Relationships between Psychological Factors and Experimental Pain Outcomes in Healthy Individuals: Results from 8 Studies

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Abstract

Psychological factors, such as anxiety, depression, and pain catastrophizing, may affect how healthy individuals experience experimental pain. However, current literature puts forth contradictory results, possibly due to differing study methodologies, such as the type of psychophysical measure or survey. To better understand such results, this paper analyzed the relationships between psychological factors and experimental pain outcomes across eight different studies (total $n = 595$) conducted in different populations of healthy adult and adolescent participants. Analyses were conducted with and without controlling for sex, age, and race. Each study was analyzed separately and as part of an aggregate analysis. Even without correction for multiple comparisons, only a few significant relationships were found for the individual studies. Controlling for demographic factors had minimal effect on the results. Importantly, even the few statistically significant models showed relatively small effect sizes; psychological factors explained no more than 20% of the variability in experimental pain sensitivity of healthy individuals. The aggregate analyses revealed relationships between anxiety and PPT / cold pain ratings and between pain catastrophizing and PPT. Sample size calculations based on the aggregate analyses indicated that several hundred participants would be required to correctly detect relationships between these psychological factors and pain measures. These overall negative findings suggest that anxiety, depression, and pain catastrophizing in healthy individuals may not be meaningfully related to experimental pain outcomes. Furthermore, positive findings in the literature may be subject to small group effects and publication bias towards positive findings.

Introduction

Individual differences in how people experience pain are profound and may be influenced by various demographic, physiological, genetic and psychological factors. The most commonly examined psychological factors related to experimental pain outcomes are anxiety, depression and pain catastrophizing [22, 25, 35, 40, 42, 47, 63, 68, 73, 77, 85]. Although it is well accepted that psychological factors relate to experimental pain outcomes, contradictory results exist, especially in healthy individuals, with some studies finding significant relationships [4, 26, 45] and others not finding such relationships [9, 31, 53, 65, 69]. Although it is not clear why these contradictory results exist, one explanation may be differing cross-study methodologies (psychological survey, pain stimuli, study sample).

Our laboratory has performed multiple studies where healthy participants completed psychological surveys and underwent experimental pain testing. However, the relationships between psychological factors and pain are often not explored. The goal of the current study was to focus on the relationships between psychological factors and experimental pain outcomes in healthy participants using data from eight different studies conducted by our group. These studies were conducted in different populations (adults or adolescents) using several different types of psychological surveys, which may allow us to identify patterns present only within certain surveys or populations. If such patterns exist, they could explain the inconsistent findings on the relationships between psychological parameters and experimental pain outcomes across currently published studies. Understanding these relationships is important not only for the

identification of factors contributing to how individuals process and respond to pain but also for the development of pain interventions targeting those factors.

Methods

This manuscript includes data from eight different studies including unpublished studies, involving psychological and experimental pain outcome parameters [7, 8, 54, 57]. For psychological measures, we focused on anxiety, depression and pain catastrophizing. For experimental pain outcomes, we focused on pressure pain thresholds (PPT), conditioned pain modulation (CPM) response, cold pain tolerance, and pain intensity and unpleasantness ratings of cold-water immersion. These measures were chosen for being the most common across all the studies. The studies were analyzed separately due to minor, but potentially critical, differences between the studies. These differences allowed us to see with greater detail potentially subtle patterns in variable relationships among different populations and measures. Information about the specific studies can be found in Table 1 and Supplementary 1. In addition, aggregate analyses combining the results of all studies were conducted. Data from this study will be shared at the request of other investigators for purposes of replicating procedures and results.

Participants

All participants included in these analyses were healthy with 1) no psychiatric or neurological disorders, 2) no chronic pain diagnoses, and 3) no current pain medication use on a regular basis. Specific inclusion criteria for each of the studies are described in Supplementary 1.

Quantitative Sensory Testing (QST) measures

Pain Ratings of Suprathreshold Pain- In all studies (except for study 8), participants were asked to indicate the magnitude of pain sensation with a visual analog scale (VAS). The VAS is a simple rating scale with ratio scale properties [60]. Participants were instructed to move a 15cm hand-held slider to the right, exposing a red colored strip underneath, until the amount of red showing matched their perception of pain intensity or unpleasantness. Pain intensity (how strong the pain feels) and pain unpleasantness (how disturbing the pain is) were defined for the participant before testing began using an analogy about the volume of a radio [61]. Both intensity and unpleasantness dimensions ranged between a minimum value of 0, meaning no pain or unpleasantness sensation, and a maximum value of 10, meaning most intense or unpleasant sensation imaginable, and were recorded with a precision of 0.1 units. Participants were not able to see the numerical value of the ratings they gave. In study 8, participants were asked to report their perceived pain intensity using a verbal numerical pain scale ranging from 0 ("no pain"), to 10 ("worst pain imaginable").

Pressure Pain Thresholds (PPT)- Pressure stimulation (AlgoMed – Computerized Pressure Algometer, Medoc, Ramat Yishai, Israel) was gradually increased until the participant felt a sensation of pain. The participant was instructed to press a hand-held button as soon as they first felt a painful sensation, which was used to indicate their pain thresholds. The force of the pressure at the time of the button push

was recorded. This procedure was repeated two or three times. Details on PPT locations for each study can be found in Table 1.

Conditioned Pain Modulation (CPM)– CPM is based on a “pain-inhibits-pain” concept that represents a spatial filtering mechanism [55]. In the CPM paradigm, one noxious stimulus (i.e., conditioning stimulus) inhibits the pain intensity of another noxious stimulus (i.e., test stimulus) that is delivered to a remote area of the body [1]. The CPM response is defined as a reduction in the perceived magnitude of pain from the test stimulus when it is delivered alone versus when it is delivered concurrently with the conditioning stimulus. An inhibitory CPM response is represented by negative values. We included all paradigms in the cases in which more than one CPM paradigm was collected. Details of the differing methods of assessing CPM are included in Table 1.

Cold pain tolerance- Participants immersed their hand or foot in a cold-water bath (temperature range for studies 0-4°C, Table 1). Pain tolerance was defined by the time of limb withdrawal (seconds). Pain ratings of cold pain intensity and pain unpleasantness were collected upon limb withdrawal (see next section).

Pain ratings of cold-water immersion- Participants were asked to rate their perception of pain intensity and unpleasantness with a VAS during or following hand/foot immersion into cold water. In some studies, this stimulus of cold-water immersion served as the conditioning stimulus of the CPM paradigm, while in others it was used to assess cold-pain tolerance. If several cold-water immersions were applied in the same study using identical stimulus parameters, only the first immersion was included in the analysis.

Psychological surveys

Each of the eight studies included one or more of the widely used surveys described below, assessing anxiety, depression or pain catastrophizing (Table 1). Adult versions were used for participants ages 18-44. Adolescent versions were used for participants ages 14-17.

Anxiety-

1. The Patient-Reported Outcomes Measurement Information System (PROMIS®)

Anxiety questionnaire [11, 12] has 8 items assessing fear, uneasiness, and hyperarousal over the past 7 days. Both the adult and pediatric version use a scale from “Never” (1) to “Always” or “Almost Always” (5). Scores are summed across all items, with higher scores indicating greater anxiety. The pediatric version of this measure uses age-appropriate wording (i.e., “I felt worried” vs. “I felt anxious”) and has specifically been validated in pediatric populations.

2. The Spielberger State Trait Anxiety Inventory (STAI)- The STAI has participants self-report perceived anxiety at the state (temporary) and trait (enduring, stable) levels. Both the state and trait subscales consist of 20 items scored on a scale ranging from “Almost Never” (1) to “Almost Always” (4) [70]. For the current study, only trait anxiety was examined to reduce the number of comparisons and for a better comparison with the other anxiety surveys.

Depression-

1. The PROMIS Depression questionnaire [11, 12] has 8 items assessing depressive symptoms such as negative mood, anhedonia, negative views of self, and negative social cognition over the past seven days. Each question has five response options with

a range between 1-5. Scores are summed across all items, with higher scores indicating greater depressive symptoms.

2. Beck Depression Inventory (BDI)- The BDI is a widely used self-report survey that measures characteristic attitudes and symptoms of depression. The BDI has 21-items, each scored on a scale between 0 to 3. Anchors for each score are written next to the score for each question. The scores are summed for a total score of level of depression. Score of <10 indicate normal state, 11-16 mild mood disturbance, 17-20 borderline clinical depression, 21-30 moderate depression, 31-40 severe depression, >40 extreme depression [6].

Pain Catastrophizing-

Pain Catastrophizing Scale (PCS)- Pain catastrophizing is defined as a tendency to mentally aggrandize pain experiences. The PCS contains 13 items representing the 3 components of rumination, magnification, and helplessness; a total score represents overall levels of pain catastrophizing. Each item is rated on a scale ranging from “Not at All” (0) to “All the Time” (4). Participants completed the questionnaire referring to previous pain events. The total score of pain catastrophizing was calculated [74].

Statistical analysis

For each study, we first computed descriptive statistics for all available psychological and experimental pain variables. Next, we ran separate linear regressions using each psychological variable as a predictor of each experimental pain variable.

After computing all univariate models between psychological variables and experimental pain outcomes, we reran all models with the covariates of age, sex, and race

simultaneously. These models allowed us to test whether psychological variables were related to pain outcomes above and beyond the effects due to age, sex, or race. A separate dummy code (0/1) variable was created for each racial category (Asian, Black, Other, Mixed) for each study, with White serving as the reference group. If a study did not include any participants from a particular racial group, the dummy code for that group was not included in the analyses. All statistics were run with SPSS Version 25.

Additional aggregate analyses combining the results of all studies were conducted using R statistical software [76], the R meta-analysis package “metafor” [82], and R-Studio were employed for the meta-analyses [67]. While these aggregate analyses were conducted in a similar way to a meta-analysis, they are not formal meta-analyses, as since they are derived from these studies of our group alone rather than an assessment of the published literature. Aggregate analyses were performed only in cases of at least three studies for a specific analysis. Aggregate analyses employed Fisher’s z-transformation, as conventionally done for meta-analyses. DerSimonian and Laird’s random-effects model was used for determining relationships [16]. These analyses were performed only in cases of at least three studies for a specific analysis. The aggregate analyses were conducted on the data that was not controlled for sex, age and race to better mimic common analyses of across studies in which controlling for demographic variables is usually not possible.

For aggregate analyses that were significant or trending towards significance ($p < 0.1$), a sample size calculation for future studies was conducted based on the grand mean

results found in the aggregate analyses. Sample calculations were conducted using G*Power (version 3.1.9.7) [20] and used alpha of 0.05 and power of 0.80.

Results

Study (1)

Twenty regression models were tested for this study (adolescents, n=58). A significant positive relationship was found between both anxiety / depression levels and pain intensity / pain unpleasantness ratings of foot immersion into cold water. This indicates that greater anxiety and depression were each associated with greater pain sensitivity, demonstrated by higher ratings of cold pain intensity and unpleasantness. No significant associations were found between anxiety / depression and the QST data of PPT / the two CPM responses (using heat or PPT as the test stimulus). After controlling for sex, age, and race, the associations between pain intensity / pain unpleasantness ratings of cold water and anxiety / depression remained significant. None of the other associations were significant (Table 2).

Study (2)

Sixteen regression models were tested for this study (adolescents, n=20). No associations were found between the psychological factors of anxiety and depression and the QST measures of PPT, CPM response, and pain intensity and unpleasantness of cold-water immersion. These results remained unchanged after controlling for sex, age, and race of the participants (Table 3).

Study (3)

Thirty-six regression models were tested for this study (adolescents, n=33). No associations were found between the psychological factors of anxiety, depression and pain catastrophizing and any of the QST measures (PPT tested at the trapezius and at the forearm, pain intensity and unpleasantness ratings of cold-water immersion and the two CPM responses). No associations were found even after controlling for sex, age, and race (Table 4).

Study (4)

Sixteen regression models were tested for this study (adults and adolescents, n=31). A significant association was found between anxiety and CPM. No other associations were found between anxiety and depression and cold pain tolerance, pain intensity or pain unpleasantness ratings of cold-water immersion). After controlling for sex, age, and race, the association between anxiety and CPM was no longer significant. However, the association between anxiety and cold pain tolerance, which was not significant, was significant after controlling for the demographic factors (Table 5).

Study (5)

Twenty-four regression models were tested for this study (adults and adolescents, n=122). Significant associations were found between anxiety and both pain intensity and pain unpleasantness ratings of cold-water immersion. There were no significant associations between anxiety and CPM or cold pain tolerance, and none of the pain measures were associated with depression or pain catastrophizing. After controlling for sex, age, and race the association between anxiety and pain intensity and pain unpleasantness ratings of cold-water immersion remained significant (Table 6).

Study (6)

Six regression models were tested for this study (adults, n=21). No associations were found between the psychological factors of anxiety, depression and pain catastrophizing and PPT in healthy adults. These results were not changed when we controlled for sex, age and race of the participants (Table 7).

Study (7)

Twelve regression models were tested for this study (adults, n=84). No associations were found between the psychological factors of anxiety and depression and the QST measures of cold tolerance (time, pain intensity and pain unpleasantness). These results were not changed when we controlled for sex, age and race of the participants (Table 8).

Study (8)

Six regression models were tested for this study (adults, n=226). No associations were found between pain catastrophizing and the QST measures of PPT, CPM, and pain intensity of cold-water immersion. These results were not changed when we controlled for sex, age and race of the participants (Table 9).

Aggregate analyses across studies

There was no evidence for significant associations between anxiety and CPM response or cold pain tolerance across studies (Figure 1, Table 10). However, a significant association was found between anxiety and PPT (Fisher's z -0.10 [-0.19, -0.01]) as well as between anxiety and cold pain intensity (Fisher's z 0.18 [0.04, 0.32]). A non-significant trend towards a relationship between anxiety and cold pain unpleasantness

was also noted. Given the small effect sizes of these relationships, sample size calculation indicated that for future prospective studies 767 participants would be required in order to correctly detect the association between anxiety and PPT. To correctly detect the association between anxiety and cold pain intensity, 237 participants would be required. In addition, to correctly detect the association between anxiety and cold pain unpleasantness, a sample size of 297 participants would be required.

There was also no evidence for significant association between depression and any of the pain sensitivity measures across studies, although a non-significant trend towards a relationship between depression and cold pain unpleasantness was noted (Figure 1, Table 10). Sample size calculation indicated that for future studies, 647 participants would be required to correctly detect the association between depression and cold pain unpleasantness.

Across studies, PPT was the only pain sensitivity measure found to be related to pain catastrophizing (Fisher's z -0.14 [-0.26, -0.02]); however, there was no evidence for significant association between pain catastrophizing and CPM or cold pain intensity (Figure 1, Table 10). Sample size calculation indicated that 399 participants would be required to correctly detect the association between pain catastrophizing and PPT.

Discussion

Few associations were found between psychological factors and experimental pain outcomes within each of the eight studies. This overall lack of associations was determined even without any corrections for multiple comparisons. Across all studies,

136 regression models were conducted with an alpha value of 0.05. Without corrections for multiple comparisons, and simply by chance, approximately 7 results should be significant. We found that 8 models were significant without controlling for multiple comparisons. Thus, these positive findings are close to the number that would be predicted by chance and may not represent real effects. Even when statistically significant associations were found, the maximum explained variability remained less than 20%. In most cases, controlling for demographic factors such as sex, age and race did not change the results. Thus, demographic factors may have a small effect on the relationships between psychological factors and experimental pain sensitivity.

The aggregate analyses integrated the results of the individual studies across hundreds of participants and found small, yet statistically significant relationships between anxiety and PPT and anxiety and cold pain intensity as well as between pain catastrophizing and PPT. The significance of these findings is questionable given the small effect sizes detected. The sample size calculation, which was based on the aggregate analyses, indicated that in order to correctly detect associations between these psychological factors and pain measures, the minimum number of participants would range from approximately 240 to 760 participants. Thus, positive findings of associations between psychological factors and experimental pain measures in healthy participants may be subject to small group effects and publication bias towards positive findings. Although several associations were significant, the majority of our findings were negative. These overall negative findings are important because they challenge conventional wisdom

that psychological factors in healthy individuals are associated with experimental pain outcomes.

Anxiety

In the aggregate analyses, higher anxiety levels were related to higher pain sensitivity of lower PPT and higher cold pain intensity ratings. It is not clear why anxiety would be related only to these experimental pain measures. A previous meta-analysis also found that anxiety was related only to CPM paradigm that used PPT as the test stimulus and cold pain as the conditioning stimulus [56], which may suggest that anxiety has greater influence on these pain measures.

Within the individual studies, anxiety was associated with pain sensitivity in two out of six studies, but without corrections for multiple comparisons. The difference between one study that found a significant association and the studies that did not may be partially due to the type of anxiety survey that was used. The PROMIS survey was used in study 5 that found an association while STAI was used in studies 4 and 7 which did not find associations. The STAI reflects more general distress or negative affect and the PROMIS Anxiety assesses more of the specific symptoms of fearfulness/anxiety [2]. Thus, in healthy individuals, the PROMIS survey measures may be more related to pain perception in that people who are generally more worried and fearful are the ones reporting pain as being more unpleasant and intense.

Pain Catastrophizing

Pain catastrophizing measures people's tendency to magnify or ruminate over real or imagined pain experiences. In the present investigation, pain catastrophizing was not correlated with PPT, CPM, cold pain tolerance, or pain intensity and unpleasantness of cold-water immersion in any of the three studies in which it was tested. However, aggregate analysis across these studies found a relationship between higher pain catastrophizing and lower PPT (greater pain sensitivity). It is not clear why PPT would be the only parameter related to pain catastrophizing. One possibility is that PPT was the only threshold measure examined across studies and that individuals with higher tendencies to catastrophize mislabeled innocuous sensations as painful. Across all three studies, the PCS was used to assess pain catastrophizing. Other surveys that assess different aspects of pain catastrophizing, such as the Coping Strategies Questionnaire (CSQ) [66], might have revealed different relationships with experimental pain in healthy individuals.

Depression

No significant associations between depression and any of the pain measures were found in the aggregate analysis across studies. Significant associations between depression and pain intensity and unpleasantness of cold-water immersion in healthy adolescents were found in only one study, and in light of the aggregate analyses, may represent a false positive. Similar to anxiety surveys, there are several surveys that assess depression which differ in some parameters. The PROMIS depression scale is a narrower and more precise measure of mood and has participants rate the

frequency/duration of those symptoms in the past 7 days, whereas the BDI is a multidimensional measure which assess various aspects including sleep, appetite, and self-worth. Participants are asked to report the intensity of their symptoms. The BDI is more diagnostically aligned with clinical symptoms of depression [75].

Factors contributing to weak associations in healthy individuals vs patients

The overall lack of associations that were found in the individual studies between anxiety, depression and pain catastrophizing and experimental pain sensitivity may be surprising. Various studies have shown significant relationships between anxiety, depression and pain catastrophizing, and levels of clinical pain and experimental pain sensitivity in pain patients [10, 24, 37, 38, 42, 43, 68, 83]. However, psychological factors may affect pain differently in healthy individuals and pain patients. Interestingly, pain catastrophizing predicted postoperative pain after breast surgery in patients who had chronic pain before the surgery – but not in patients without chronic pain before the surgery [68]. This emphasizes the possibility of an interaction between the influence of psychological factors on pain and the presence or absence of chronic pain. Patients with chronic pain have been found to experience higher levels of anxiety, depression and pain catastrophizing compared to healthy controls [30, 35, 36, 39, 44, 58, 80]. Conversely, several studies have shown that pain-free individuals with psychiatric disorders such as depression or post-traumatic stress disorder have reduced sensitivity to pain [23, 33, 71]. However, other studies have found no differences between the groups [72] or increased pain sensitivity in these patients [14, 15, 48]. Thus, it is possible that anxiety, depression and pain catastrophizing have only minor effects on

pain in healthy controls, while individuals with higher levels of psychological factors or pain have interactions that can be observed.

The results of the present study are in line with the results of a previous meta-analysis that examined the relationships between CPM and psychological factors [56]. In the meta-analysis, when all studies were grouped together, no relationships were found between CPM response and psychological factors (anxiety, depression, pain catastrophizing) in both healthy and chronic pain patients. [56]. This is similar to the aggregate analysis that grouped all studies together and found no associations between any of the psychological factors and CPM. However, another meta-analysis focused only on Irritable Bowel Syndrome (IBS) patients and found that CPM responses were correlated with anxiety and pain catastrophizing [41]. Thus, the relationships between experimental pain and psychological parameters may be specific to chronic pain patients or a sub-group of patients, to pain measures, or to psychological factors.

Controlling for sex, age, and race had minimal effect on the results. This may indicate that although demographic factors can affect both pain and psychological measures, they may not be involved in the relationships between psychological factors and experimental pain sensitivity in healthy individuals. Sex, age, and race differences in pain are well characterized in previous literature [3, 5, 9, 21, 27, 34, 45, 46, 49, 64, 79]. In addition, sex, age, and race can affect levels of anxiety, depression and pain catastrophizing [9, 21, 45, 50-52] . Several studies found that sex can affect the relationships between psychological factors and pain sensitivity, with different relationships reported for men and women [78, 79]. However, another study did not find

this relationship [50]. Since controlling for sex, age, and race had a minimal effect on the results, we suggest that it may not be necessary to control for these factors in future studies assessing the relationships between psychological and experimental pain in healthy participants.

Conclusions

Although the common notion is that psychological factors affect experimental pain sensitivity, we found only a few associations between these factors in healthy participants. Furthermore, relatively high numbers of healthy participants would be required to find these associations due to their small effect sizes. These findings have two important implications for the design of future studies of healthy participants. First, these results raise the possibility of small group effects where positive relationships are found by chance despite lacking an adequate sample of the population. In future studies where such relationships are of interest, relatively large numbers of participants should be recruited to ensure an experiment will be adequately powered to detect these small effects. Second, in psychologically healthy individuals for whom these variables contribute minimally to individual differences in pain, the time and effort needed to obtain this data in detail may be avoided. Instead, rapidly administered screening tools could be implemented to ensure that key factors like anxiety and depression fall within healthy ranges.

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Figure legends

Figure 1. Aggregate analyses across studies.

Aggregate analyses were performed only in cases of at least three studies for a specific analysis. The aggregate analyses were conducted on the data that was not controlled for sex, age and race to better mimic common analyses of across studies in which controlling for demographic variables is usually not possible. Significant correlation was found between anxiety and PPT, anxiety and cold pain intensity and between pain catastrophizing and PPT.

Table 1- Description of Demographic, QST, and Psychological Measures for Studies Included in the Analysis

STUDY	QST PARAMETERS (Location, Intensity, Duration - if applicable)						PSYCHOLOGICAL PARAMETERS ^c				
	DEMOGRAPHICS			Pressure Pain Thresholds (PPT)	Conditioned Pain Modulation (CPM)	Cold Water Immersion	PROMIS Anxiety	Spielberger Trait Anxiety	PROMIS Depression	Beck Depression Inventory-II	Catastrophizing
	Total Participants (Females)	Age (years)	Race								
1	58 (38)	14.2 ±1.7	White: 43 Black: 15 Asian: 0 Other: 0	LG	<u>TS #1</u> : PPT (LG) <u>TS #2</u> : Heat stimuli (46°C, 30s, LG) <u>CS</u> : Foot immersion (8°C, 60s)	Int & Unp (Foot, 8°C, 60s) ^b	P	-	P	-	-
2	20 (16)	13.8 ±2.5	White: 14 Black: 3 Asian: 0 Other: 3	Trap	<u>TS</u> : PPT (Trap) <u>CS</u> : Foot immersion (8°C, 60s)	Int & Unp (Foot, 8°C, 60s) ^b	P	-	P	-	-
3	33 (30)	15.5 ±1.4	White: 29 Black: 3 Asian: 0 Other: 2	Trap FA	<u>TS #1</u> : PPT (Trap) <u>TS #2</u> : PPT (FA) <u>CS</u> : Hand immersion (10°C, 60s)	Int & Unp (Hand, 10°C, 60s) ^b	P	-	P	-	P
4^a	31 (12)	28.7 ±7.4	White: 21 Black: 7 Asian: 3 Other: 0	-	<u>TS</u> : Heat stimuli (48°C, 30s, FA) <u>CS</u> : Foot immersion (8°C, 60s)	CPTo Int, & Unp (4°C, max 120s)	-	$\frac{A}{P}$	-	$\frac{A}{P}$	-
5^a	122 (83)	27.9 ±6.8	White: 104 Black: 22 Asian: 5 Other: 0	-	<u>TS</u> : Heat stimuli (48°C, 30s, FA) <u>CS</u> : Foot immersion (8°C, 60s)	CPTo Int, & Unp (Hand, 4°C, max 120s)	$\frac{A}{P}$	-	$\frac{A}{P}$	-	$\frac{A}{P}$
6	21 (17)	27.8 ±7.2	White: 13 Black: 3	FA	-	-	A	-	A	-	A

Table 2. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #1

	Anxiety					Depression				
	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value
PPT (n=56)										
Without	-.002	.005	-.058	-.431	.669	-.002	.005	-.063	-.466	.643
With	.000	.005	-.011	-.075	.941	.000	.005	.006	.039	.969
CPM - Pressure (n=56)										
Without	-.005	.008	-.089	-.655	.515	-.002	.007	-.042	-.312	.756
With	-.003	.008	-.052	-.375	.709	-.002	.007	-.047	-.336	.738
CPM - Heat (n=53)										
Without	-.048	.046	-.146	-1.055	.296	-.028	.039	-.101	-.723	.473
With	-.040	.048	-.120	-.837	.407	-.028	.040	-.098	-.686	.496
CP-Int (n=56)										
Without	1.054	.358	.372	2.945	.005	.834	.327	.328	2.548	.014
With	1.084	.359	.383	3.023	.004	.916	.328	.360	2.792	.007
CP-Unpl (n=56)										
Without	.868	.329	.338	2.642	.011	.697	.299	.302	2.328	.024
With	.888	.328	.346	2.712	.009	.718	.301	.311	2.390	.021

PPT, Pressure Pain Thresholds; CPM, Conditioned Pain Modulation Response; CP-Int, Cold Pain Intensity Ratings; CP-Unpl, Cold Pain Unpleasantness Ratings.

Table 3. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #2

	Anxiety					Depression				
	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value	Unstandardiz ed β	Coefficients Std. error	Standardized β	T Value	P Value
PPT (n=20)										
Without	-.001	.005	-.039	-.164	.872	-.002	.003	-.141	-.604	.554
With	.001	.006	.062	.224	.826	-.004	.004	-.292	-.968	.348
CPM (n=20)										
Without	.006	.010	.129	.552	.588	.000	.006	.007	.030	.997
With	.007	.010	.162	.708	.490	-.001	.006	-.035	-.135	.894
CP-Int (n=20)										
Without	.030	.354	.020	.085	.933	.148	.199	.173	.744	.467
With	-.112	.351	-.075	-.320	.753	.104	.224	.121	.463	.650
CP_Unpl (n=20)										
Without	-.210	.255	-.190	-.823	.421	.018	.148	.029	.121	.905
With	-.303	.252	-.275	-1.205	.247	.013	.169	.021	.078	.939

PPT, Pressure Pain Thresholds; CPM, Conditioned Pain Modulation response; CP-Int, Cold Pain Intensity Ratings; CP-Unpl, Cold Pain Unpleasantness Ratings.

Table 4. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #3

	Anxiety					Depression					Pain Catastrophizing				
	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value
PPT-Trapezius (n=32)															
Without	-.009	.012	-.135	-.748	.460	.007	.013	.102	.559	.580	-.004	.012	-.053	-.293	.771
With	-.006	.013	-.086	-.440	.664	.007	.014	.104	.522	.606	-.005	.012	-.080	-.439	.665
PPT-Forearm (n=32)															
Without	-.007	.013	-.091	-.502	.619	.007	.014	.086	.473	.639	-.017	.013	-.233	-1.310	.200
With	-.008	.015	-.111	-.556	.583	.002	.016	.024	.119	.907	-.014	.013	-.195	-1.073	.293
CPM-Trapezius (n=32)															
Without	.020	.020	.185	1.028	.312	.004	.021	.036	.198	.844	.012	.020	.109	.602	.551
With	.021	.022	.190	.956	.348	.011	.024	.098	.481	.634	.009	.020	.081	.432	.669
CPM-Forearm (n=32)															
Without	.025	.021	.212	1.190	.243	.002	.023	.018	.097	.924	-.018	.021	-.153	-.846	.404
With	.016	.024	.136	.655	.519	-.005	.026	-.038	-.177	.861	-.019	.022	-.161	-.840	.408
CP-Int (n=32)															
Without	-.045	.458	-.018	-.099	.922	.042	.488	.016	.086	.932	-.161	.457	-.064	-.353	.727
With	-.155	.535	-.062	-.290	.774	.172	.576	.064	.298	.768	.052	.496	.021	.105	.917
CP-Unpl (n=32)															
Without	-.091	.419	-.040	-.217	.830	-.099	.446	-.040	-.221	.826	-.354	.413	-.154	-.855	.399
With	-.241	.482	-.105	-.500	.621	-.080	.521	-.033	-.153	.880	-.129	.448	-.056	-.289	.775

PPT, Pressure Pain Thresholds; CPM, Conditioned Pain Modulation Response; CP-Int, Cold Pain Intensity Ratings; CP-Unpl, Cold Pain Unpleasantness Ratings.

Table 5. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #4

	Anxiety					Depression				
	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value
CPM (n=26)										
Without	-.070	.031	-.422	-2.281	.032	-.086	.064	-.264	-1.339	.193
With	-.075	.039	-.453	-1.917	.070	-.017	.070	-.052	-.241	.812
CP Tolerance (n=31)										
Without	.018	.012	.261	1.459	.155	-.010	.024	-.077	-.415	.681
With	.028	.014	.413	2.067	.049	-.030	.024	-.232	-1.254	.222
CP-Int (n=31)										
Without	.223	.226	.180	.988	.331	-.328	.440	-.137	-.744	.463
With	.263	.257	.212	1.023	.316	-.198	.446	-.083	-.444	.661
CP-Unpl (n=31)										
Without	.292	.214	.245	1.364	.183	-.043	.427	-.019	-.100	.921
With	.332	.256	.279	1.298	.206	.065	.451	.028	.144	.887

CPM, Conditioned Pain Modulation Response; CP Tolerance, Cold Pain Tolerance; CP-Int, Cold Pain Intensity Ratings; CP-Unpl, Cold Pain Unpleasantness Ratings.

Table 6. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #5

	Anxiety					Depression					Pain Catastrophizing				
	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value
CPM (n=63)															
Without	.009	.028	.043	.333	.740	.002	.019	.015	.116	.908	.060	.059	.128	1.009	.317
With	.013	.026	.058	.483	.631	.004	.020	.024	.184	.855	.062	.059	.134	1.056	.295
CP Tolerance (n=98)															
Without	-.015	.012	-.132	-1.307	.194	-.003	.010	-.028	-.270	.788	.006	.024	.025	.240	.811
With	-.009	.012	-.081	-.772	.442	.000	.010	.003	.026	.980	.008	.026	.035	.326	.745
CP-Int (n=98)															
Without	.377	.169	.222	2.232	.028	.038	.143	.027	.267	.790	.385	.360	.108	1.067	.289
With	.436	.165	.256	2.633	.010	.055	.146	.039	.374	.709	.432	.367	.122	1.179	.242
CP-Unpl (n=98)															
Without	.394	.158	.246	2.486	.015	.151	.134	.114	1.126	.263	.570	.337	.170	1.692	.094
With	.410	.158	.256	2.602	.011	.162	.138	.123	1.176	.243	.626	.346	.187	1.811	.073

CPM, Conditioned Pain Modulation Response; CP Tolerance, Cold Pain Tolerance; CP-Int, Cold Pain Intensity Ratings; CP-Unpl, Cold Pain Unpleasantness Ratings.

Table 7. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #6

	Anxiety					Depression					Pain Catastrophizing				
	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value	Unstand-ardized β	Coeff. Std. error	Stand-ardized β	T Value	P Value
PPT (n=21) Without	-.012	.011	-.243	-1.093	.288	-.011	.008	-.315	-1.445	.165	-.020	.013	-.333	-1.537	.141
With	-.008	.019	-.154	-.416	.683	-.002	.006	-.056	-.319	.755	-.019	.022	-.307	-.862	.403

PPT, Pressure Pain Threshold.

Table 8. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #7

	Anxiety					Depression				
	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value
CP Tolerance (n=84)										
Without	.020	.021	.106	.968	.336	-.015	.014	-.114	-1.039	.302
With	.008	.022	.043	.370	.712	-.017	.015	-.126	-1.120	.266
CP-Int (n=84)										
Without	.301	.321	.103	.940	.350	.145	.225	.071	.643	.522
With	.533	.328	.182	1.623	.109	.254	.228	.124	1.110	.270
CP-Unpl (n=84)										
Without	.247	.320	.085	.773	.441	.181	.224	.089	.807	.422
With	.581	.339	.200	1.717	.090	.330	.235	.162	1.405	.164

CP Tolerance, Cold Pain Tolerance; CP-Int, Cold Pain Intensity Ratings; CP-Unpl, Cold Pain Unpleasantness Ratings.

Table 9. Relationships between psychological factors and experimental pain sensitivity with and without controlling for demographic factors- Results of Study #8

	Pain Catastrophizing Scale				
	Unstandardized β	Coefficients Std. error	Standardized β	T Value	P Value
PPT (n=224)					
Without	-.013	.007	-.122	-1.828	.069
With	-.012	.007	-.110	-1.715	.088
CPM (n=105)					
Without	.010	.014	.067	.681	.498
With	.009	.014	.062	.662	.510
CP-Int (n=91)					
Without	.590	.405	.153	1.457	.149
With	.449	.402	.116	1.117	.267

PPT, Pressure Pain Thresholds; CPM, Conditioned Pain Modulation Response;
CP-Int, Cold Pain Intensity Ratings.

Table 10. Summary of aggregate analyses.

Psychological Factors	Pain Modalities	No. Included Studies (n participants)	P-value	τ^2	τ	I^2 (%)	H^2	Cochran's Q Test for Heterogeneity	Grand Mean Correlation r (95% CI) in Original Units
Anxiety	PPT	5 (129)	0.033	0 (SE = 0.0255)	0	0.00	1.00	Q(df = 4) = 0.5897, p = 0.9642	r = -0.1010 (-0.1873 to -0.0131)
	CPM	7 (197)	0.804	0.0128 (SE = 0.0235)	0.1132	31.69	1.46	Q(df = 6) = 8.7831, p = 0.1861	r = -0.0207 (-0.2121 to 0.1723)
	Cold Pain Tolerance	3 (213)	0.720	0.0205 (SE = 0.0376)	0.1430	55.86	2.27	Q(df = 2) = 4.5310, p = 0.1038	r = 0.0461 (-0.4094 to 0.4832)
	Cold Pain Intensity	6 (321)	0.021	0 (SE = 0.0134)	0	0.00	1.00	Q(df = 5) = 4.5980, p = 0.4669	r = 0.1810 (0.0413 to 0.3137)
	Cold Pain Unpleasantness	6 (321)	0.068	0.0070 (SE = 0.0180)	0.0836	24.82	1.33	Q(df = 5) = 6.6503, p = 0.2480	r = 0.1618 (-0.0180 to 0.3315)
Depression	PPT	5 (129)	0.571	0 (SE = 0.0255)	0	0.00	1.00	Q(df = 4) = 2.7271, p = 0.6045	r = -0.0422 (-0.2278 to 0.1465)
	CPM	7 (197)	0.274	0 (SE = 0.0159)	0	0.00	1.00	Q(df = 6) = 1.8926, p = 0.9293	r = -0.0418 (-0.1263 to 0.0432)
	Cold Pain Tolerance	3 (213)	0.136	0 (SE = 0.0162)	0	0.00	1.00	Q(df = 2) = 0.3292, p = 0.8482	r = -0.0690 (-0.1890 to 0.0531)
	Cold Pain Intensity	6 (321)	0.217	0.0020 (SE = 0.0147)	0.0443	8.47	1.09	Q(df = 5) = 5.4629, p = 0.3620	r = 0.0860 (-0.0706 to 0.2384)
	Cold Pain Unpleasantness	6 (321)	0.068	0 (SE = 0.0134)	0	0.00	1.00	Q(df = 5) = 3.4236, p = 0.6350	r = 0.1099 (-0.0119 to 0.2284)
Pain Catastrophizing	PPT	4 (277)	0.036	0 (SE = 0.0195)	0	0.00	1.00	Q(df = 3) = 1.3262, p = 0.7229	r = -0.1397 (-0.2574 to -0.0178)
	CPM	4 (200)	0.319	0 (SE = 0.0165)	0	0.00	1.00	Q(df = 3) = 1.6899, p = 0.6392	r = 0.0602 (-0.1004 to 0.2178)
	Cold Pain Intensity	3 (221)	0.171	0 (SE = 0.0155)	0	0.00	1.00	Q(df = 2) = 1.0431, p = 0.5936	r = 0.1035 (-0.1091 to 0.3070)

PPT indicates pressure pain threshold; CPM indicates conditioned pain modulation; H^2 : total variability/within-study variance; I^2 : % of total variability due to heterogeneity; τ : square root of τ^2 ; τ^2 : estimate of the total amount of heterogeneity.

Supplementary 1- Methods for the Specific Studies

Study 1

This study was conducted in healthy adolescents at Cincinnati Children's Hospital. One female investigator and two male investigators conducted this study. Full procedures for this study are described in ¹.

Participants

Study inclusion criteria: 1) age 12-17, 2) no chronic pain disorders, 3) no psychiatric or neurological (except for attention deficit disorder) disorders, 4) not taking medications on a regular basis (except oral contraceptives). This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center. Written, informed consent was obtained from all participants' parent or guardian prior to participating in the study, and assent was obtained from all participants prior to participating in the study.

Psychological Questionnaires

Participants completed The Patient-Reported Outcomes Measurement Information System (PROMIS®) adolescent anxiety and depression instruments.

Quantitative Sensory Testing

Pressure Pain Threshold- Pressure Pain Threshold was delivered with a pressure algometer (1cm diameter probe, Medoc, Israel), to the lower dominant leg (tibialis anterior muscle). The increase rate was 60 kilopascal (kPa). The participants were instructed to press a button once the sensation of pain was experienced, and the force at the pain threshold was recorded.

Conditioned Pain Modulation – Two CPM paradigms were collected. The paradigms differed in the modality of the test stimulus. Since CPM responses evoked using different test stimulus measures do not correlate with each other and may represent different inhibitory mechanisms ^{1, 2}, we included both CPM results.

The test stimuli were 1) tonic heat stimulus (delivered to the lower dominant leg for 30 seconds at an intensity of 46.0°C), and 2) pressure pain thresholds. The conditioning stimulus was cold-water immersion of the non-dominant foot into a cold-water bath (8°C) for 60 seconds. The test stimuli were delivered alone and then concurrently with the conditioning stimulus. The CPM was repeated three times. For this analysis, only the first CPM repetition from each paradigm was included.

Pain ratings of cold-water immersion- Participants rated pain intensity and pain unpleasantness from the conditioning stimulus after 20 seconds of immersion using a mechanical visual analog scale (VAS).

Study 2

This study was conducted in healthy adolescents at Cincinnati Children's Hospital. One female investigator conducted this study's visits. Full procedures for this study are described in ³.

Participants

Study inclusion criteria: 1) age 10-17 years old; 2) no chronic pain disorders; 3) no current use of opioids, antipsychotics, antimanic, barbiturates, benzodiazepines, muscle relaxants, sedatives, tramadol, nutraceuticals, SSRIs, SSNRIs; 4) no neurological or psychiatric diseases; and 5) not pregnant. Informed parental permission and participant

assent were obtained before study procedures began. The study was approved by the Cincinnati Children's Hospital Institutional Review Board (IRB).

Psychological Questionnaires

Participants completed the anxiety and depression adolescent instruments of The Patient-Reported Outcomes Measurement Information System (PROMIS®).

Quantitative sensory testing

Pressure pain threshold- Pressure was delivered to the trapezius with a pressure algometer (1cm diameter probe, Medoc, Israel). The pressure from the algometer was increased at a rate of 60 kilopascals (kPa) per second until the participant felt the first sensation of pain (i.e., threshold). Once the sensation of pain was experienced, the participants were instructed to press a button (at which time the pressure was removed from the trapezius), and the force applied at pain threshold was recorded (using kPa).

CPM- CPM paradigm was examined using pressure pain thresholds as the test stimulus and cold-water immersion for the conditioning stimulus. Participants were instructed to immerse their non-dominant foot into a cold-water bath (8°C) for up to 60 seconds. Pressure pain thresholds was delivered alone and concurrently during the last 30 seconds of the conditioning stimulus.

Pain ratings of cold-water immersion- Participants rated pain intensity and unpleasantness from this stimulus after 20 seconds of immersion using a VAS.

Study 3

This study was conducted in healthy adolescents at Cincinnati Children's Hospital. One male investigator and one female investigator conducted this study's visits.

Participants

Study inclusion criteria: 1) age range between 12-17, 2) not diagnosed with autoimmune disease, 3) no current cold or flu symptoms, 4) no uncontrolled diabetes, 5) no recent surgery or injury requiring hospitalization (< 6 weeks), 6) no developmental delays, neurological disorders or uncontrolled psychological disorders, 7) no use of opioids, and 8) no diagnosed pain conditions. Cincinnati Children's Hospital Medical Center Institutional Review Board approved all study procedures. Parents or guardians of participants gave written informed consent, and participants gave assent stating they understood that they would experience pressure and cold stimuli, that the experimental procedures were clearly explained, and that they could withdraw at any time without prejudice.

Psychological Questionnaires

Participants completed the PROMIS Anxiety measure for adolescents and PROMIS Depression measure for adolescents, as well as the Pain Catastrophizing Scale for Children (PCS-C).

Quantitative Sensory Testing

Pressure Pain Thresholds- Two PPT trials were completed at the forearm or the trapezius in a counterbalanced order: forearm first for participants with an even ID number and trapezius trials first for participants with odd ID number. Participants were asked to press a button and say the word "pain" out loud when they first experienced a painful sensation from the pressure. In each trial there were three PPT repetitions. The PPT value was based on the average of the last two repetitions.

Conditioned Pain Modulation – Two CPM paradigms were collected. The paradigms differed in the location of the test stimulus. Since CPM responses evoked using different test stimulus measures do not correlate with each other and may represent different inhibitory mechanisms ^{1, 2}, we included both CPM results.

The test stimuli were 1) PPT at the forearm and 2) PPT at the trapezius. The conditioning stimulus was cold-water immersion in which participants submerged their dominant hands in a circulating water bath (10°C) up to wrist level for a total submersion time of around 60 seconds. In order to prevent a boundary layer of warmth from forming around the hand, participants were asked to keep their fingers spread apart while in the water.

Pain ratings of cold-water immersion- The Cold Pressor test was performed twice (for the two CPM paradigms). For the current analyses, pain ratings from only the first Cold Pressor test were included. After 20 seconds of submersion, participants provided a rating of cold pain intensity and unpleasantness on a Visual Analogue Scale.

Study 4

This study was conducted in healthy adults at Cincinnati Children's Hospital. One male investigator and two female investigators conducted this study's visits.

Participants

Study inclusion criteria: 1) age 14-44, 2) good general health, 3) able to undergo an MRI scan, 4) no psychiatric or neurological conditions, 5) no medications which may alter pain sensitivity or brain activity, 6) not pregnant, 7) no history of chronic pain conditions, 8) not diabetic, 9) no skin conditions/damage on arms or legs near sites of sensory

testing. This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center. Written, informed consent was obtained from all adult participants, and for the one adolescent in the study the participants' parent or guardian provided consent and the adolescents provided assent.

Psychological Questionnaires

Participants completed the Spielberger State-Trait Anxiety Inventory and Beck Depression Inventory-II.

Quantitative Sensory Testing

Cold pain tolerance- Assessed by having participants immerse one hand in a cold (4°C) water bath. Tolerance was defined by the time of hand withdrawal. VAS ratings of pain intensity and pain unpleasantness were recorded upon hand withdrawal. Limb immersion in the cold-water bath was terminated after 120 seconds if participants did not withdraw their hand before then.

Conditioned Pain Modulation – The test stimulus was a tonic heat stimulus delivered to the ventral forearm for 30 seconds at an intensity of 48.0°C. Real time pain intensity ratings were obtained using a computerized VAS. The conditioning stimulus was immersion of the foot into a cold-water bath (8°C) for 60 seconds. The test stimulus was delivered alone and then concurrently with the conditioning stimulus.

Pain ratings of cold-water immersion- VAS ratings of pain intensity and pain unpleasantness were recorded at the end of the cold pain tolerance test and upon hand withdrawal.

Study 5

This study was conducted in healthy adults at Cincinnati Children's Hospital. Three male investigator and two female investigators conducted this study's visits.

Participants

Study inclusion criteria: 1) age 14-44, 2) good general health, 3) able to undergo an MRI scan, 4) no psychiatric or neurological conditions, 5) no medications which may alter pain sensitivity or brain activity, 6) not pregnant, 7) no history of chronic pain conditions, 8) not diabetic, 9) no skin conditions/damage on arms or legs near sites of sensory testing. This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center. Written, informed consent was obtained from all adult participants, and for the seven adolescents in the study the participants' parent or guardian provided consent and the adolescents provided assent.

Psychological Questionnaires

Participants completed The Patient-Reported Outcomes Measurement Information System (PROMIS®) adult or adolescent anxiety, depression, and Pain Catastrophizing Scale.

Quantitative Sensory Testing

Cold pain tolerance- Assessed by having participants immerse one hand in a cold (4°C) water bath. Tolerance was defined by the time of hand withdrawal. Limb immersion in the cold-water bath was terminated after 120 seconds if participants did not withdraw their hand before then.

Conditioned Pain Modulation – The test stimulus was a tonic heat stimulus delivered to the ventral forearm for 30 seconds at an intensity of 48.0°C. Real time pain intensity

ratings were obtained using a computerized visual analog scale, which ranges between “no pain sensation” and “most intense pain imaginable”. The conditioning stimulus was immersion of the foot into a cold-water bath (8°C) for 60 seconds. The test stimulus was delivered alone and then concurrently with the conditioning stimulus.

Pain ratings of cold-water immersion- VAS ratings of pain intensity and pain unpleasantness were recorded at the end of the cold pain tolerance test and upon hand withdrawal.

Study 6

This study was conducted in healthy adults at Cincinnati Children’s Hospital. One male investigator conducted this study’s visits. Full procedures for this study are described in 4.

Participants

Participants were recruited from Cincinnati Children’s Hospital and the surrounding area using print and social media. Study inclusion criteria were: 1) age 18-50, 2) English-speaking, 3) no cancer treatment in the past year, 4) not diagnosed with or in current treatment for diabetes, thyroid disorder, cardiovascular disorder, hypertension, pulmonary disease, or neurological disorder, 5) no psychiatric disorder requiring hospitalization in the past year, 6) not pregnant, 7) not using opioids, and 8) no hospitalizations or surgeries in the last 6 months. This study was approved by the Institutional Review Board at Cincinnati Children’s Hospital Medical Center.

Psychological Questionnaires

Participants completed the PROMIS depression, PROMIS anxiety, and Pain Catastrophizing Scale.

Quantitative Sensory Testing

Pressure Pain Threshold— Pressure was delivered with a pressure algometer (1cm diameter probe, Medoc, Israel), which was delivered to the forearm. The pressure from the algometer was gradually increased until the participant felt the first sensation of pain (e.g., threshold). Once the sensation of pain was experienced, the participants were instructed to press a button, and the force applied at pain threshold was recorded (using kPa).

Study 7

This study was conducted in healthy adults at Wake Forest University School of Medicine. One female investigator conducted this study's visits.

Participants

Study inclusion criteria: 1) no history of chronic pain conditions, 2) no chronic disease conditions, diabetes, or psychiatric or neurological disorders, 3) no current medication use, 4) BMIs <25 or <29.9 kg/m². Participants gave written informed consent stating they understood that they would experience painful thermal stimulation, that the experimental procedures were clearly explained, and that they could withdraw at any time without prejudice. Wake Forest University School of Medicine Institutional Review Board approved all study procedures.

Psychological Questionnaires

Participants completed the Spielberger State-Trait Anxiety Inventory and Beck Depression Inventory-II.

Quantitative sensory testing

Cold pain tolerance- Participants submerged their left hands in an ice water bath (0-2°C) up to wrist level for 120 seconds or until pain tolerance occurred. In order to promote circulation and prevent a boundary layer of warmth from forming around the hand, participants were instructed to continuously open and close their hands for the duration of the test. In addition, participants were instructed to notify the experimenter when they first felt pain and to remove their hand when they could no longer tolerate the pain. The duration of submersion before the participant removed their hand was recorded as tolerance.

Pain ratings of cold-water immersion- VAS ratings of pain intensity and unpleasantness were collected at termination of the cold pain tolerance test.

Study 8

This study was conducted in healthy adults at the University of Kentucky. One male investigator conducted this study's visits. Full procedures for this study are described in

5.

Participants

Participants were recruited from the undergraduate population at the University of Kentucky using the psychology subject pool which assigns course credits for participating in research. Study inclusion criteria: 1) age 18 or older, 2) no history of chronic pain disorders, 3) no neurodegenerative, stroke, psychiatric, or neurological

disorders, 4) no current psychotropic, statin, blood pressure or pain medication, including over-the-counter pain medications in the past 24 hrs., and 5) no current pain (i.e., answer of 0 on a 0-5 scale to the question of current pain). This study was approved by the Institutional Review Board at the University of Kentucky. Participants provided signed informed consent before participating in the study.

Psychological Questionnaires

Participants completed the Pain Catastrophizing Scale.

Quantitative Sensory Testing

Pressure Pain Threshold Ratings - An experimenter placed the participant's intermediate phalange of the ring finger of their nondominant hand in a pressure algometer with a 1 cm diameter tip and applied pressure at a steady rate of approximately 30 kPA/sec. Participants were given a trigger to hold in their dominant hand and were instructed to press the trigger when the pressure first turned to pain. Three consecutive ratings spaced 5 sec apart were taken for each participant and averaged to improve reliability.

Conditioned Pain Modulation – A subset of the sample (N = 91 with complete psychological and pain data) were asked to additionally complete a conditioned pain modulation test. The test stimulus was pressure pain threshold and the conditioning stimulus was cold water immersion. Participants were asked to place their nondominant foot in a circulating ice bath of 4.4°C water. After 20 seconds of their foot being in the water, they provided three additional pressure pain thresholds using the procedures described above.

Pain ratings of cold-water immersion- Participants were asked to rate their pain intensity using verbal numerical pain scale at the end of the conditioning stimulus.

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Anxiety

Depression

Pain Catastrophizing

PPT

CPM

CP Tolerance

CP Intensity

CP Unpl.