Clinical Pain Research

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Pain catastrophizing levels differentiate between common diseases with pain: HIV, fibromyalgia, complex regional pain syndrome, and breast cancer survivors

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Abstract

Objectives – Pain catastrophizing is a core psychological factor determining pain experience. We addressed the question of whether patients with different pain syndromes group into different pain catastrophizing phenotypes.

Methods – A total of 727 patients with chronic pain associated with four primary syndromes: Breast cancer (BC) survivors (n = 400), fibromyalgia (FM, n = 52), complex regional pain syndrome (CRPS, n = 155), and HIV (n = 120) were first studied for differences in levels of pain catastrophizing (Pain Catastrophizing Scale, PCS) and pain intensity by analysis of variance. Subsequently, individual scores of the PCS subscales "rumination", "magnification," and "helplessness" from the pooled cohorts were submitted to multivariate k-means clustering to explore subgroups.

Results – Three clusters defined by the level of catastrophizing were identified. The "low catastrophizing" cluster (n = 377) included most of the BC patients (71.0%) and the "moderate catastrophizing" cluster (n = 256) most of the FM patients (61.5%). HIV (31.9%) and CRPS (44.7%) patients were over-represented in the "high catastrophizing" cluster (n = 94) with the highest catastrophizing tendencies in all dimensions. These patients reported more helplessness than the patients in the two other clusters.

Conclusions – The primary syndrome causing the pain has an impact on self-reported pain-related catastrophizing. Helplessness is a predominant feature in HIV and CRPS patients and therefore an important target in pain rehabilitation.

Keywords: breast cancer, HIV, fibromyalgia, complex regional pain syndrome, pain catastrophizing

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1 Introduction

Pain catastrophizing is an important factor in clinical psychometric pain assessment. It is commonly assessed by using the Pain Catastrophizing Scale (PCS) [1]. Pain catastrophizing is considered in the fear-avoidance model as a part of a reciprocal reinforcement circle of pain symptoms [2]. Its level is understood to determine how much the pain experience effects function and pain interference [3]. Since this psychological construct was introduced to pain research [4], there has been growing evidence for its associations with the persistence of pain and pain impact [5]. For a long time, pain catastrophizing has been conceptualized as a trait-like variable describing a stable psychological tendency to react to pain or other clinical perturbations. However, in the early

literature, catastrophizing was also recognized as a latent individual factor, with the level changeable in a state-like manner under different aversive conditions, like pain [6]. Especially, the second suggests that under different conditions (i.e., syndrome characteristics, unpredictability of pain and its progression, and psychological stigma) catastrophizing levels might differ. Identifying disease state dependent catastrophizing phenotypes would allow more targeted psychological interventions to support pain rehabilitation or rehabilitation process and quality of life in general.

There is little research suggesting that pain catastrophizing profiles would differ in patients having different pain syndromes [7]. A recent meta-analysis of the psychometric properties of the PCS suggests highest association in patients with chronic widespread pain [8].

Here, we pursue the hypothesis that patients with different conditions with pain cluster to pain catastrophizing phenotypes. Four cohorts from original studies were secondary analyzed – HIV, fibromyalgia (FM), complex regional pain syndrome (CRPS), and breast cancer (BC) survivors. Catastrophizing profiles of these independent cohorts were first explored on a group level. Then, clustering was performed on the pooled pain catastrophizing data of the four cohorts for identifying phenotypic groups. Overrepresentation of a pain condition would inform on the specificity of pain catastrophizing as cognitive bias and allow more targeted psychological interventions.

2 Methods

2.1 Subjects and study desingnt

This study is a multicenter collaboration of the Helsinki University Hospital (HUH) (BC and FM), University Medical Centre Mainz (CRPS), and Imperial College London (HIV). This is a *post-hoc* analysis on data, and not a predesigned

Table 1: Demographic and clinical characteristics of the BC, fibromyalgia, HIV, and CRPS patient cohorts

Patient group		Age (years)	Sex (*N*, men)	Avarage pain intensity	Catastrophizing sum score	Rumination subscale	Magnification subscale	Helplessness subscale	Depression row score
BC	*N*	400	0						
									HADS-D
	Mean	61.7	—	2.1	7.5	2.7	1.7	3.1	3.1
	Median	63.0	—	2.0	4.0	1.0	1.0	2.0	4.0
	SD	8.1	—	2.1	8.6	3.5	2.1	4.0	3.4
	Min	39	—	0	0	0	0	0	0
	Max	75	—	10	42	15	10	22	18
FM	*N*	52	0						
									VAS 0–10
	Mean	45.2	—	5.3	17.8	5.6	3.3	8.8	3.4
	Median	47	—	6.0	16.5	6.0	3.0	8.0	2.1
	SD	12.6	—	1.9	10.2	3.9	2.5	5.1	2.8
	Min	18	—	1	0	0	0	0	0
	Max	66	—	9	48	14	10	24	10
HIV	*N*	120	98						
									HADS-D
	Mean	52.9	—	3.5	17.9	6.2	3.7	8.0	7.2
	Median	53.0	—	3.0	15.5	6.0	3.0	7.0	7.5
	SD	9.5	—	2.9	13.9	4.8	3.3	6.8	4.9
	Min	28	—	0	0	0	0	0	0
	Max	77	—	9	52	16	12	24	21
CRPS	*N*	155	35						
									BDI II
	Mean	51.5	—	4.9	20.0	7.4	3.6	9.1	13.3
	Median	54.0	—	5.0	19.0	7.0	3.0	8.0	11.0
	SD	13.4	—	2.3	12.4	4.6	3.1	6.2	10.8
	Min	18	—	0	0	0	0	0	0
	Max	91	—	10	52	25	12	24	54

Abbreviations: BC = breast cancer, FM = fibromyalgia, HIV = human immunodeficiency virus, CRPS = complex regional pain syndrome, SD = standard deviation, HADS-D = Hospital Anxiety and Depression Scale-Subscale Depression, VAS = visual analogue scale, BDI II = Beck's depression scale revised.

study. Only patients with complete data on PCS subscales and average pain intensity were included in the analyses. Patients of all four cohorts had persistent pain (Table 1) and had been treated according to disease-related standards, independent from their participation in the original studies. Data on depression levels were additionally available, however assessed in each cohort using different psychometric measures. Thus, these data were exclusively used for descriptive statistics.

2.1.1 BC treated patient cohort

The BC cohort was recruited from the original 1,000 patient cohort of women operated for BC at the HUH during 2006–2010. The patient selection and study procedures of the original cohort have been described in detail elsewhere [9]. The present patient sample of 400 patients was recruited during 2014–2016 from that cohort. The current patient sample consisted of women who had undergone surgery for unilateral BC 4–9 years earlier and who had a surgeon-defined nerve injury and/or pain in the surgical area. The study protocol for the entire cohort of the 400 patients has been described earlier in detail [10].

2.1.2 FM patient cohort

Fifty-two consecutive FM patients were recruited from the HUH clinics and primary health care units of the Helsinki metropolitan area during 2015–2018. Inclusion criteria were diagnosis of FM according to the American College of Rheumatology 1990 criteria and age of 18–65 years [11].

2.1.3 HIV patient cohort

The HIV cohort (n = 120) was recruited from the HIV outpatient clinics associated with the Chelsea & Westminster Hospital NHS Foundation Trust and by advertisements to national HIV charities during 2014–2017 (original cohort n = 148). Subjects were required to have a serological diagnosis of HIV and to be aged ≥18 years. Full inclusion and exclusion criteria have been outlined in the studies of Kemp et al. [12].

2.1.4 CRPS patient cohort

CRPS patients were (n = 202, upper and lower extremity) consecutively recruited at the specialized outpatient neurological clinic at the University Medical Hospital Mainz, Germany. Data were collected during 2014–2019. Inclusion criteria for this cohort were being ≥18 years and fulfilling the diagnostic criteria for CRPS type 1 or 2 according to the Budapest criteria for research purposes [13]. Standardized clinical examination included recording of the presence or absence of signs mentioned in the Budapest criteria. Clinical data were confirmed in the CRPS severity score (CSS) [14]. From this cohort, 155 CRPS patients who had filled in the PCS questionnaire were included in the present analysis, from which 90 cases were published elsewhere [15].

2.2 Data acquisition

2.2.1 Pain intensity

Past week average pain intensity was acquired for all cohorts using the patient reported 11-point numerical rating scale (NRS, with “0” labeled as “no pain” and “10” labeled as “strongest pain imaginable”). For the BC and HIV cohorts, the average pain ratings were completed as part of the long form of the Brief Pain Inventory (BPI) [16]. In the BC cohort, the patients filled in the BPI separately for any pain and the pain in the surgical area. The highest average pain value from either area was used in the analyses. In the HIV cohort, the questionnaire was completed with instructions to describe any pain the patient may experience. FM and CRPS patients were asked to rate their average pain intensity on the NRS.

2.2.2 Pain catastrophizing

Pain-related catastrophic thinking was assessed by the PCS [1]. Patients evaluate the extent to which they experience each item (0 [not at all] to 4 [all the time]) when recalling former experiences with pain. The sum score of all items (varying from 0 to 52) is calculated to indicate the overall tendency for catastrophic thinking. Several studies have also verified the three-subscale factor structure of PCS [17–19]. These subscales are “Rumination,” “Magnification,” and “Helplessness.” There are four items referring to rumination (e.g., “I keep thinking about how much it hurts”), three items for magnification (e.g., “I become afraid that the pain will get worse”), and six items for helplessness (e.g., “There is nothing I can do to reduce the intensity of the pain”).

For the BC and FM cohorts, the Finnish translation, and for the CRPS cohort the German version [18] were applied. The Finnish version was translated by a native speaker in a back-forward procedure. The estimated Cronbach’s alphas support its reliability (subscales *Rumination*

0.869, *Magnification* 0.759, and *Helplessness* 0.894, *total scale* 0.933).

2.2.3 Assessment of depression levels

In the BC and HIV cohorts, the Hospital Anxiety and Depression Scale (HADS [20,21]) was used. In the FM cohort symptoms of depression were asked using a visual analogue scale (VAS 0 – 10), higher values indicating higher amount of depressive symptoms. In the CRPS cohort the severity of depressive symptoms in the preceding 2 weeks was assessed by the German version of the Beck's depression inventory (BDI II [22]; German version by Kuhner et al. [23]).

2.3 Data analysis

Statistical analyses were performed using the SPSS (version 22 for Windows; IBM SPSS Inc., Chicago, USA). Statistical significance was defined for all analyses as an alpha level of 0.05. Normal distributions of the studied variables were observed by estimating the kurtoses and skewness. Group differences in age, average pain intensity, PCS sum, and subscale scores were analyzed each by one-way analysis of variances (ANOVA). Due to the sex dominance in the HIV and BC cohorts, differences in distribution among cohorts were not tested on a group level. Associations among the average pain intensity and each of the pain catastrophizing variables were analyzed using Pearson correlations.

Individual scores of the PCS subscales "Rumination," "Magnification," and "Helplessness" from the pooled sample were submitted to multivariate *k*-means clustering for identifying pain catastrophizing phenotypes. The rational for applying a clustering procedure additional to the group statistics was to (i) identify an over-representation of a certain phenotype in one or more of the cohorts and (ii) a specificity of the cognitive bias of these patients by clustering on the PCS subscales. The *k*-means clustering algorithm estimates from the features (the three PCS subscale scores) of the data points (patients) K centroids which define the clusters [24]. Data points are then assigned to the nearest centroid using squared Euclidean distances. The algorithm iterates ten times between these two steps until certain criteria are met, e.g., no data points change cluster membership. Validation of the *k*-means model that best fits the data was performed based on the total within cluster sum of squares (total WCSS). The total WCSS is a measure of intra-cluster variation and is an indicator of cluster cohesion. The total WCSSs for k = [2–10] cluster solutions was visualized via scree plot [25]. The optimal cluster solution was determined based on the elbow criterion. Description of the clusters' key characteristics, i.e., PCS sum and subscale scores and number of patients having BC, HIV, FM, or CRPS, was performed via standard descriptive statistics. Differences in PCS subscales and sum scores, age, and average pain intensity among the clusters separated by the *k*-means algorithm were tested by ANOVA. If significant differences were found, paired Bonferroni *post-hoc* comparisons between clusters were conducted. Cross-tabulation statistics were used to test differences in the distribution of sexes among clusters.

3 Results

3.1 Demographic and clinical characteristics of the cohorts

The total number of patients analyzed was n = 727 (BC n = 400, FM n = 52, CRPS n = 155, and HIV n = 120). In the HIV cohort 81.7% (n = 98) were men and in the CRPS cohort 77.4% (n = 120) were women. All patients in the BC and FM cohorts were women.

The key descriptive statistics for all cohorts are shown in Table 1.

ANOVA group comparisons revealed significant differences between the cohorts in age distributions (Table 1; $F(3,0) = 76.0$, $p < 0.001$). The BC patients were significantly older than the other cohorts ($p < 0.001$), whereas FM patients were significantly younger ($p \leq 0.001$). There were also differences in the average pain intensity between the groups ($F(3,0) = 72.2$, $p < 0.001$). The average pain intensity was similar between CRPS and FM patients ($p > 0.05$), whereas all other groups differed significantly from each other ($p < 0.001$; Table 1). The FM patients reported the highest mean pain rating of 5.3, and the BC patients the lowest mean rating of 2.1. The four cohorts displayed different levels of depressive symptoms. In 39% of the CRPS, 26% of HIV, and 4% of BC patients mean scores surpassed the respective cut-off scores for clinically relevant levels of depression (Table 1). Table 2 displays the correlation coefficients between the pain catastrophizing variables (sum score, rumination, magnification, and helplessness) and the average pain intensities in each patient cohort. Pain intensity was more strongly correlated with catastrophizing in HIV patients, compared with all other groups.

Table 2: Pearson correlations among measures of pain intensity, and pain catastrophizing sum and subscale scores

	BCT	FM	HIV	CRPS
	Pain intensity			
Pain catastrophizing total	0.37*	0.32*	0.66**	0.30**
Rumination	0.29**	0.32*	0.54**	0.28**
Magnification	0.30**	0.24	0.56**	0.19*
Helplessness	0.40**	0.29*	0.70**	0.30**

Abbreviations: BC = breast cancer, FM = fibromyalgia, HIV = human immunodeficiency virus, CRPS = complex regional pain syndrome; **correlation is significant at the 0.01 level (2-tailed), *correlation significant at the 0.05 level.

3.2 Differences in pain catastrophizing levels among the cohorts

Descriptive statistics of the PCS sum and subscale scores are shown in Table 1 for each patient cohort. There were significant main effects of group for PCS sum as well as subscales score (ANOVA: PCS total $F(3,0) = 69.6$; $p < 0.001$, subscale "Rumination" $F(3) = 62.4$, $p < 0.001$; subscale "Magnification" $F(3,0) = 34.0$, $p < 0.001$; subscale "Helplessness" $F(3,0) = 68.7$, $p < 0.001$). The results of the Bonferroni corrected *post-hoc* tests revealed differences between the groups: BC patients had the lowest catastrophizing sum, magnification, and helplessness scores in comparison to all other groups ($p < 0.001$ for all comparisons). The other groups did not differ from each other in sum scores but there were differences in the subscale of rumination. The BC cohort reported lower rumination levels compared with all other cohorts ($p < 0.001$). The FM cohort had significantly lower rumination scores compared with the CRPS cohort ($p < 0.001$).

3.3 Clustering of patients based on individual pain catastrophizing levels

The individual scores of the three PCS subscales were analyzed using multivariate *k*-means clustering for statistically driven separation of patients, having different pain etiologies, to pain catastrophizing phenotypes (*k* variation from 2 to 10). Figure 1 displays the scree plot showing that the three-cluster solution represented the best data fit, i.e., the highest minimization of intra-cluster variation. The *k*-means algorithm grouped $n = 94$, $n = 256$, and $n = 377$ patients from the pooled cohorts into clusters 1–3 displaying a "high," "moderate," and "low" catastrophizing phenotype, respectively.

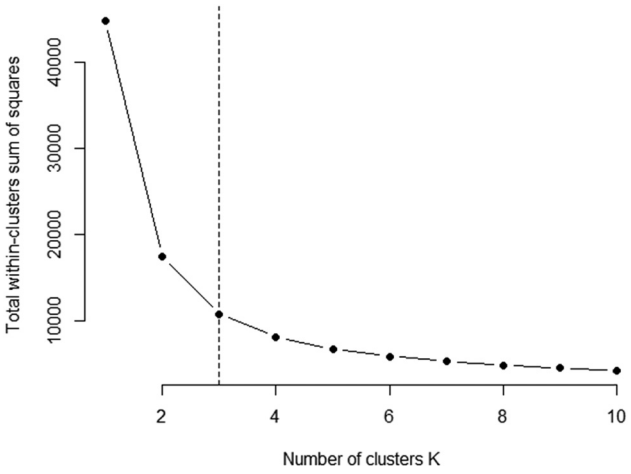

Figure 1: Scree plot visualizing the $k = [2–10]$ solutions against the total number of within-cluster sum of squares. Based on the elbow criterion, the plot indicates the best data fit with $k = 3$ clusters, i.e., less than three clusters explain less degree of variation in the data and more than three did not further improve the data fit.

Centroids of the optimal three-cluster solution are shown in Figure 2.

Scores of cluster centers for PCS rumination, magnification, and helplessness were for the "high" cluster 11.9, 6.9, and 17.1; for the "moderate" cluster 6.7, 3.4, and 7.6; and for the "low" cluster 1.1, 0.8, and 1.4. Frequency distributions of patients from the four pain cohorts among clusters 1–3 are shown in Figure 3.

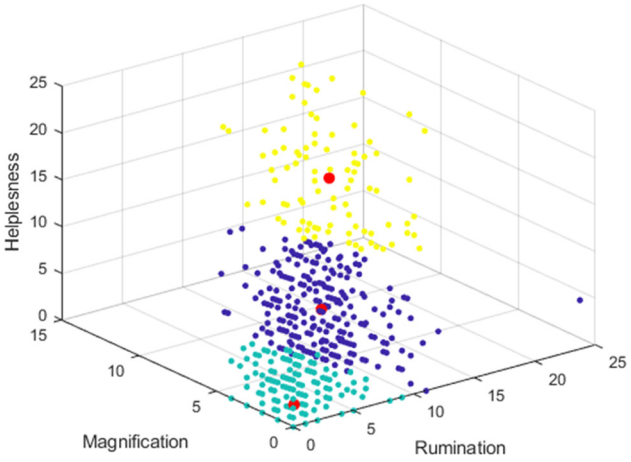

Figure 2: Three-cluster solution resulting from *k*-means clustering on the individual scores of the three PCS subscales "Rumination," "Magnification," and "Helplessness" from the four pooled cohorts ($n = 727$). Centroids 1–3 clustered on the three PCS dimensions represent the "high," "moderate," and "low" catastrophizing groups which are visualized in yellow, magenta, and turquois; red dots defining the clusters centers.

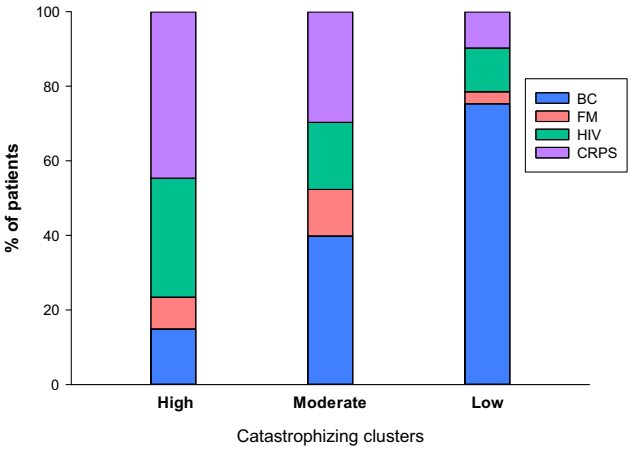

Figure 3: Distribution of patients (%) from the four pain cohorts to "high," "moderate," and "low" catastrophizing clusters. Abbreviations: BC = breast cancer treatment, FM = fibromyalgia, HIV = human immunodeficiency virus, CRPS = complex regional pain syndrome.

The most represented pain conditions in the different clusters were CRPS in the "high" (44.7%, n = 94) and BC in the "low" pain catastrophizing phenotype (75.3%, n = 377).

PCS subscales and sum scores, age, and average pain ratings were significantly different among clusters ($F(2,0)$ = [17.31 – 2116.98], $p < 0.001$). *Post-hoc* Bonferroni-corrected pairwise comparisons were computed for all variables. All three contrasts were highly significant for PCS subscales and sum scores as well as the average pain ratings ($p < 0.004$). Figure 4 displays the distribution, mean, and standard deviations of clusters 1–3 for PCS scores, pain ratings, and depression z-scores. Significant differences for age could be shown between the "high" and the "low," and the "low" and the "moderate" clusters ($p < 0.001$).

4 Discussion

We explored whether patients with four distinct conditions exhibit different pain catastrophizing phenotypes. The results indicate that pain experience under specific conditions associates differently with catastrophizing. Three clusters, defined after multivariate clustering on catastrophizing subscales, were identified with unequal distribution of patients from every cohort. Most individuals of the BC group were classified into the "low catastrophizing," and most of the FM patients into the "moderate catastrophizing" cluster. HIV and CRPS patients were over-represented in the cluster with the highest catastrophizing scores in all dimensions.

Pain catastrophizing is originally conceptualized as a trait-like variable. Its premorbid level influences coping behavior and hereby the individual outcome [26]. However, catastrophizing also acts as an intrapersonal latent factor that needs a cue (such as pain) to become functional in a state-like manner [27]. The results of the present study appear to represent both of these aspects. Specifically, there were individuals from every patient cohort in all of the clusters (trait-like), but some conditions were over-represented in either cluster (the individuals' state-like reaction to the painful disease). This state-like reaction, i.e., heightened catastrophic thinking, could also be interpreted in terms of a "psychological sensitization" [28,29].

As by theoretical conceptualization and evidence from previous research, a positive association between pain intensity and pain catastrophizing was shown. Differences in the levels of pain catastrophizing between the cohorts were revealed. These suggest already at the level of group comparisons that HIV and CRPS patients tend to score higher in the catastrophizing questionnaire compared to BC and FM patients. Taken together, the results pattern imply that CRPS and HIV are associated with conditions, under which suffering and catastrophizing reinforce each other in the vicious circle of pain chronification as proposed by the fear-avoidance model [30].

Flink et al. conceptualized pain-related catastrophizing as "a form of *negative repetitive thinking*, which is *abstract*, *intrusive*, and *difficult to disengage* from" [31]. They suggest that a term "catastrophic worry" would describe pain catastrophizing content more precisely. Crombez et al. found in their item content analyses that most of the questionnaires used to measure catastrophizing (including PCS) are actually measuring mostly "pain-related worry" [32]. Our results could also be interpreted in terms of specific worries that promote heightened catastrophic thinking in those patients with diagnoses that are difficult to treat/heal or the disease progression is unpredictable, as suggested [8].

Pain related to BC treatments (e.g., surgery and radiotherapy) is mainly neuropathic in nature and can be related to treatment procedures [33,34]. For these reasons pain might be more understandable and acceptable for the patient. The BC cohort in this study reported significantly less catastrophizing compared with the other cohorts. A recent study of normative values for common measures used in pain patients reports on lower catastrophizing scores in cancer-related pain than in other pain conditions [35]. Patients in the BC cohort in this study were all survivors and the results may not be generalized to patients with active cancer. Furthermore, the same study [35] concluded that patients with a greater number of pain sites reported higher catastrophizing. Pain related to BC treatments is commonly localized in the area of primary surgery and especially to the area innervated by the

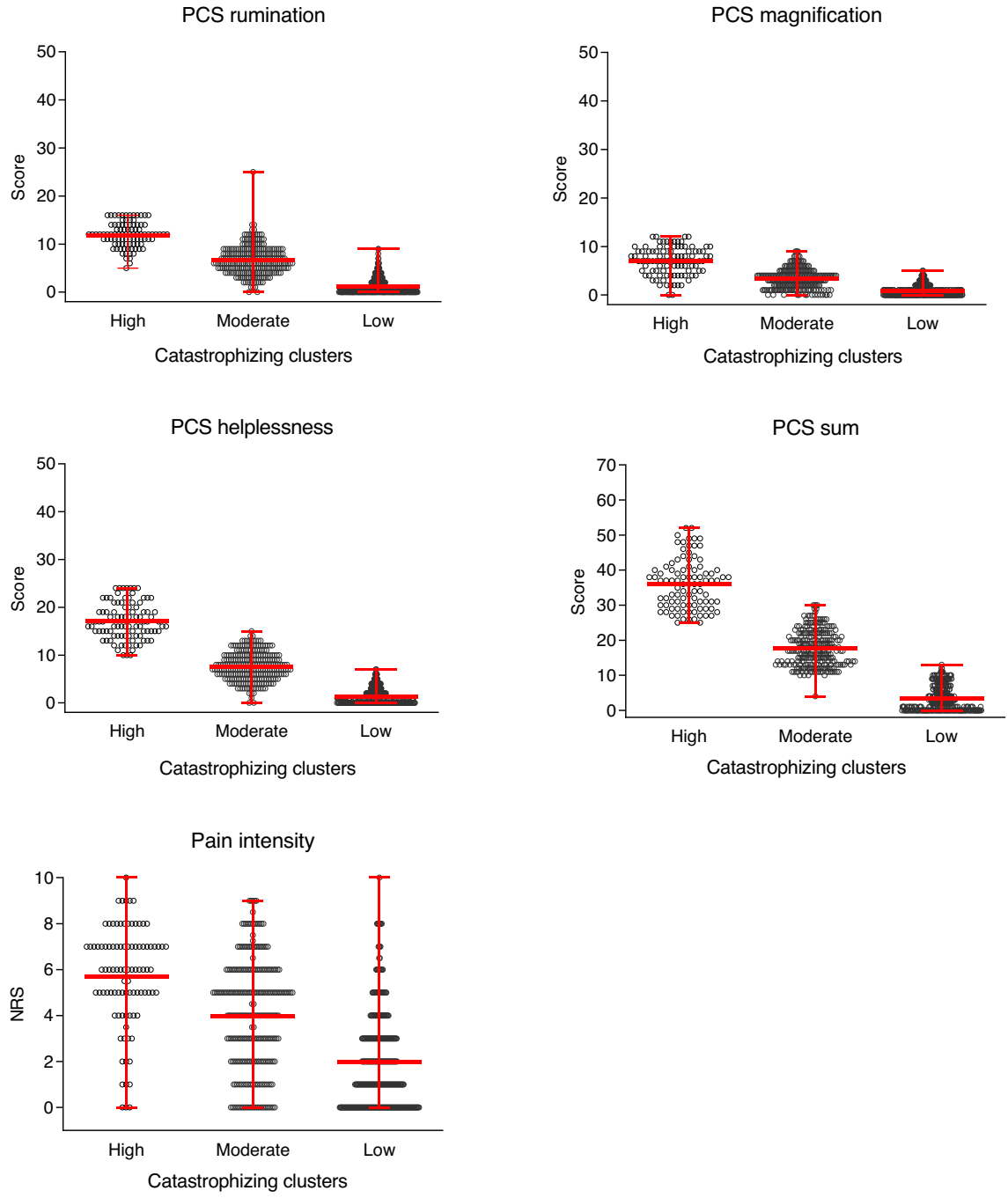

Figure 4: Distributions means and ranges of PCS subscales and sum scores, and average pain intensity for the "high," "moderate," and "low" catastrophizing clusters in comparison. All *post-hoc* pairwise comparisons are significant at the level of $p < 0.001$ between the clusters.

intercostobrachial nerve (upper arm and axilla). In CRPS, autonomic, sensory, and trophic signs and pain often spread distally and are not limited to the innervation territories [36]. Pain in FM is more widespread and CRPS-related pain is typically very intrusive and covers the entire upper/lower extremity. It is well recognized that people living with HIV report multi-site, multi-etiology chronic pain, despite painful HIV-SN usually being restricted to the distal lower limbs [37,38]. People living with HIV may hold feelings of stigma which may influence pain experience [8] and pain has been described as an "unwanted reminder" of the infection [39]. Diagnostic uncertainty surrounding neuropathic pain in HIV may also contribute to differences in interpretation of painful symptoms [39]. CRPS pain can be controlled by not moving the limb, and vice versa incautious movements can maximize the pain. Pain catastrophizing tendency maintains this

interaction. It even impacts CRPS pathophysiology, since CRPS would get better, if the affected limb is mobilized despite the pain. It becomes worse if movements are avoided. A meta-analysis of the psychosocial features associated with pain in HIV, however, identified a lack of evidence when investigating the relevance of fear-avoidance models in this cohort [39].

FM is a female predominant primary pain condition with widespread pain of still unclear etiology. Its pathophysiology is only partly understood; neuropathic, inflammatory, and psychological factors seem to have major roles [40]. High catastrophizing is likely to reduce physical activity and may lead to heightened pain in conjunction with increased physical activity [41]. Thus, similar to CRPS, a maladaptive behavior with physical inactivity first minimizes FM pain but finally ends with deconditioning and pain after even minimal physical activity. Continued physical activity has been reported to decrease catastrophizing with FM patients, supporting the state-like aspect of catastrophizing [42].

The subscale "helplessness" was especially high in the "high catastrophizing" cluster, over-represented by CRPS and HIV patients. This may reflect the way the patients interpret their pain and perceive their capabilities to cope with their painful condition. Severeijns et al. have suggested that the subscales of rumination and magnification are primary appraisals and reflect the threat of pain, whereas helplessness is a secondary appraisal of pain, reflecting an individual's inability to cope with pain adversity [43]. It is also possible that pain related to CRPS and HIV interfere more with the everyday life of the patients and therefore evokes more feeling of helplessness. We did not have information about pain interference from all cohorts, and therefore, this could not be tested in the present study.

The finding that helplessness is pronounced in HIV and CRPS patient suggests a specific cognitive bias for these conditions. Especially for CRPS, targeting feelings of helplessness might also be crucial for physiotherapeutic interventions in CRPS rehabilitation. It also seems that early treatment changes, especially in helplessness, are predictive for improvements in pain-related outcomes like pain-related interference and severity [44]. Modification of helplessness cognitions and enhancement of self-efficacy might be of special benefit for CRPS and HIV patients in pain rehabilitation.

4.1 Limitations

Self-reported questionnaire was used as a measurement of catastrophizing. Concerns of the use of self-reported measures of catastrophizing have been raised [32], since it lacks the contextual information and expert judgment about one's pain. Previous studies provide evidence for gender differences in levels of pain catastrophizing [45,–49]. However, in the meta-analysis of Wheeler et al., no effect could be discovered [8]. Sex differences could not be regarded in the analysis because of the unbalanced sex distribution between the four cohorts. The sex/gender issue limits the generalization of our results to other pain syndromes. However, both sexes are represented in the three clusters – a result supporting the differentiating effect of pain catastrophizing. Also, we used four patient cohorts from three different countries. Cultural background and language used in the PCS may have an effect on the scores. However, all cohorts represent quite closely the same Western European economic and cultural background. Other risk factors than depression, i.e., anxiety, post-traumatic stress, and resilience style, would have provided a more comprehensive pattern for differentiating catastrophizing phenotypes.

5 Conclusions

Based on pain catastrophizing levels, a low, moderate, and high group could be identified across the studied conditions. Specifically, CRPS and HIV patients displayed a high catastrophizing phenotype denoted by thoughts of helplessness. This finding may be essential when interventions for pain and broader wellbeing are planned. The tendency of helplessness is linked to an individual's feeling of capability in her/his own rehabilitation, and therefore important to acknowledge in the rehabilitation process.

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Research ethics and Informed consent: The study followed the Declaration of Helsinki and was approved by the respective local Ethics Committees: the Coordinating Ethics Board of the Helsinki and Uusimaa Hospital District (registered in ClinicalTrials.gov Registration No. NCT02487524 and ethics board number 149/13/03/00/14 for the breast cancer treatment cohort, ClinicalTrials.gov Registration No. NCT03300635 and ethics board number 229/13/03/02/15 for the fibromyalgia cohort, ClinicalTrials.gov Registration No. NCT02555930, England's National Research Ethics Service (14/LO/1574) for the HIV cohort, and the Rhineland Palatinate Medical Association (No. 9142-F; German registry for clinical studies (https://www.germanctr.de/, Registration No. DRKS00008964) for CRPS cohort)). Written informed consent was obtained from each patient.

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References

[1] Sullivan M, Bishop S, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess. 1995;7:527–32.
[2] Vlaeyen JW, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. Pain. 2012;153(6):1144–7.
[3] Suso-Ribera C, Garcia-Palacios A, Botella C, Ribera-Canudas MV. Pain catastrophizing and its relationship with health outcomes: does pain intensity matter? Pain Res Mang. 2017;2017:9762864.
[4] Sullivan MJ, Thorn B, Haythornthwaite JA, Keefe F, Martin M, Bradley LA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain. 2001;17(1):52–64.
[5] Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87(Pt B):168–82.
[6] King R. Cognitive therapy of depression. Aaon Beck, John Rush, Brian Shaw, Gary Emery. New York: Guilford, 1979. Aust N Z J Psychiatry. 2002;36(2):272–5.
[7] Larsson B, Gerdle B, Bernfort L, Levin LA, Dragioti E. Distinctive subgroups derived by cluster analysis based on pain and psychological symptoms in Swedish older adults with chronic pain – a population study (PainS65+). BMC Geriatr. 2017;17(1):200.
[8] Wheeler CHB, Williams ACC, Morley SJ. Meta-analysis of the psychometric properties of the Pain Catastrophizing Scale and associations with participant characteristics. Pain. 2019;160(9):1946–53.
[9] Kaunisto MA, Jokela R, Tallgren M, Kambur O, Tikkanen E, Tasmuth T, et al. Pain in 1,000 women treated for breast cancer: a prospective study of pain sensitivity and postoperative pain. Anesthesiology. 2013;119(6):1410–21.
[10] Sipila R, Hintsa T, Lipsanen J, Tasmuth T, Estlander AM, Kalso E. The relationship between anger regulation, mood, pain, and pain-related disability in women treated for breast cancer. Psychooncology. 2019;28(10):2002–8.
[11] Zetterman T, Markkula R, Partanen JV, Miettinen T, Estlander AM, Kalso E. Muscle activity and acute stress in fibromyalgia. BMC Musculoskelet Disord. 2021;22(1):183.
[12] Kemp HI, Kennedy DL, Vollert J, Davies NWS, Scott W, Rice ASC. Chronic pain and cognitive impairment: a cross-sectional study in people living with HIV. AIDS Care. 2023;35(8):1201–14.
[13] Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for Complex Regional Pain Syndrome. Pain. 2010;150(2):268–74.
[14] Harden RN, Bruehl S, Perez RS, Birklein F, Marinus J, Maihofner C, et al. Development of a severity score for CRPS. Pain. 2010;151(3):870–6.
[15] Dimova V, Herrnberger MS, Escolano-Lozano F, Rittner HL, Vlckova E, Sommer C, et al. Clinical phenotypes and classification algorithm for complex regional pain syndrome. Neurology. 2020;94(4):e357–67.
[16] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap. 1994;23(2):129–38.
[17] Osman A, Barrios FX, Gutierrez PM, Kopper BA, Merrifield T, Grittmann L. The pain catastrophizing scale: further

psychometric evaluation with adult samples. J Behav Med. 2000;23(4):351–65.
[18] Meyer K, Sprott H, Mannion AF. Cross-cultural adaptation, reliability, and validity of the German version of the Pain Catastrophizing Scale. J Psychosom res. 2008;64(5):469–78.
[19] Chibnall JT, Tait RC. Confirmatory factor analysis of the Pain Catastrophizing Scale in African American and Caucasian Workers' Compensation claimants with low back injuries. Pain. 2005;113(3):369–75.
[20] Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69–77.
[21] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
[22] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
[23] Kuhner C, Burger C, Keller F, Hautzinger M. Reliability and validity of the Revised Beck Depression Inventory (BDI-II). Results from German samples. Nervenarzt. 2007;78(6):651–6.
[24] Lloyd SP. Least squares quantization in PCM. IEEE Trans Inf Theory. 1982;IT-28(2):129–37.
[25] Cattell RB. The scree test for the number of factors. Multivar Behav Res. 1966;1(2):245–76.
[26] Turner JA, Aaron LA. Pain-related catastrophizing: what is it? Clin J Pain. 2001;17(1):65–71.
[27] Beck AT, Rush AJ, Shaw BF, Emery G, DeRubeis RJ, Hollon SD. Cognitive therapy of depression. NY, USA: Guildford Press; 1979.
[28] Hohmeister J, Demirakca S, Zohsel K, Flor H, Hermann C. Responses to pain in school-aged children with experience in a neonatal intensive care unit: cognitive aspects and maternal influences. Eur J Pain. 2009;13(1):94–101.
[29] Dimova V, Horn C, Parthum A, Kunz M, Schofer D, Carbon R, et al. Does severe acute pain provoke lasting changes in attentional and emotional mechanisms of pain-related processing? A longitudinal study. Pain. 2013;154(12):2737–44.
[30] Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85(3):317–32.
[31] Flink IL, Boersma K, Linton SJ. Pain catastrophizing as repetitive negative thinking: a development of the conceptualization. Cogn Behav Ther. 2013;42(3):215–23.
[32] Crombez G, De Paepe AL, Veirman E, Eccleston C, Verleysen G, Van Ryckeghem DML. Let's talk about pain catastrophizing measures: an item content analysis. PeerJ. 2020;8:e8643.
[33] Jung BF, Ahrendt GM, Oaklander AL, Dworkin RH. Neuropathic pain following breast cancer surgery: proposed classification and research update. Pain. 2003;104(1–2):1–13.
[34] Jung BF, Herrmann D, Griggs J, Oaklander AL, Dworkin RH. Neuropathic pain associated with non-surgical treatment of breast cancer. Pain. 2005;118(1–2):10–4.
[35] Nicholas M, Vlaeyen JWS, Rief W, Barke A, Aziz Q, Benoliel R, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. Pain. 2019;160(1):28–37.
[36] Birklein F. Complex regional pain syndrome. J Neurol. 2005;252(2):131–8.
[37] Jiao JM, So E, Jebakumar J, George MC, Simpson DM, Robinson-Papp J. Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization. Pain. 2016;157(4):931–7.
[38] Merlin JS, Long D, Becker WC, Cachay ER, Christopoulos KA, Claborn K, et al. Brief report: the association of chronic pain and long-term opioid therapy with HIV treatment outcomes. J Acquir Immune Defic Syndr. 2018;79(1):77–82.
[39] Scott W, Garcia Calderon Mendoza Del Solar M, Kemp H, McCracken LM, CdCW A, Rice ASC. A qualitative study of the experience and impact of neuropathic pain in people living with HIV. Pain. 2020;161(5):970–8.
[40] Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience. 2016;338:114–29.
[41] Lazaridou A, Paschali M, Schreiber K, Galenkamp L, Berry M, Paschalis T, et al. The association between daily physical exercise and pain among women with fibromyalgia: the moderating role of pain catastrophizing. Pain Rep. 2020;5(4):e832.
[42] Izquierdo-Alventosa R, Ingles M, Cortes-Amador S, Gimeno-Mallench L, Chirivella-Garrido J, Kropotov J, et al. Low-intensity physical exercise improves pain catastrophizing and other psychological and physical aspects in women with fibromyalgia: a randomized controlled trial. Int J Environ Res Public Health. 2020;17(10):3634.
[43] Severeijns R, Vlaeyen JWS, van den Hout MA. Do we need a communal coping model of pain catastrophizing? An alternative explanation. Pain. 2004;111(3):226–9.
[44] Burns JW, Kubilus A, Bruehl S, Harden RN, Lofland K. Do changes in cognitive factors influence outcome following multidisciplinary treatment for chronic pain? A cross-lagged panel analysis. J Consult Clin Psychol. 2003;71(1):81–91.
[45] Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000;87(3):325–34.
[46] Forsythe LP, Thorn B, Day M, Shelby G. Race and sex differences in primary appraisals, catastrophizing, and experimental pain outcomes. J Pain. 2011;12(5):563–72.
[47] Rivest K, Cote JN, Dumas JP, Sterling M, De Serres SJ. Relationships between pain thresholds, catastrophizing and gender in acute whiplash injury. Man Ther. 2010;15(2):154–9.
[48] D'Eon JL, Harris CA, Ellis JA. Testing factorial validity and gender invariance of the pain catastrophizing scale. J Behav Med. 2004;27(4):361–72.
[49] Sullivan MJL, Tripp DA, Santor D. Gender differences in pain and pain behavior: the role of catastrophizing. Cognit Ther Res. 2000;24:121–34.