Pain-related cognitions and emotional distress are not associated with conditioned pain modulation

an explorative analysis of 1142 participants with acute, subacute, and chronic pain

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ABSTRACT

Reduced conditioned pain modulation (CPM) and psychological distress co-occur frequently in many pain conditions. This study explored whether common negative pain cognitions and emotional factors were related to lower CPM in individuals across the spectrum from acute to chronic pain. Previously collected data on the CPM effect, pain-related cognitions (fear of movement, pain catastrophizing), and emotional distress (depression, anxiety) from questionnaires in 1142 individuals with acute, subacute, or chronic pain were used. The presence of negative psychological factors was dichotomized according to cut-off values for questionnaires. Associations between the presence of each negative psychological factor and the amplitude of pain reduction in the CPM paradigm was explored with Generalized Linear Models adjusted for sex, age, body mass index, and pain duration. A secondary analysis explored the cumulative effect of psychological factors on CPM. When dichotomized according to cut-off scores, 20% of participants were classified with anxiety, 19% with depression, 36% with pain catastrophizing, and 48% with fear of movement. The presence of any negative psychological factor nor the cumulative sum of negative psychological factors were associated with lower CPM (individual factor: β between -0.15 and 0.11, P≥0.08; Total: β between --0.27 and -0.12, P≥0.06). Despite the common observation of psychological factors and reduced CPM in musculoskeletal pain, these data challenge the assumption of a linear relationship between these variables across individuals with acute, subacute, and chronic pain. Arguably, there was a non-significant tendency for associations in non-expected directions, which should be studied in a more homogenous population.

Keywords: Conditioned pain modulation, cognitions, emotional distress, pain, psychological factors

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PAIN-related cognitions and emotional distress are not associated with conditioned pain modulation: an explorative analysis of 1142 participants with acute, subacute, and chronic pain

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1. INTRODUCTION

Conditioned pain modulation (CPM) is a psychophysical test that reflects the capacity of the descending pain modulatory systems to enhance or diminish pain [34]. The CPM effect is quantified by comparison of the pain response to a noxious test stimulus applied before and during (or immediately after) a noxious conditioning stimulus to another body region [3]. Although CPM is a relatively robust phenomenon with mainly inhibitory responses (e.g., increased pain thresholds caused by the conditioning) in pain-free participants [46], inter-individual variation in CPM is large [13,55] as a result of individual difference and aspects of CPM protocols.

The CPM effect is frequently lower in individuals with chronic pain than those without pain [24], and in pain groups, less efficient CPM have been associated with a higher number of pain sites [53], higher levels of disability [32], and poorer surgical [41], pharmacological [12] and non-pharmacological [7] treatment outcomes. Less efficient CPM effects co-occur with psychological features such as depression, anxiety, and catastrophizing in many pain conditions [6,24,27,30]. This might suggest a link between psychological distress and less efficient CPM. This hypothesis is supported by the dual role of areas of the frontal lobe in both regulation of emotions and behaviors and influencing pain processing and descending control systems [17,20,42]. A relationship between CPM and psychological factors has been investigated, but evidence is equivocal. One recent meta-analysis found no overall association between CPM and psychological factors in pain-free individuals or those with chronic pain [33], although one modality-specific CPM effect was associated with anxiety in pain-free individuals [33]. Another meta-analysis found associations between CPM and anxiety, stress, depression, and pain catastrophizing in studies of irritable bowel syndrome [28].

We have previously investigated CPM in individuals with a variety of acute, subacute, and chronic pain conditions [21,26,38,52-54]. In these studies, information was also collected on pain-related cognitions (fear of movement, pain catastrophizing) and emotional distress (symptoms of depression and anxiety) through self-reported validated questionnaires commonly used in clinical practice. The primary aim of this study was to explore the relationship between the presence of a range of cognitions and emotional factors commonly assessed in acute and chronic pain, and the CPM effect. As previous studies have shown that the presence of more psychological factors can have a cumulative effect on the risk of recovery [58], a secondary aim was to explore the relationship between the cumulative number of psychological factors present and the CPM effect. It was hypothesized that the presence of each psychological factor would be associated with less efficient CPM.

2. METHODS

2.1 Participants

This study is a secondary analysis of previously published data [21,26,38,52-54]. All studies were granted ethical approval from respective institutional boards and were conducted in accordance with the Helsinki Declaration. All participants gave verbal and written informed consent.

Participants were recruited across two research sites: (1) The University Hospital Interdisciplinary Pain Center, Odense, Denmark (n = 693) and (2) The University of Queensland, Australia (n = 449). Australian participants were originally recruited into condition-specific studies and as such were diagnosed as having specific musculoskeletal complaints as their primary problem: low back pain (n = 128); lateral elbow tendinopathy (n = 132); gluteal tendinopathy (n = 39); and patellofemoral pain (n = 150). Danish participants had diverse chronic non-malignant chronic pain, mainly of multisite distribution (n = 693) as described previously [37,53].

Volunteers for the Australian studies were recruited from areas local to the respective research facilities, and the Danish population were patients referred to an interdisciplinary university pain center. Methods of recruitment for each participant group have been published elsewhere [21,26,38,52-54,57]. All eligible and consenting participants completed construct-specific psychological measures and attended a session to test CPM at the University of Queensland or the Pain Center at the University Hospital Odense, Denmark.

2.2 Assessment of conditioned pain modulation

All CPM protocols used mechanical modalities as the test stimulus; four employed handheld algometry (n = 449 participants), and one used computer-controlled cuff algometry (n = 693 participants). For the conditioning stimulus, three studies used cold pressor (n = 321 participants), one used thermode-delivered heat (n = 128 participants), and one used computer-controlled cuff pressure (n = 693 participants). All five protocols are available in full in Supplementary file 1, including details around participant eligibility criteria, the testing stimulus, conditioning stimulus, and detailed testing protocols. All protocols used contralateral conditioning at sites within the same segment or in a different body segment (Table 1).

2.3 Pain-related cognitions

Pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS, n = 1114 participants). The 13 items of the PCS assess thoughts of pain-related worrying/catastrophizing [48]. Each item scores from 0-4, producing an overall score ranging from 0-52. Scores greater than 24 have been associated with higher pain ratings following multi-disciplinary intervention [43]. Participants with a score ≥25 were coded as having high levels of pain catastrophizing and participants with a score <25 were coded as not having high levels of pain catastrophizing [43]. Reliability and validity of the PCS has been established [35,36].

Fear of movement was assessed with the Tampa Scale for Kinesiophobia (TSK, n = 970). The TSK consists of 17 items assessing feelings of fear and vulnerability to painful injury or re-injury [31]. Each item is scored from 1-4, producing an overall score ranging from 17-68. Higher values indicate greater fear of movement. A TSK score of 37 has been proposed as the cut-off between individuals with high and low kinesiophobia [56]. Therefore, participants with a score ≥37 were coded as having high levels of fear of movement and participants with a score <37 were coded as not having high levels of fear of movement. The TSK demonstrates excellent test-retest reliability and correlates with fear-avoidance measures [14].

2.4 Emotional distress

Depression was assessed using either the Patient Health Questionnaire-9 (PHQ9, n = 480), Centre for Epidemiological Studies of Depression Scale (CES-D, N = 127), or the depression subscale from the Hospital Anxiety and Depression Scale (HADS-D, n = 321).

PHQ9: Nine items based on the core symptoms of depression are assessed on a 4-point Likert scale, ranging from 0 = 'not at all' to 3 = 'nearly every day', with a higher score indicating higher depression severity. Participants with a score ≥15 (moderate-severe depressive symptoms) [40] were coded as having depressive symptoms and participants with a score <15 were coded as not having depressive symptoms. PHQ9 is widely used to measure depressive symptoms in chronic pain populations [4] and acceptable validity and reliability [25] have been demonstrated.

CES-D: The 20-item questionnaire evaluates depressive symptoms over the past week. Respondents rate how often over the past week they experienced symptoms associated with depression using a four-point Likert scale ranging from 0 ("rarely or none of the time") to 3 ("most or all of the time"), for an overall score out of 60. Scores >15 identify individuals at high risk for clinical depression with high sensitivity and specificity [22]. Participants with a score ≥16 were coded as having depressive symptoms and participants with a score <16 were coded as not having depressive symptoms. Extensive evidence supports the CES-D as a reliable and valid self-report measure for assessing aspects of depression in a broad range of clinical and non-clinical populations [8,9].

HADS-D: Seven-items on depressive symptoms [59] are scored from 0-4 with higher scores representing higher levels of depressive symptoms. A score of eight or above have been found to successfully identify cases [5]. Participants with a score ≥8 were coded as having depressive symptoms and participants with a score <8 were coded as not having depressive symptoms.

Anxiety was assessed using the Generalized Anxiety Disorder-7 questionnaire (GAD7, n = 635 participants) or the anxiety subscale from the Hospital Anxiety and Depression Scale (HADS-A, n = 171 participants).

GAD7: Seven items assessed on a 4-point Likert scale, ranging from 0 = 'not at all' to 3 = 'nearly every day', was used to assess the level of generalized anxiety with a higher score indicating higher anxiety severity. Participants with a score ≥10 (moderate anxiety) were coded as having anxiety and participants with a score <10 were coded as not having anxiety, based on published cut-off scores derived from n=2149 people presenting to their primary care, with good sensitivity and specificity >0.80 [47]. The GAD-7 has previously shown acceptable validity and reliability [44], and is often used to measure anxiety symptoms in persons with chronic pain conditions [4].

HADS-A: Seven-items on anxiety symptoms [59] are scored from 0-4 with higher scores representing higher levels of anxiety. A score of eight or above have been found to successfully identify cases with anxiety [5]. Participants with a score ≥8 were coded as having anxiety and participants with a score <8 were coded as not having anxiety.

2.5 Statistical analysis

Statistical analyses were performed in SPSS version 28.0 (IBM, New York, NY, USA). Normality was assessed visually (histograms, quantile-quantile plots). Nominal and ordinal data were presented as frequencies and percentages, and continuous data were presented in means and standard deviations (SD).

CPM effect scores were calculated by subtracting the test stimulus scores *during conditioning* from test stimulus scores *before conditioning*. CPM effect scores were then converted to Z-scores, separately for each CPM protocol, after which all CPM effect Z-scores were combined in one continuous variable for the analyses. We also presented the CPM response as a percentage difference between the test stimulus scores obtained before and during the conditioning stimulus; 100*(conditioning – baseline)/baseline, and as responders (>0%) and non-responders to show similarities and differences between the different participant cohorts.

Statistical analysis was conducted in two steps. Associations between the presence of each psychological factor and the CPM effect was explored with Generalized Linear Models (GLMs). A separate GLM was conducted for each psychological factor to maximize the number of cases included in each model. The continuous CPM effect score was entered as the dependent variable, and binary psychological factors as the independent variables. Sex, age, body mass index (BMI), and pain duration (acute, subacute, chronic) were included as covariates as these have been shown in previous studies to influence responses to noxious stimuli [2,11,39,45].

A secondary analysis explored the cumulative effect of psychological factors on the CPM effect. Anxiety was not measured in n=336 (29%) of the total population. To maximize the total number of participants included in the analysis, we therefore chose to include only depression, pain catastrophizing and fear of movement. A four-level independent variable (0-3) was created, reflecting the sum of psychological factors that were deemed ‘cases’ based on pre-defined cut-off scores, ‘0’ being no cases across the psychological factors. Cases of depression were based on PHQ9, CES-D, HADS-D cut-off scores; cases of catastrophizing were based on PCS cut-off scores; and fear of movement cases were based on TSK cut-off scores. The continuous CPM effect score (Z-score) was entered as the dependent variable, the cumulative psychological categorical score as the independent variable (three factors present as reference), and sex, age, BMI, and pain duration (acute, subacute, chronic) as covariates.

Sensitivity analyses were run to account for the limitation of merging several types of participants as well as various assessment measures in one sample. As part of the sensitivity analysis, all analyses as described above were run for each protocol separately.

Beta values and 95% confidence intervals were presented to explain the direction of CPM effect in the presence of psychological cases for all analyses. Significance was set on $P<0.05$.

3. RESULTS

3.1 Participants

The combined sample (n = 1,142) was 63% female (n = 721) with an average (SD) age of 43 (13) years and BMI of 26.8 (5.4) kg/m^2 (Table 2). Across the entire sample, the majority of participants had multiple pain sites (n = 844, 74%). Chronic pain (>3 months in duration) characterized most of the combined sample (n = 898, 79%), followed by acute pain that was defined as a pain duration of two weeks or less (n = 128, 11%), and subacute pain (n = 116, 10%) (Table 2). Pain intensity results across groups are presented in Table 2. Ratings of pain intensity were assessed differently in the original studies; some participants rated average pain and others rated worst pain. The reference period for assessment of pain (e.g., average pain over the last 24 hours or last week) also differed between studies.

3.2 CPM-effect

The mean CPM effect, calculated as the percentage difference between the test stimulus scores obtained before and during the conditioning stimulus, was 18.5 (SD 26.5) for the overall cohort (range of means 11.2 – 31.5 between subgroups; Supplementary file 2). The number of CPM responders was 69% across all participants and ranged from 60-86% between cohorts.

3.3 Associations between psychological factors and the CPM effect

Based on cut-off scores from the questionnaires, 20% of participants were classified with anxiety, 19% with depression, 36% with pain catastrophizing and 48% with fear of movement (Supplementary file 3). None of the psychological factors were significantly associated with the CPM effect, when controlling for sex, age, BMI and pain duration (Beta-values between -0.15 and 0.11; P≥0.08; Table 3).

3.4 Associations between cumulative psychological factors and the CPM effect

The cumulative number of psychological factors (0-3 psychological factors) was not significantly associated with CPM effect, when controlling for sex, age, BMI, and pain duration (Beta-values between -0.27 and -0.12; P≥0.06; Table 4).

3.5 Sensitivity analyses

Analyses of all separate protocols showed similar findings to our primary analysis with the combined cohort. There were no changes in the relationship between psychological factors and CPM effect (e.g., all associations were p>0.05) when models were run for each cohort separately, except for a significant relationship between anxiety and CPM effect in the 150 participants with patellofemoral pain (Beta-value: 0.43 (95%CI 0.01;0.84), p=0.04) (Supplementary file 4). Further, no changes in the relationship between the cumulative number of psychological factors and CPM effect were found, except for 1 psychological factor compared to the reference value of 3 psychological factors (Beta-value -2.50 (95%CI -4.60, -0.41), p=0.02) in the 39 participants with gluteal tendinopathy (Supplementary file 4).

4. DISCUSSION

This study used a large sample of participants with acute, subacute and chronic pain to investigate the relationship between several psychological factors commonly assessed in musculoskeletal pain and the CPM effect. The CPM effect was not significantly associated with the presence of any of the psychological factors above cut-off values on questionnaires, when accounting for age, sex and BMI and pain duration. The CPM effect was also not associated with cumulative number of psychological factors, indicating that the added burden of comorbidly-presenting psychological factors was not associated with a less efficient CPM effect across acute, subacute and chronic pain.

We did not find a simple linear association between psychological factors and the CPM effect. Our findings are in line with a review by Nahman-Averbuch et al.[33] that conducted 6 meta-analyses across 37 articles to examine the correlations between anxiety, depression, and pain catastrophizing, and CPM responses in healthy individuals and pain patients. The review did not find significant correlations between CPM response and anxiety, depression, and pain catastrophizing, however, secondary analyses revealed that certain psychological factors were associated with modality specific CPM response (e.g., pressure based, heat-based or electrical based) [33]. The modality specific CPM response was only seen in pain-free individuals (not in people with pain), which may have been influenced by the altered inhibitory systems of people with (chronic) pain.

Not finding a relationship between psychological factors and the CPM effect in our painful populations is particularly interesting for pain catastrophizing. Numerous studies have demonstrated a relationship between CPM and pain catastrophizing in individuals with chronic pain [10] and in pain-free individuals [50]. Previous work suggests a bi-directional link between pain catastrophizing and CPM – pain inhibition is greater for some, but less for others [18,51]. In young, pain-free adults, both Traxler et al. [51] and Goodin et al.[18] found that higher pain catastrophizing was associated with lower levels of pain inhibition [18,51]. These studies suggest pain catastrophizing is associated with CPM when an individual is not experiencing concurrent acute or chronic pain. Notwithstanding, there are many factors that influence both pain catastrophizing and CPM, and it is possible that psychological constructs like pain catastrophizing traits may present as different constructs in pain-free participants and patients.

There is evidence that cognitive processes at the time of CPM testing and acute manipulation of pain-related cognitions have an effect on CPM. Lewis et al. [23], exposed a sample of healthy men to a noxious stimulus and then primed them to expect higher levels of pain inhibition to a subsequent noxious stimulus of the same magnitude; an approach that, created a larger magnitude of perceived pain inhibition. Throughout the experiment, the investigators also evaluated nociceptive flexion reflex, which lowered during exposure to pain but did not differ between the first (unprimed) and second (primed) noxious stimuli. The reduction in perceived pain without a change in flexion reflex suggests that brain-related processes, rather than spinal were responsible for pain modulation due to expectations. Other examples have demonstrated that CPM can be reduced by inducing a stress reaction prior to testing [15,16]. Together, these results highlight that acute (at time of testing) cognitive processes and elevated psychological questionnaire scores represent different psychological states and play different roles in CPM. Although an elevated score on a psychological measure evaluating symptoms during the last weeks may not be associated with CPM, modulatory interactions of psychological processes and pain-related cognitions cannot be discounted [29].

4.1 Clinical and research implications

For those wishing to further investigate relationships between psychological factors and CPM, considering a broader range of psychological constructs e.g. personality-related may reveal results that differ to ours. Further, the consideration of psychological factors as continuous variables rather than dichotomous may be advantageous. In a cross-sectional study of persons with knee pain, Thompson et al. [49] identified that optimism moderated the relationship between psychological resilience and CPM which, in turn, mediated the relationship between optimism and clinical pain severity. Thus, demonstrating that optimism and psychological resilience may be related to CPM and clinical pain. Psychological state versus trait may also be an important research consideration when it comes to understanding how pain-related cognitions interact with pain modulation. By increasing psychosocial stress, Geva et al. [15] demonstrated concomitant effects of increasing state anxiety and less efficient CPM. Yet, trait anxiety seems to perform differently. Both startle potential and self-reported measures of trait anxiety have been found to be unrelated to CPM [19]. The corollary of these findings is that an individual's psychological state at the time of testing should be the focus of investigators attempting to better understand supraspinal pain modulation. In clinical terms, our finding highlights that psychological factors, as commonly measured in musculoskeletal pain conditions, are poor indicators of CPM effect – one element of an individual's capacity to modulate pain. As such, clinicians should ensure not to infer pain modulation capabilities from self-reported psychological measures.

4.2 Strengths and limitations

With respect to CPM studies, our cohort is one of the most heterogeneous in terms of demographics, diversity of musculoskeletal pain conditions, and the use of various methodological assessments of CPM and psychological factors, which may have impacted our findings. We have therefore conducted several sensitivity analyses, including analyzing each protocol separately, which revealed similar findings as our primary analysis, supporting the use of one large, diverse cohort. Inclusion of a battery of psychological measures that highlight important features in people with pain (acute and chronic) increase the generalizability of our results. However, the inclusion of so many diverse measures come with some limitations regarding analyses. Using recognized psychological measure cut-points, we were able to apportion cases and non-cases which, in turn, enabled us to group measures by construct (e.g., anxiety and depression) and run whole-group analyses. While measure cut-points have been shown to validly identify cases that have psychological impairments, they do so in a reductionist manner that decreases sensitivity [1]. Information lost by way of dichotomizing measures may, thus, have reduced the statistical power to detect a relationship between the independent, psychological variables as opposed to using continuous variables.

4.3. Conclusion

In a large cohort of acute, subacute, and persistent musculoskeletal pain conditions, no relationship was found between the presence of and cumulative number of psychological factors and the CPM effect.

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6. DATA SHARING

Raw data can be made available upon request to the corresponding author.

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Summary

Analysis of 1142 people with acute, subacute and chronic pain showed that pain-related cognitions and emotional distress are not associated with reduced conditioned pain modulation.

Table 1. Sites of application (number (%)) for test and conditioning stimuli across conditioned pain modulation protocol.

	Test stimulus				Conditioning stimulus			
	R upper limb	**L upper limb**	**R lower limb**	**L lower limb**	**R upper limb**	**L upper limb**	**R lower limb**	**L lower limb**
NSMP (n = 693)				Mechanical cuff 693 (100%)			Mechanical cuff 693 (100%)	
PFP (n = 150)			Mechanical HHA 81 (54%)	Mechanical HHA 69 (46%)	Cold 69 (46%)	Cold 81 (54%)		
LBP (n = 128)	Mechanical HHA 128 (100%)					Heat 128 (100%)		
LET (n = 132)	Mechanical HHA 72 (54%)	Mechanical HHA 60 (45%)						Cold 132 (100%)
GT (n = 39)			Mechanical HHA 22 (56%)	Mechanical HHA 17 (44%)	Cold 22 (56%)	Cold 17 (44%)		

NSMP, non-specific multisite pain; PFP, patellofemoral pain; LBP, low back pain; LET, lateral elbow tendinopathy; GT, gluteal tendinopathy; HHA, handheld algometry

Table 2

Table 2. Participant characteristics across protocols/studies

	All (n = 1142)	**NSMP** (n = 693)	**PFP** (n = 150)	**LBP** (n = 128)	**LET** (n = 132)	**GT** (n = 39)
Age	43 (13)	47 (13)	32 (10)	29 (8)	48 (8)	52 (10)
Female, n (%)	732 (63%)	471 (68%)	97 (65%)	66 (52%)	50 (38%)	37 (95%)
Body Mass Index	26.8 (5.4)	27.6 (5.7)	25.2 (4.5)	24.2 (4.0)	27.2 (5.0)	28.6 (6.3)
Multiple pain sites, n (%)*	844 (74%)	604 (87%)	124 (83%)	0 (0%)	85 (64%)	31 (80%)
Pain duration, n (%)#						
Acute	128 (11%)	-	-	128 (100%)	-	-
Sub-acute	116 (10%)	-	11 (7%)	-	105 (80%)	-
Chronic	898 (79%)	693 (100%)	139 (93%	-	27 (20%)	39 (100%)
Pain intensity						
Average pain over 24 hours	-	6.7 (1.7)	-	-	3.8 (1.7)	-
Worst pain over 24 hours	-	8.3 (1.4)	-	-	6.0 (2.2)	-
Average pain over last week	-	-	3.3 (1.6)	5.1 (1.8)	-	4.3 (1.3)
Worst pain over last week	-	-	5.5 (1.6)	-	7.1 (1.9)	6.7 (1.5)

Values are expressed as mean, standard deviation (SD) unless stated otherwise.

* Assessed with the Nordic Questionnaire: pain in upper limb, lower limb, neck, upper back, lower back.

Pain duration: acute <6 weeks; sub-acute 6-12 weeks; chronic >3 months

NSMP, non-specific multisite pain; PFP, patellofemoral pain; LBP, low back pain; LEP, lateral elbow tendinopathy; GT, gluteal tendinopathy

Table 3. Generalized linear models assessing the association between the conditioned pain modulation effect score (z-scores) as dependent variable and anxiety, depression, catastrophizing and fear of movement as independent variables, adjusted for age, sex, body mass index and pain duration.

Variables	N	Beta	SE	P-value	95%CI
Anxiety (non-case)	771	-0.01	0.09	0.91	-0.19, 0.17
Sex		0.30	0.08	<0.001*	0.15, 0.45
Age		-0.01	0.00	0.07	-0.01, 0.00
BMI		-0.01	0.01	0.24	-0.02, 0.01
Pain duration		0.01	0.10	0.91	-0.19, 0.22
Depression (non-case)	896	-0.15	0.09	0.08	-0.31, 0.02
Sex		0.27	0.07	<0.001*	0.14, 0.41
Age		-0.00	0.00	0.21	-0.01, 0.00
BMI		-0.01	0.01	0.17	-0.02, 0.00
Pain duration		0.06	0.05	0.20	-0.03, 0.16
Catastrophizing (non-case)	1067	0.03	0.07	0.64	-0.10, 0.16
Sex		0.29	0.06	<0.001*	0.16, 0.41
Age		-0.01	0.00	0.06	-0.01, 0.00
BMI		-0.01	0.01	0.12	-0.02, 0.00
Pain duration		0.07	0.05	0.15	-0.03, 0.17
Fear of movement (non-case)	924	0.11	0.07	0.11	-0.02, 0.24
Sex		0.32	0.07	<0.001*	0.19, 0.45
Age		-0.01	0.00	0.04*	-0.01, 0.00

BMI	-0.01	0.01	0.25	-0.02, 0.01
Pain duration	0.05	0.10	0.65	-0.15, 0.25

Abbreviations: BMI, body mass index; N, number of participants; SE, standard error; 95%CI, 95% confidence interval. *Indicates a significant P-value.

Table 4. Generalized linear model with the cumulative psychological score (0-3, sum of cases for depression, catastrophizing, fear of movement) as the independent variable and continuous conditioned pain modulation effect (Z-score) as the dependent variable.

Variables	**Beta**	**SE**	**P-value**	**95%CI**
0 psych cases (n=324)	-0.12	0.14	0.38	-0.38, 0.15
1 psych cases (n=207)	-0.27	0.14	0.06	-0.54, 0.01
2 psych cases (n=160)	-0.20	0.14	0.17	-0.48, 0.08
3 psych cases (n=69)	0	-	-	-
Sex	0.31	0.08	<0.001*	0.16, 0.46
Age	-0.01	0	0.09	-0.01, 0.00
BMI	-0.01	0.01	0.24	-0.02, 0.01
Pain duration	0.04	0.11	0.73	-0.17, 0.25

Abbreviations: BMI, body mass index; N, number of participants; SE, standard error; 95%CI, 95% confidence interval. *Indicates a significant P-value.

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