (CO), mean (SD)	34.9 (5.0)
Self-Transcendence (ST), mean (SD)	13.7 (6.7)

[a]In the previously operated area, including the breast, the axilla, and the upper arm. Abbreviations: N, number of patients; SD, standard deviation; IQR, interquartile range; BMI, body mass index; BCS, breast-conserving surgery; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; ICBN, intercostobrachial nerve; CPSNP, chronic post-surgical neuropathic pain; NRS, Numerical Rating Scale (0–10); CPT, Cold Pressor Test; HADS-A, Hospital Anxiety and Depression Scale – anxiety (α=0.82); HADS-D, Hospital Anxiety and Depression Scale – depression (α=0.88); PCS, Pain Catastrophizing Scale (α=0.93); TCI, Temperament and Character Inventory. Data: N=241.

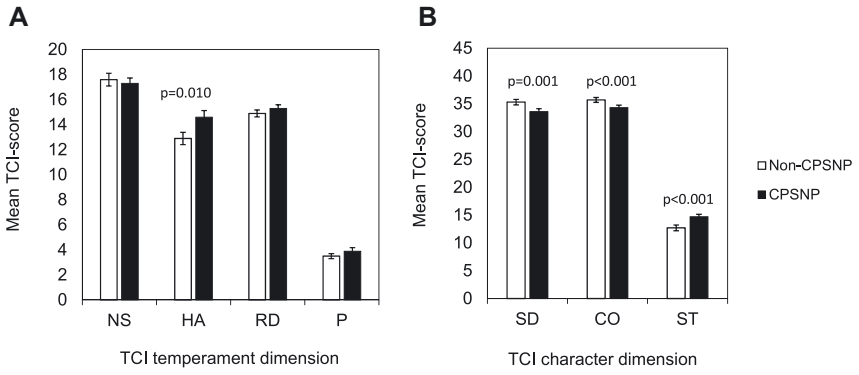

Figure 2: Mean TCI (temperament and character inventory) scores between patients with (CPSNP) and without chronic post-surgical neuropathic pain (non-CPSNP) for A) temperament dimensions of Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P) and for B) character dimensions of Self-Directedness (SD), Cooperativeness (CO), and Self-Transcendence (ST). N=135 for CPSNP and N=106 for non-CPSNP.

Temperament and general measures of the cold pressor test

Correlations of temperament and character dimensions with age, clinical and experimental pain variables, and other psychological variables are presented in Table 2. Of all temperament and character dimensions, only HA showed a significant negative correlation with CPT withdrawal time ($p<0.05$) and a positive correlation with CPT unpleasantness ($p<0.05$). We found HA to correlate positively with the intensity of the worst CPSNP ($p<0.05$), depressive symptoms ($p<0.001$), anxiety ($p<0.001$), and pain catastrophizing ($p<0.01$). None of the character dimensions correlated with experimental pain variables. However, SD and CO showed strong negative correlations with anxiety, depressive symptoms, and pain catastrophizing. Intercorrelations between all other variables are presented in Table S2.

Based on the significant correlations, stepwise linear regression models were built for CPT withdrawal time and CPT unpleasantness (Table 3). In a baseline model (Model 1), HA was associated negatively with CPT withdrawal time ($B=-0.131$, $p=0.029$). With all covariates (Model 3), the association of HA remained significant ($B=-0.187$, $p=0.010$). The separate analysis with HA subscales showed that the association was explained by the subscales of Fear of Uncertainty ($B=-0.167$, $p=0.010$) and Fatigability ($B=-0.235$, $p=0.003$). No significant interaction was found between HA and intensity of the worst CPSNP ($p=0.332$), or HA and CPSNP (dichotomous variable) ($p=0.661$) on CPT withdrawal time.

Table 2: Pearson's correlation coefficients for total scores of the TCI temperament and character dimensions with age, clinical pain variables, experimental pain variables, and psychological variables.

	NS	HA	RD	P	SD	CO	ST
Age, years	**−0.261[c]**	**0.164[a]**	−0.125	−0.089	0.010	0.001	0.049
Intensity of worst CPSNP*, NRS 0-10	−0.034	**0.157[a]**	0.101	0.020	−0.086	−0.037	0.109
Intensity of other chronic pain, NRS 0-10	0.010	0.028	−0.037	0.102	−0.025	−0.033	0.054
Withdrawal time at CPT, seconds	−0.050	**−0.152[a]**	−0.053	0.100	0.061	0.079	0.031
Pain intensity at end of CPT, NRS 0-10	0.034	0.021	0.060	0.002	−0.034	−0.037	0.037
Pain unpleasantness at end of CPT, NRS 0-10	−0.007	**0.131[a]**	0.057	0.032	−0.104	−0.100	0.074
Anxiety (HADS-A)	−0.016	**0.423[c]**	0.092	**0.183[b]**	**−0.410[c]**	**−0.154[a]**	**0.186[b]**
Depression (HADS-D)	−0.084	**0.443[c]**	−0.035	0.120	**−0.489[c]**	**−0.265[c]**	0.118
Pain catastrophizing (PCS)	−0.029	**0.193[b]**	0.072	0.056	**−0.228[c]**	**−0.137[a]**	0.121

*In the previously operated area, including the breast, the axilla, and the upper arm. Abbreviations: TCI, Temperament and Character Inventory; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reward Dependence; P, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence; CPSNP, chronic post-surgical neuropathic pain; NRS, Numerical Rating Scale; CPT, Cold Pressor Test; HADS-A, Hospital Anxiety and Depression Scale – anxiety; HADS-D, Hospital Anxiety and Depression Scale – depression; PCS, Pain Catastrophizing Scale.
Statistical method: Pearson's correlation. Bolded values indicate statistically significant results. For two-tailed significance: [a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$. Data: N=241.

Table 3: Temperament dimension of Harm Avoidance and stepwise linear regression analyses on CPT Withdrawal time (seconds) and CPT Unpleasantness (NRS 0–10).

	CPT withdrawal time, seconds						CPT unpleasantness (NRS 0–10)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
	B	p	B	p	B	p	B	p	B	p	B	p
Age, years	0.074	0.218	0.073	0.223	0.083	0.265	−0.066	0.242	−0.062	0.282	−0.060	0.277
NRS at end of CPT	−0.378	**<0.001**	−0.388	**<0.001**	−0.375	**<0.001**	0.537	**<0.001**	0.560	**<0.001**	0.531	**<0.001**
Harm avoidance	−0.131	**0.029**	−0.180	**0.010**	−0.187	**0.010**	0.162	**0.018**	0.068	0.357	0.062	0.404
Anxiety (HADS-A)			0.052	0.573	0.036	0.707			0.204	**0.039**	0.197	**0.048**
Depressive symptoms (HADS-D)			0.046	0.608	0.086	0.356			0.054	0.570	0.042	0.660
Pain catastrophizing (PCS)			−0.041	0.535	−0.004	0.968			0.039	0.585	0.042	0.572
Worst other pain (NRS)					−0.001	0.986					0.066	0.341
Intensity of worst CPSNP (NRS)					−0.143	**0.035**					0.056	0.430
Adjusted R^2	0.173		0.178		0.203		0.309		0.314		0.319	

Model 1 (baseline model): adjusted for age and NRS ad the end of CPT. Model 2: adjusted for age, NRS at the end of CPT, anxiety and depressive symptoms, and pain catastrophizing. Model 3: adjusted for age, NRS at the end of CPT, anxiety and depressive symptoms, pain catastrophizing, worst other pain and intensity of worst CPSNP. Abbreviations: NRS, Numerical Rating Scale; CPT, Cold Pressor Test; HADS-A, Hospital Anxiety and Depression Scale – anxiety; HADS-D, Hospital Anxiety and Depression Scale – depression; PCS, Pain Catastrophizing Scale; CPSNP, chronic post-surgical neuropathic pain. For linear regression model: B, standardized regression coefficient. Bolded values indicate statistically significant results. Data: N=241.

HA was positively associated with CPT unpleasantness (B=0.162, p=0.018) after adjusting for age and pain intensity at the end of CPT (Model 1). The separate analysis with HA subscales showed that the association was explained by Fear of Uncertainty (B=0.141, p=0.012). After including anxiety, depressive symptoms, and pain catastrophizing in the model (Model 2), the association between HA and CPT unpleasantness was non-significant (B=0.068, p=0.357). However, anxiety showed a significant positive association with CPT unpleasantness in Model 2 (B=0.204, p=0.039) and Model 3 (B=0.197, p=0.048). No significant interaction was found between HA and intensity of the worst CPSNP (p=0.516), or HA and CPSNP (dichotomous variable) (p=0.269) on CPT unpleasantness.

Temperament and cold pain intensity during cold pressor test

The results of the linear mixed analysis for each temperament dimension are presented in Table 4. Time components showed positive linear and negative quadratic associations with NRS values in each model, indicating increasing and saturating values of self-reported pain over time.

Of all temperament and character dimensions, we found a significant main effect of HA on NRS values (F(1, 253)=4.510, p=0.035) and a significant interaction with HA and linear time component on NRS values (F(1, 522)=10.459, p=0.001). The main effect of HA on NRS values was non-significant after adjusting for all potential variables referred to in previous linear regressions (F(1, 237)=0.055, p=0.814). However, the interaction between HA and the linear time component remained significant after multivariable adjustment (F(1, 487)=9.783, p=0.002). Separate analyses with fully adjusted models showed that this interaction was explained by the subscales of Fear of Uncertainty (F(1, 476)=5.606, p=0.018) and Fatigability (F(1, 476)=8.759, p=0.003).

In the fully adjusted model, higher scores of HA were associated with a greater increase in NRS values during CPT than lower scores of HA. The associations between HA and NRS values during CPT are illustrated in Figure 3.

Table 4: Results of linear mixed-effect models[a] for TCI temperament and character dimensions and reported pain intensity ratings on NRS during CPT.

TCI dimension	Model	Estimate	S.E.	df	t	p
Novelty Seeking (NS)	time (seconds)	1.438	0.096	500.758	14.973	**<0.001**
	time^2 (seconds^2)	−0.788	0.117	143.617	−6.741	**<0.001**
	NS total score	0.008	0.026	251.441	0.321	0.749
	NS total score × time	0.004	0.005	501.844	0.802	0.423
	NS total score × time^2	0.001	0.006	147.896	0.085	0.933
Harm Avoidance (HA)	time (seconds)	1.301	0.073	509.609	17.876	**<0.001**
	time^2 (seconds^2)	−0.773	0.087	144.384	−9.863	**<0.001**
	HA total score	0.050	0.024	253.427	2.124	**0.035**
	HA total score × time	0.016	0.010	522.331	3.234	**0.001**
	HA total score × time^2	−0.001	0.006	153.938	−0.053	0.958
Reward Dependence (RD)	time (seconds)	1.490	0.132	505.157	11.305	**<0.001**
	time^2 (seconds^2)	−0.649	0.158	144.413	−4.103	**<0.001**
	RD total score	0.036	0.041	251.959	0.888	0.375
	RD total score × time	0.001	0.009	505.798	0.157	0.875
	RD total score × time^2	−0.009	0.010	146.493	−0.840	0.402
Persistence (P)	time (seconds)	1.753	0.073	499.297	24.094	**<0.001**
	time^2 (seconds^2)	−0.672	0.090	145.491	−7.430	**<0.001**
	P Total score	0.003	0.086	245.084	0.033	0.974
	P Total score × time	0.006	0.006	466.320	−0.918	0.359
	P Total score × time^2	−0.029	0.021	141.343	−1.363	0.175
Self-Directedness (SD)	time (seconds)	1.760	0.188	498.107	9.376	**<0.001**
	time^2 (seconds^2)	−0.841	0.231	133.620	−3.634	**<0.001**
	SD total score	−0.023	0.028	239.410	−0.830	0.407
	SD total score × time	−0.007	0.005	495.301	−1.354	0.176
	SD total score × time^2	0.002	0.007	132.363	0.279	0.781
Cooperativeness (CO)	time (seconds)	1.468	0.213	473.171	6.906	**<0.001**
	time^2 (seconds^2)	−1.026	0.272	121.329	−3.769	**<0.001**
	CO total score	−0.042	0.033	247.603	−1.290	0.198
	CO total score × time	0.001	0.006	471.497	0.200	0.841
	CO total score × time^2	0.007	0.008	120.967	0.919	0.360
Self-Transcendence (ST)	time (seconds)	1.543	0.077	509.120	20.143	**<0.001**
	time^2 (seconds^2)	−0.778	0.091	147.187	−8.563	**<0.001**
	ST total score	−0.009	0.024	240.669	−0.382	0.703
	ST total score × time	−0.002	0.005	513.648	−0.474	0.636
	ST total score × time^2	−0.001	0.006	144.506	−0.017	0.986

[a]All the models were adjusted for age, CPT withdrawal time, anxiety and depressive symptoms (HADS-A and HADS-D) and pain catastrophizing (PCS). Time variables were centred to reduce collinearity. Data: N=241. Abbreviations: TCI, Temperament and Character Inventory; NS, Novelty Seeking, HA, Harm Avoidance; RD, Reward Dependence; P, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence; NRS, Numerical Rating Scale; CPT, Cold Pressor Test; HADS-A, Hospital Anxiety and Depression Scale – anxiety; HADS-D, Hospital Anxiety and Depression Scale – depression; PCS, Pain Catastrophizing Scale; S.E., standard error. Bolded values indicate statistically signiticant results.

Discussion

Main findings

Patients with higher harm-avoidance (HA) temperament showed a greater increase in pain intensity during the cold pressor test (CPT) than patients with lower scores of HA. HA temperament associated with cold pain sensitivity, reflected reduced CPT withdrawal time, increased CPT unpleasantness, and increased pain intensity during CPT. HA subscales Fear of Uncertainty and Fatigability mainly explained the associations. Further, patients with chronic post-surgical neuropathic pain (CPSNP) had higher scores on HA and Self-Transcendence (ST) and lower scores on Self-Directedness (SD) and Cooperativeness (CO) than non-CPSNP patients.

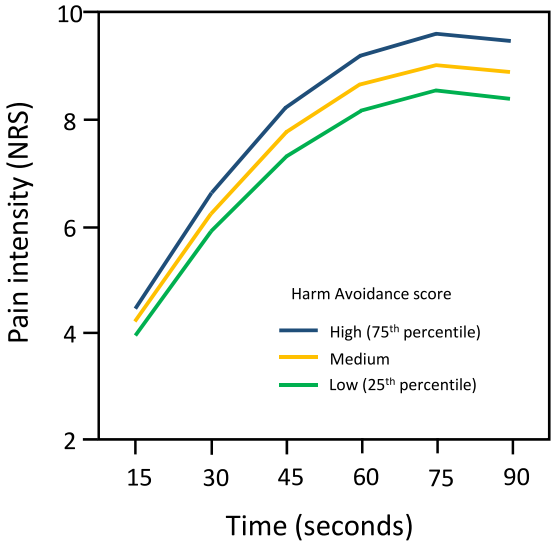

Figure 3: Association between Harm Avoidance (HA) and pain intensity (NRS) during cold pressor test in an adjusted linear mixed effect model. For illustration, HA score was divided into quartiles to indicate low (25th percentile), medium (from 25th to 75th percentile), and high (75th percentile) levels of HA temperament. Abbreviation: NRS, Numerical Rating Scale.

Temperament and character in chronic post-surgical neuropathic pain (CPSNP)

In previous studies, higher HA temperament, lower SD, and lower CO have been the most prevalent combination in patients having various chronic pain conditions [5, 6]. This temperament and character combination may reflect poorer ability to cope with pain and disability. The association of higher ST with chronic pain has also previously reported, but poorly understood [5]. Consistently with previous studies, we found that patients with CPSNP, compared with non-CPSNP patients, showed higher scores in HA, lower scores in SD and CO, and higher scores in ST. A positive correlation emerged between the intensity of CPSNP and HA, but not with other pain. These results may reflect and confirm a common shared personality profile related to chronic pain [6]. However, between-group differences and the effect sizes were relatively small and in line with previous studies [5, 6].

Harm Avoidance is a heritable tendency to respond intensely to signals of aversive stimuli with learned inhibition and passive-avoidant behavior such as fear of uncertainty and development of conditioned fear responses [9]. Previously, chronic pain patients have shown higher levels of Fatigability subscale compared with pain-free controls, but no difference has been found in levels of Fear of Uncertainty subscale [7]. However, in our cohort, we found Fear of Uncertainty and Fatigability to be associated with experimental pain sensitivity. Additionally, Fear of Uncertainty was associated with experimental pain unpleasantness in CPT.

Our findings in Fatigability and Fear of Uncertainty may reflect clinical differences between HA subscales. Fatigability has i.e. previously associated with anxiety symptoms in chronic pain patients [27]. Individuals with lower levels of the Fatigability subscale are vigorous and recover more quickly from exertion [9]. High scoring of Fear of Uncertainty subscale has been associated with caution, tension, and worrying during novel and unfamiliar situations and with unconfident behavior in general [9]. These features present often in chronic pain patients and may be of importance in chronic pain evolvement and in targeting interdisciplinary therapy interventions.

Temperament and character reflect different types of information perception and processing [8]. Temperament is a biologically determined part of personality that is related to primitive reactions and appraisals of emotions in novel situations. Character, by contrast, is conceptualized as a collection of self-concepts learned during social development, and it is related to effective adaptation and self-satisfaction in changing situations. It is possible that character is related especially to long-term adaptation to pain [6], but not to acute and novel pain such as experimental pain, as we used in our study. As we previously showed a heightened post-surgical experimental cold pain sensitivity in patients with CPSNP [12], we aimed to study whether specific psychological factors, particularly an association between temperament and character on experimental pain sensitivity is associated with CPSNP.

Previously, in healthy volunteers, CO character dimension has correlated with cold pain sensitivity [28]. In our cohort, we found no association between character dimensions and experimental pain. In contrast, we found character dimensions SD and CO associating with CPSNP, supporting the possible role of character in the process of chronic pain perception.

Personality profiles were different in CPSNP vs. non-CPSNP patients, but in CPT the character did not play a role. These results confirm the specific tasks that temperament and character have in pain perception.

Previous experimental pain studies have shown the role of HA in heightened experimental cold pain sensitivity [15, 16]. In our cohort, patients with higher HA scores had a heightened pain perception in response to cold pain stimuli. This finding showed and independent role in lower cold pain tolerance and greater pain sensitivity during the CPT procedure, even after controlling for confounding factors.

The association of HA with experimental pain sensitivity has been suggested to be partly explained by genetic polymorphism in genes modulating nociceptive transduction and opioid analgesia, such as *TRPV1* and *OPRD1* [15]. Another study used the conditioned pain modulation paradigm and found reduced endogenous analgesia in high-HA individuals [14]. Increased amygdala activity has been shown to correlate positively with HA temperament during heat pain expectancy, suggesting that in high-HA individuals vigilance and enhanced emotional response toward warning cues, such as expecting pain, are possibly mediated via the limbic system [13]. In line with high HA and pain expectancy, our study showed an association between HA and pain intensity (NRS) during the CPT, but not at the end of CPT. These results may reflect the suggested association of HA with early perception of pain and avoidance behavior of expected pain [13], but also the effect of endogenous pain modulation presenting in the end of the CPT.

The autonomic nervous system (ANS) may have an important role in mediating the effects of HA on different homeostatic processes [29]. We have previously reported the results of ANS responses to CPT in this patient cohort. There, ANS reactions associated with pain sensitivity in CPT. Additionally, ANS functioning differed between CPT tolerant vs. non-tolerant patients [30]. Thus, HA temperament possibly associates with endogenous pain modulation systems via ANS.

We used experimental pain unpleasantness as a measure of the affective component of pain [31]. HA showed an independent association with unpleasantness even after controlling for the intensity of experimental pain. This may suggest that HA influences both sensory and affective information processes [20]. However, the association was non-significant after adjustment for mood. These results suggest that the association of HA with unpleasantness is explained especially by anxiety, which has previously shown consistent association with increased pain sensitivity [32] and experimental pain unpleasantness [31].

The overall tendency to negative emotions and threat-biased perception may explain the strong association of HA with anxiety and depressive symptoms [7], but it may also predispose to pain-specific catastrophic thinking [5, 6]. We found a significant correlation between HA and pain catastrophizing. However, no association existed between pain catastrophizing and experimental pain.

Fear of pain has been proposed to have a stronger influence on acute experimental pain than catastrophizing [33]. The causal and mediating relationship between temperament and other psychological factors associated with pain perception remains poorly understood. Our results suggest that HA is independently associated with experimental pain sensitivity, but the association with the affective component of pain might be mediated by other psychological factors.

Strengths and limitations of the study

Strengths of this study are a homogeneous and a relatively large cohort of patients with and without CPSNP, all with a surgeon-defined ICBN lesion. Patients filled out a large TCI questionnaire. We studied temperament and character both in clinical and experimental pain settings. A wide range of possible confounding variables were taken into account in the analyses.

The first limitation of the study is that the patients were breast cancer treated women and thus the results cannot be directly generalized to healthy participants or males. As a second limitation, the study design was observational and cross-sectional. Therefore, we cannot draw definite conclusions about causality between temperament, character, and chronic pain. Additionally, as between-group differences in TCI dimensions are relatively small, conclusions about the clinical relevance cannot be drawn.

Conclusions

This study demonstrated and confirmed the different roles of temperament and character in pain processing. Psychobiological temperament, the innate core of personality, is independently related to primary pain processing, which we measured with experimental cold pain stimuli. Against our hypothesis, only HA temperament, but not character, the cognitive core of personality, has a role in experimental pain process. Instead, both HA temperament and character dimensions associate with CPSNP, forming a shared, common personality profile for chronic pain patients.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District (reference number: 149/13/03/00/14).

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