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REVIEW

A systematic review of structural and functional MRI studies on pain catastrophizing

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Objectives: Pain catastrophizing is reliably associated with pain reports during experimental pain in healthy, pain-free subjects and in people with chronic pain. It also correlates with self-reports of clinical pain intensity/severity in a variety of disorders characterized by chronic pain in adults, adolescents and children. However, processes, through which it exerts its effects are yet unclear. In this paper, our primary aim was to synthesize neuroimaging research to open a window to possible mechanisms underlying pain catastrophizing in both chronic pain patients and healthy controls. We also aimed to compare whether the neural correlates of pain catastrophizing are similar in these two groups.

Methods: PubMed and the Web of Science were searched for magnetic resonance imaging (MRI) studies that explored neural correlates of pain catastrophizing.

Results: Twenty articles met the inclusion criteria. The results of our review show a connection between pain catastrophizing and brain areas tightly connected to pain perception (including the somatosensory cortices, anterior insula, anterior cingulate cortex and thalamus) and/or modulation (eg, the dorsolateral prefrontal cortex). Our results also highlight that these processes - in relation to pain catastrophizing - are more pronounced in chronic pain patients, suggesting that structural and functional brain alterations (and perhaps mechanisms) related to pain catastrophizing may depend on prior and/or relatively stable/constant pain experience. However, we also found methodological issues and differences that could lead to divergent results.

Discussion: Based on our results, pain catastrophizing might be related to salience detection, pain processing, and top-down attentional processes. More research is recommended to explore neural changes to specific types of catastrophizing thoughts (eg, experimentally induced and/or state). Furthermore, we provide ideas regarding pain catastrophizing studies in the future for a more standardized approach.

Keywords: pain catastrophizing, DLPFC, anterior insula, chronic pain, neuroimaging

Introduction

Among cognitive factors, pain catastrophizing, defined as a tendency to magnify and ruminate about pain and having a helpless attitude toward actual or anticipated pain,[1] is reliably associated with pain reports during experimental pain in healthy pain-free subjects and in people with chronic pain.[2] Pain catastrophizing affects not just the actual experience of painful stimuli, but it can bias pain recall[3] even several months after surgery.[4]

Pain catastrophizing has been demonstrated to be associated with self-reports of clinical pain intensity/severity in a variety of disorders characterized by chronic pain in adults, for instance in rheumatic diseases,[5] in low back pain,[6] in headache[7]

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and in children and adolescents.[8,9] Pain catastrophizing is also associated concurrently and prospectively with pain reports or self-reports of consequences of chronic pain – eg, with disability in migraine[10,11] and in rheumatic diseases,[5] loss of work in low back pain[12] and medication consumption in chronic musculoskeletal pain.[13] In addition, pain catastrophizing is suggested to have a prognostic value in the maintenance of pain and in the development of chronic pain[14,15] and has also been demonstrated to influence the success of pharmacological and psychosocial treatments of chronic pain.[16–18]

While pain catastrophizing is associated concurrently and prospectively with pain reports or self-reports of consequences of chronic pain (see above), its relationship with pain threshold is contradictory.[19–22] Studies on nociceptive flexion reflex threshold (NFR), as an indirect index for spinal nociceptive processing,[23] consistently reported no relationship between NFR and pain catastrophizing either in healthy subjects[19,24,25] or in chronic pain patients.[21,26] Based on these results the question is whether pain catastrophizing simply affects verbal reports of pain, or exerts an influence also on neurobiological (supraspinal) processes to noxious stimuli. Therefore, it is important to identify the mechanisms by which catastrophizing may influence pain perception. Convergent evidence from experimental studies targeting attentional processes suggest that pain catastrophizing may modulate top-down attentional processes, which results in a deficit in attentional disengagement from pain-related information.[27–30]

Neuroimaging has begun to provide evidence that pain-related brain activity is related to pain catastrophizing. The first study that demonstrated that pain catastrophizing relates to pain processing was done in fibromyalgia (FM),[31] and then this question was tested in other chronic pain samples and in healthy samples as well. In this paper, our primary aim was to synthesize neuroimaging research to open a window to possible mechanisms underlying pain catastrophizing.

Since pain catastrophizing shows a robust association with perceived/self-reported pain (see above), brain areas implicated in pain perception – especially in the sensory aspect (such as somatosensory areas (both primary, S1 and secondary, S2), posterior insula (pINS), thalamus) and affective/emotional aspect (anterior cingulate cortex (ACC) and anterior insula (aINS)) of pain perception[32,33] – were expected as correlates of pain catastrophizing.

Based on experimental studies,[28–30] individual differences in trait pain catastrophizing are thought to modulate the activity of brain areas involved in selective attention. Attentional processing of salient (eg, emotional) information has been proposed to evoke dorsolateral prefrontal cortex (DLPFC) activity,[34,35] supported also by the evidence on non-invasive brain stimulation applied over the DLPFC.[36] If pain catastrophizing acts as an attentional modulation, then it is logical to hypothesize that dorsolateral prefrontal cortex has a role in this process. In addition, DLPFC – as a functionally heterogeneous brain area – has been implicated in the processing of painful stimuli,[37] especially in processing the non-spatial sensory information – such as intensity – of painful stimuli.[38] DLPFC also plays a role in pain modulation: involvement of this area in the descending modulation of pain might be exerted via attentional and other cognitive control processes.[39] Therefore, it is a plausible hypothesis that activity of the DLPFC is related to pain catastrophizing.

To investigate potential mechanisms underlying pain catastrophizing, it is essential to address whether the neural correlates of pain catastrophizing are similar among pain-free controls and among chronic pain patients. It is important to note that chronic pain is considered to be associated with alterations in gray matter (GM) and in functional connectivity (FC).[40] In addition, prospective studies suggest that structural and functional connectivity in cortico-limbic circuitry predict risk for chronic pain,[41–43] indicating that representation of chronic/clinical pain differ from that of acute pain.[44,45] These findings corroborate our notion that neural correlates of pain catastrophizing might depend upon the presence of chronic pain.

In 2017 Malfliet et al published a systematic review on brain changes associated with cognitive and emotional factors in chronic pain. In that paper,[46] pain catastrophizing was also addressed, but our review differs from that article at least in four important ways. Firstly, our starting point was pain catastrophizing (and not chronic pain as it was in Malfliet et al's review), and we aimed to reveal potential mechanisms underlying pain catastrophizing. Therefore, as a second difference, we also included studies that exclusively used a healthy control group, and thirdly, since several papers found that pain catastrophizing is an important factor in migraine-related disability,[10,11,47,48] we also included studies with migraine patients (both type of studies were excluded from Malfliet et al's review). Migraine is characterized by recurrent headaches with moderate or severe pain[49] and it has been proposed to be associated with similar structural and functional neural changes identified in other chronic pain populations.[50]

Therefore, our decision was to include studies with migraine patients as well. Fourthly, in our review we aimed to compare whether the neural correlates of pain catastrophizing are similar among pain-free controls and among chronic pain patients.

Summarizing and highlighting the overall goals (based on the PICO framework): the aim of the study was to answer what the neural correlates (O; Outcome) of pain catastrophizing (E; Exposure) are among chronic pain patients and/or pain-free control subjects (P; Population). We also aimed to review correlates of pain catastrophizing in pain patients compared to pain-free healthy controls (C; Comparator). Regarding study design, we included cross-sectional studies and those treatment studies which measured changes in catastrophizing along with changes in structural and/or functional neural changes (S; Study design) measured with magnetic resonance imaging (MRI) (I; diagnostic instrument).

Materials and methods

Study selection

The articles we used were selected from PubMed and the Web of Science – as they include several databases – after a thorough search. To identify the papers, we searched with the following key search terms in titles and abstracts: pain catastrophizing AND (brain activity OR neuro imaging OR imaging OR MRI OR magnetic resonance imaging) and also checked the identified references of the reviews and included studies.

The inclusion criteria were (1) articles published in English (2) between 2004 and 2016 (the last search was conducted on September 1, 2016), which used (3) the Pain Catastrophizing Scale (PCS)[51] or the catastrophizing subscale of Coping Strategies Questionnaire (CSQ)[52] (E: Exposure) as these are the most often used self-report measures of pain catastrophizing.[53] Other inclusion criteria were to (4) measure pain catastrophizing on a sample size of at least 12 adult participants – according to Desmond and Glover[54] – diagnosed with some type of chronic pain or who were pain-free controls (P: population) and (5) report any correlation between MRI data (I: diagnostic instrument) and the catastrophizing scales (O: outcomes). We included treatment studies as well if they reported any relationship (r or t/z scores reported) between changes in pain catastrophizing and any changes in GM or in connectivity and/or activity of any brain areas.

Screening, identification and eligibility (as seen on Figure 1) were conducted by two independent researchers (A.G. and Z.N.) with the initial level of agreement of 97%.

With this method we found 419 articles from which 40 were duplicated. We further discarded most of the articles (333) as they were not eligible based on the title and abstract. From the remaining 46 articles, after full text analysis, an additional 26 were discarded as they were reviews, meta-analyses or did not investigate the connection between one of the pain catastrophizing scales and the neural activity measured by magnetic resonance imaging (either structural or functional [fMRI]) techniques (see in Appendix S1). Thus, 20 articles remained and were reviewed. The process, which was based on the PRISMA protocols, is shown on Figure 1.

Data extraction

Sample characteristics (size, mean age), group characteristics (whether there were chronic pain and control groups), the used questionnaires and imaging methods, confounding variables and the reported statistical thresholds (see Table 1) along with the main findings were extracted (see Table 3). In the case of task-based studies, we also recorded the type of the pain task, the modality of the painful stimulus and the body part it was given on, and also pain intensity and whether participants had to rate pain during the scan (see Table 4 for detailed information). The identification and selection of the articles were conducted by A.G. and Z.N. Data extraction from the included articles were done by A.G., Gy.K. and A.E.É. After this process, Gy.K. and N.K. thoroughly reviewed the extracted data before A.G. and E.Sz. did the risk of bias evaluation (for details, see the next section).

Data synthesis

We have focused on the data in line with our aims: we checked whether the authors compared a chronic pain group with healthy controls or just used one group. If they used multiple groups, we checked whether they reported results in both groups or only for one group. If they reported results for both groups, we checked what were the similarities and differences. With task-based studies we focused on the chosen pain task, pain intensity and the place of the stimuli.

Risk of bias

The risk of bias tool used here was based on the work of different authors.[56–58] We utilized the relevant parts of widely used evaluating tools but added important (but interestingly not studied so far) new items: we

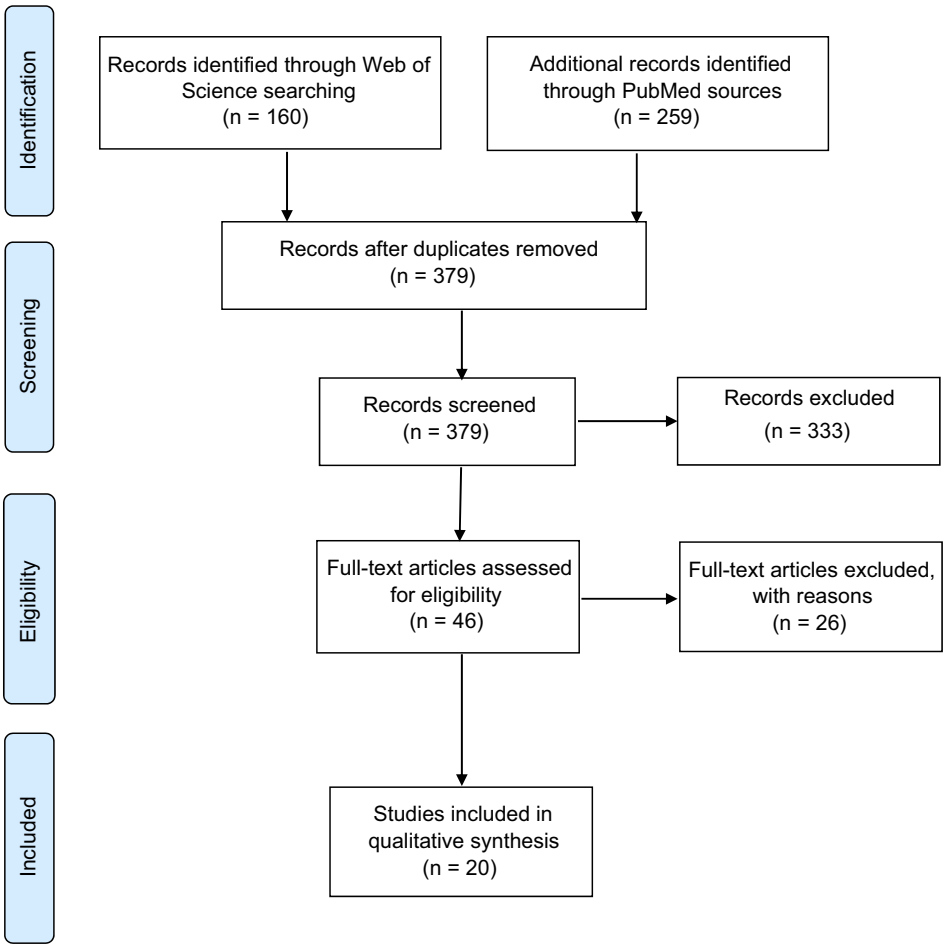

Figure 1 Flowchart: Selection process. Adapted from Moher D, Liberati A, Tetziaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med*. 2009;6(6):e1000097.[55]

checked for sampling method, response rate and study design, but also monitored for MRI task instructions, MRI data quality checks, used and reported thresholds (as a family wise error/false discovery rate (FWE/FDR) corrected analysis is much stronger than one with an uncorrected *p*-value) and reported outcomes (for a detailed description, see Appendix S2). We also checked for response rate and drop out rate, and although usually in smaller, cross-sectional studies it is not reported, we think that it is an important component of a study's strength. We used a simple "yes/no/unclear/not applicable" evaluation system – based on Armijo-Olivo et al's work[56]- with small exceptions (eg, at study design, percentage of response rate or the used thresholds). The more "yes" responses a study had, the stronger it was (or the lower its risk of bias was).

With this method, we obtained seven major categories (Selection bias, Study design, Detection bias, Data collection and quality check, Drop-out rate described, Confounding variables controlled for and Reporting bias). To compute the category ratings, we used the Effective Public Health Practice Project's evaluation system,[56] where categories can be marked as strong, moderate or weak. We checked the yes/no/unclear ratio in every category and marked them as weak if there were more no and unclear ratings than "yes" ratings, moderate if the yes/no/unclear ratio was equal and strong if it only had clearly reported values. Global ratings were computed as weak if there were two or more categories marked as weak, moderate with only one weak category and strong with no weak ratings.

In our system, two categories were measured with greater weight: the controlling of confounding variables and the reported threshold. With reported thresholds, we marked a study as weak if the reported threshold was uncorrected or was not reported at all. The rating was moderate if the authors controlled for multiple testing (FDR or FWE correction) but left out z or r or F or

t scores or did not report every result set out in the aim of the study. Although threshold reporting varies greatly in neuroimaging literature and stricter standards on this reporting have only been in place in very recent years, we think that it should be taken into account while evaluating the risk of bias of former neuroimaging articles as well; therefore, we decided to apply this category.

Pain catastrophizing, depression, anxiety and fear of movements are correlated significantly; however, a number of studies suggested that pain catastrophizing is a distinct construct and has a unique effect on experienced pain intensity beyond and above depression,[59] neuroticism,[60] anxiety,[9] and fear of pain.[61] Therefore, in our systematic review we aimed to record whether confounding variables were controlled for in (MRI) studies, although we did not examine these variables separately, only checked whether they were taken into account in the studies. We rated the article as weak if there was nothing reported, moderate if the authors controlled for either task (eg, age for GM studies), group comparison or catastrophizing (eg, depression, neuroticism) relevant variables, and strong if the authors controlled for both task/group (if relevant) and catastrophizing relevant variables.

Selective reporting within studies – eg, presenting neural correlates of pain catastrophizing only in the patient group without explicitly stating whether it was tested in the control group – may bias the results or possible interpretation of the findings; therefore, we emphasized it in reporting the main findings (see Table 3). Similarly, we checked whether there were any fMRI studies in the excluded studies that used PCS, but did not use it in the analyses as a covariate.

Results

Study characteristics

From the 20 studies, we found that five studies used anatomical scan and then analyzed the data with voxel-based morphometry (VBM) or cortical thickness analysis or surface based analysis,[62–66] one study used quantitative arterial spin labelling (qASL)[67] and five studies used resting state fMRI measures.[63,64,68–70]

Ten studies used a task during the fMRI scan.[31,71–79] With four exceptions[31,66,71,75] the studies used the PCS to measure pain catastrophizing.

From the studies we identified, twelve used a case-control study design,[62–65,68,69,71–73,75,78,80] two used cohort-analytic design,[66,76] five used observational study design,[31,67,74,77,79] and one study used a randomized controlled trial.[70]

For evaluating the neural correlates of catastrophizing, the effect of potential confounds (eg, depressive mood, anxiety or neuroticism) are suggested to be controlled for. From the 20 studies selected for our review, only four studies controlled clearly for depression and/or anxiety/neuroticism when pain catastrophizing was entered in the analysis.[31,66,79,80] The included studies and their characteristics are presented and summarized in Table 1.

Participants

Apart from three studies, which only examined healthy controls,[67,74,79] all studies used a chronic pain population. Six studies examined fibromyalgia patients,[31,63,70,71,77,80] in two, the focus was on irritable bowel syndrome (IBS),[62,73] in another two, subjects with migraine participated[64,78] and there were those who studied provoked vestibulodynia (PVD),[65] osteoarthritis (OA),[72] localized provoked vulvodynia (LPVD)[68] or chronic pain connected to muscles, temporomandibular disorder (TMD)[69] or chronic low back pain.[75,76] One study made a mixed group from different chronic pain patients (low back pain, myofascial pain syndrome, headache, fibromyalgia, upper body, pelvic floor).[66]

Mean age of chronic patient groups (with one exception[65]) was above or exactly 30,[62,68,69,73] and in most cases above 40,[31,63,64,66,70–72,75–78,80] with three studies using chronic pain patients with a mean age of 50, 51 and 62.[66,71,72] In the three studies which only examined healthy controls,[67,74,79] the mean age was between 25 and 35.

Seven studies examined structural and functional correlates of pain catastrophizing on a female sample[62,63,65,68,69,71,73] while 13 articles used mixed samples with female majority (for detailed info, see Table 1).[31,64,66,67,70,72,74–80]

The average sample size was 19 participants in the chronic pain groups (ranging from 11 to 58) and 15 in the control groups (between 11 and 34) in the studies we found, which is in line with studies concerning mean sample size in fMRI studies[54,81]

Risk of bias and level of evidence

Evaluation was made by two independent researchers (A.G. and E.Sz.) with 84% initial agreement, consensus was achieved through either discussing the interpretation

Table 1 Studies included in the systematic review. Statistical thresholds as reported in the studies

Study (first author)	Sample (N)	Mean age (SD)	Measurement	Study Methods	Controlled for	Statistical thresholds
Schweinhardt[65]	14 PVD patients and 14 healthy controls (all female)	Patient: 25.7 (5.1) Control: 25.6 (6.0)	PCS	Structural	Age	$p<0.05$ cluster level correction
Blankstein[62]	11 IBS patients and 16 healthy controls (all female)	Patient: 30.2 (8.5) Control: 31.5 (9.4)	PCS	Structural	Age	VBM: $p<0.05$ FDR correction CTA: $p<0.05$ corrected for multiple comparison
Ceko[63]	28 FM patients and 28 healthy controls (all female)	Patient: 48.7 (7.8) Control: 48.8 (7.7)	PCS	Structural and resting state	Separately analyzed two age groups; pain duration	Cluster-corrected for multiple comparisons at $p<0.05$
Seminowicz[66]	13 chronic pain patients and 13 age-matched healthy controls (3–3 males)+10 healthy controls (4 males)	Patient: 51.4 (11.8) Control: 51.6 (11.9)	CSQ	Structural CBT intervention	Repeated analysis with depression or changes in depression did not alter the results	$p<0.05$ FWE cluster level correction
Hubbard[64]	17 migraine patients (13 females and 4 males) and 18 healthy controls (14 females and 4 males)	Patient: 41.7 (12.2) Control: 38.8 (11.2)	PCS	Structural and resting state	Age	$p<0.05$, cluster level correction
Henderson[67]	34 healthy subjects in two studies: 17 in study 1 (6 males and 11 females) and 19 in study 2 (12 males and 7 females), 2 subjects completed both	Control: 26.2 (2.3) in study 1, 34.7 (2.4) in study 2	PCS	fMRI - qASL	Age and gender as nuisance variables	$p<0.05$ cluster level correction
Kucyi[69]	17 TMD and 17 healthy controls (all female)	Patient: 33.1 (11.9) Control: 32.2 (10.2)	PCS	Resting state	(Repeated analysis using head motion)	$p<0.05$ cluster level correction and FWE correction
Gupta[68]	29 LPVD, 29 IBS and 29 healthy controls (all female)	LPVD: 30.31 (6.79) IBS: 30.31 (6.8) Control: 30.31 (6.8)	PCS	Resting state	Depression and anxiety (in disease-related group comparison, but it is unclear whether they were controlled for when the effects of PCS were tested in LPVD subjects)	$p<0.05$ FWE correction
Lazaridou[70]	16 FM patients (3 males and 13 females)	Patient: 45.7 (12.2)	PCS	Resting state CBT intervention	-	$p<0.05$ cluster level correction and FWE correction

(*Continued*)

Table 1 (Continued).

Study (first author)	Sample (N)	Mean age (SD)	Measurement	Study Methods	Controlled for	Statistical thresholds
Gracely[31]	29 FM patients (19 females and 10 males)	Patient (low)*: 44.6 (8.8) Patient (high): 38.9 (10.6)	CSQ	fMRI – task based	Depression	Unclear (we found in their study's Table 4 that authors corrected for multiple comparisons, a z score of 3.5 corresponded to a *p*-value of 0.05. z scores of>3.5 were determined significant activation in a region)
Seminowicz[79]	22 healthy controls (10 males and 12 females)	Control: 25.0 (4.0)	PCS	fMRI – Task based	Neuroticism, pain intensity	$p<0.001$ FDR correction
Lloyd[75]	28 chronic low back pain patients (in the original sample, the ratio is not clear after excluding 2 participants) and 17 healthy controls (8 males and 9 females)	Patient: 45.0 (12.2) Control: 31.0 (8.1)	CSQ	fMRI – Task based	-	$p<0.05$ multiple comparison corrected
Burgmer[71]	12 female FM patients and 14 healthy female controls	Patient: 50.1 (7.3) Control: 46.9 (6.8)	CSQ (trait and state versions)	fMRI – Task based	Anxiety and depression, (but it is unclear whether they were controlled for when the effects of PCS were tested)	$p<0.05$ cluster level correction
Lin[74]	15 healthy controls (6 males and 9 females)	Control: 26.3 (11.2)	PCS	fMRI – Task based		$p<0.05$ FWE correction
Hiramatsu[72]	12 OA patients (9 females and 3 males) and 11 healthy controls (8 females and 3 males)	Patient: 62.7 (5.7) Control: 56.4 (7.3)	PCS	fMRI – Task based	-	$p<0.001$ uncorrected
Hubbard[73]	14 healthy female controls and 15 female IBS patients	Patient: 31.0 (11.96) Control: 31.0 (10.91)	PCS	fMRI – Task based	-	$p<0.05$ FWE corrected
Lloyd[76]	29 nonspecific low back pain patients (16 males and 13 females)	Patient: 45.0 (12.4)	PCS	fMRI – Task based	Fear avoidance beliefs, anxiety and depression in group comparison, but not in analysis using PCS as a covariate	$p<0.05$ cluster level correction
Loggia[77]	31 FM patients (27 females 4 males)	Patient: 44.0 (11.9)	PCS	fMRI – Task based	-	$p<0.05$ cluster level correction
Kim[80]	35 FM patients (32 females and 3 males) 14 healthy controls (10 females and 4 males)	Patient: 44.9 (12) Control: 44.2 (14.2)	PCS	fMRI – Task based and resting state	Depression	$p<0.05$ cluster level correction
Mathur[78]	14 migraine patients (11 females 3 males) and 14 healthy controls (11 females and 3 males)	Patient: 40.8 (11.9) Control: 38.9 (12.5)	PCS	fMRI – Task based	-	$p<0.05$ cluster level correction and FWE correction

Note: *They compared low and high catastrophizing patient groups.

Abbreviations: SD, standard deviation; PVD, provoked vestibulodynia; VBM, voxel-based morphometry; PCS, Pain Catastrophizing Scale; CSQ, Coping Strategies Questionnaire; IBS, irritable bowel syndrome; FM, fibromyalgia; OA, osteoarthritis; qASL, quantitative arterial spin labelling; TMD, temporomandibular disorder; LPVD, localized provoked vulvodynia; CTA, cortical thickness analysis; CBT, cognitive-behavioral therapy.

of criteria again or involving a third independent reviewer (Gy.K.).

Overall, global rating was strong only in one study, while the others were rated as moderate (nine studies) or weak (10 studies); see the detailed list in Table 2. Most of the studies lacked an adequate description of subject selection procedure and/or drop-out rates. Similarly, many studies did not account for possible confounders even in group comparisons and/or in determining the neural correlates of pain catastrophizing.

Main findings

The individual results of every article reviewed here can be found in Table 3.

Studies focusing on GM alterations

Five studies[62–66] analyzed the GM alterations in healthy and clinical subjects in correlation with pain catastrophizing (see Table 3). One of the five studies was a non-randomized, not fully controlled study that investigated the effect of cognitive behavioral therapy (CBT) interventions only in a chronic pain sample.[66] The other four studies involved a patient group with pain symptoms and a pain-free control group as well. Interestingly, in most of the studies, only female subjects were scanned and in the two mixed sample studies, females were in the majority.

Since age is associated with GM volume (GMV), taking into account its effect is important when analyzing brain structural changes. Age was controlled for in the analysis only in three studies,[62,64,65] while in one study,[63] participants were assigned to different groups based on their age (younger and older participants' group). One study[63] (see Table 1) used pain duration as a confounding variable in the analysis and another study[64] reported a negative association between disease duration and the morphology of DLPFC in migraine.

To conclude, two studies[62,64] demonstrated a significant association between pain catastrophizing and DLPFC GM morphology. Both studies found an opposite relationship between DLPFC GMV/cortical thickness and pain catastrophizing according to the study groups: in patient groups the correlation was negative, while in pain-free controls, it was positive. In the migraine study,[64] this opposite relationship also emerged for other structures implicated in pain perception, including the S1, anterior midcingulate cortex (aMCC), and prefrontal cortices. Similar to the two mentioned studies, a negative correlation was also found, in fibromyalgia patients, between pain catastrophizing and GM density of aINS implicated in pain perception.[63] It is worth mentioning that the results of the treatment study[66] also confirmed that changes in morphology of brain areas involved in pain perception (insula, ACC, S1, prefrontal cortex) and/or modulation (DLPFC) is associated with changes in pain catastrophizing. The level of evidence was moderate in four studies and was weak in one case.[65] (for details, see Table 2)

Functional connectivity results: studies using resting state measures

In resting state studies, either connections of areas involved in pain perception (aINS or S1) or connections of default mode network (DMN) were tested, mainly based on theoretical consideration. According to the results, pain catastrophizing might be related to enhanced functional connectivity (FC) among areas playing a role in pain perception (S1, aINS, thalamus)[63,64,70,80] or to enhanced connectivity within the DMN (mPFC-posterior cingulate cortex (PCC)/precuneus)[69] or between the DMN and descending pain modulatory system, including the DLPFC,[64] periventricular gray (PVG)/PAG.[69] Connectivity between the DMN and areas involved in pain perception (such as the medial thalamus)[69] was also related to pain catastrophizing in patients (see Table 3).

Generally speaking, in the control group there was no association between FC of pre-defined seeds and pain catastrophizing or there was no explicit information about it. However, one study[64] yielded an interesting result: resting state functional connectivity (rsFC) between PCC and DLPFC was related positively to pain catastrophizing in migraine, but the association was negative in controls.

Studies reviewed in this section did not control for any confounding variables (or at least it is unclear whether they were controlled for in the analysis using pain catastrophizing scores). The level of evidence was moderate in three cases[63,64,68] and weak in two.[69,80] (for details see Table 2)

Task-based activations connected to pain catastrophizing

Ten studies (see Tables 3 and 4) used a pain task to observe the effects of pain catastrophizing (although Kim et al's study[80] used a pressure pain task, they were mainly interested in FC and not task evoked activation, thus we will not mention it in this part). From these 10 studies, three used only healthy controls,[67,74,79] three examined exclusively a patient group[31,76,77] and four compared

Table 2 The results of our risk of bias evaluation

Study (first author)	Selection bias		Study design	Detection bias				Data collection and quality check			Drop-out rate described	Confounding variables controlled for	Reporting bias			Global rating
	Sampling method	Response rate		Patient diagnosis	Control diagnosis	Matched groups	Baseline characteristics reported	Acquisition techniques clearly described	Task design clearly reported	Was data quality check reported?			Reported thresholds	Results clearly reported (with *r* or *z* scores)	Outcome reporting	
Blankstein[62]	Moderate		Moderate	Strong				Strong			Weak	Moderate	Strong			Moderate
Burgmer[71]	Moderate		Moderate	Strong				Moderate			Strong	Moderate	Strong			Strong
Ceko[63]	Weak		Moderate	Moderate				Moderate			Strong	Moderate	Moderate			Moderate
Gracely[31]	Weak		Moderate	Strong				Strong			Strong	Moderate	Weak			Weak
Gupta[68]	Moderate		Moderate	Strong				Strong			Weak	Moderate	Moderate			Moderate
Henderson[67]	Weak		Moderate	Strong				Strong			Weak	Moderate	Strong			Weak
Hiramatsu[72]	Weak		Moderate	Moderate				Moderate			Weak	Weak	Weak			Weak
Hubbard[64]	Moderate		Moderate	Moderate				Moderate			Weak	Moderate	Strong			Moderate
Hubbard[73]	Moderate		Moderate	Strong				Strong			Strong	Weak	Strong			Moderate
Kim[80]	Weak		Moderate	Strong				Strong			Weak	Moderate	Strong			Weak
Kucyi[69]	Weak		Moderate	Strong				Strong			Weak	Weak	Strong			Weak
Lloyd[75]	Weak		Moderate	Weak				Moderate			Strong	Weak	Strong			Weak
Lazaridou[70]	Weak		Strong	Moderate				Moderate			Strong	Weak	Strong			Weak
Lin[74]	Moderate		Moderate	Strong				Moderate			Strong	Weak	Strong			Moderate
Lloyd[76]	Weak		Moderate	Strong				Strong			Strong	Moderate	Strong			Moderate
Loggia[77]	Moderate		Moderate	Strong				Moderate			Moderate	Weak	Strong			Moderate
Mathur[78]	Moderate		Moderate	Strong				Moderate			Weak	Weak	Weak			Weak
Schweinhardt[65]	Weak		Moderate	Strong				Moderate			Weak	Moderate	Moderate			Weak
Seminowicz[79]	Weak		Moderate	Strong				Moderate			Weak	Strong	Strong			Weak
Seminowicz[66]	Weak		Moderate [++]	Moderate				Moderate			Strong	Strong	Strong			Moderate

For the global ratings (based on the work of Armijo-Olivo[60]) we checked the yes/no/unclear ratio in every category and marked them as weak if there were more "no" and "unclear" ratings than "yes" ratings; moderate if the yes/no/unclear ratio was equal, and strong if it only had "yes" ratings.

[++] case-control with intervention in patients

Table 3 Main findings of the articles reviewed here

Study	Brain analysis methods or events/tasks	Risk of bias	Main findings
Schweinhardt[65]	GM: VBM	Weak	• GMV correlated with vulvar pain catastrophizing in left parahippocampus (r=0.61) and left substantia nigra (r=0.54)
Blankstein[62]	GM: VBM and cortical thickness	Moderate	• Negative correlation (r=−0.66) between right DLPFC thickness and PCS scores in patients (opposite trend [r=0.41], though not significant in the control group)
Ceko[63]	GM: VBM and cortical thickness rsFC: seed based functional connectivity analysis	Moderate	• GM density in left aINS in younger FM patients correlated with PCS scores negatively (r=−0.54) • GM density of NAcc showed marginally significant negative correlation with catastrophizing in younger FM group (r=−0.49, p<0.1) • No correlation between GM density and pain catastrophizing in older patients • rsFC between dACC was related to PCS scores (r=0.59) in younger patients • rsFC between PCC and mPFC was not related to pain catastrophizing in older patients • No information on the association between rsFC and PCS in the control group
Seminowicz[66]	GM: VBM post CBT vs pre CBT GM in patients	Moderate	• ↓ catastrophizing and ↓ GM density in the right hippocampus and right DLPFC following CBT in patients • ↓ catastrophizing was associated with ↑ GM in the bilateral ACC/medial frontal gyrus, left DLPFC, left IFG, right PPC including S1 and S2
Hubbard[64]	GM: VBM and cortical thickness rsFC: seed based functional connectivity analysis	Moderate	• Negative association between PCS scores and cortical thickness in the left DLPFC (r=−0.70), left middle temporal gyrus (r=−0.53), right IFG (r=−0.74) in patients and positive correlation in controls (r=0.56, r=0.56 and r=0.53, respectively) • Negative associations between PCS and GMV in the left S1 (r=−0.72), left mPFC (r=−0.71), left aMCC (r=−0.43^{ns}) in patients and positive correlation in controls (r=0.64, r=0.23^{ns} and r=0.58, respectively) • Catastrophizing in patients correlated positively with rsFC between the aINS as a seed with left hippocampus (r=0.63), with bilateral thalamus (left r=0.70 and right r=0.63) and with left SMA (r=0.67) (these were negative in the control group: −0.59, −0.51, −0.77, −0.47, respectively) • For the PCC seed, catastrophizing correlated with enhanced rsFC between PCC and bilateral DLPFC in patients (left r=0.76, right r=0.63), while an inverse relation between pain catastrophizing and PCC - right DLPFC functional connectivity was found in the control group (r=−0.34)

(*Continued*)

Table 3 (Continued).

Study	Brain analysis methods or events/tasks	Risk of bias	Main findings
Henderson[67]	fMRI – qASL: CBF during a pain task Study 1: hypertonic saline infusion in the right masseter muscle to mimic acute orofacial muscle pain Study 2: open-close jaw movement while pain present	Weak	• First study: Negative correlation between PCS scores and CBF during pain in the right VLPFC (r=−0.85) and DLPFC (r=−0.85), left (r=−0.86) and right (r=−0.81) ACC/mPFC, right dACC (r=−0.74), left aINS (r= −0.79), left precuneus (r=−0.78) and bilateral parietal association cortex (r=−0.82) • Second study: During open-close jaw movement while pain was present, signal intensity changes positively correlated with PCS scores in the right trigeminal motor nucleus (r=0.78), lateral cerebellar cortex (r=0.91) and pINS (r=0.78) while the right DLPFC showed negative correlation (r=−0.70)
Kucyi[69]	rsFC: seed based functional connectivity analysis	Weak	• rsFC between mPFC, as one of the candidate seeds of DMN, and the PCC, right medial thalamus, midbrain, left anterior thalamus, left and right PCC/precuneus, right retrosplenial cortex and PVG/PAG correlated positively with the rumination subscale of PCS (all correlational coefficients were above 0.61) • correlation between rsFC of mPFC and pain catastrophizing was non-significant among controls • rsFC of PCC, as the other seed of DMN, was not related to pain catastrophizing in the TDM group
Gupta[68]	rsFC: functional connectivity of ICA derived networks	Moderate	• Moderate correlation between the left primary motor cortex's resting state activity and pain catastrophizing (r=0.45) (analyses were not executed on the control group)
Lazaridou[70]	rsFC: seed based functional connectivity analysis	Weak	• Positive correlation between the ↓ connectivity of S1-anterior and medial INS and the post-treatment ↓ of PCS scores (both in the CBT and education group) • Changes in connectivity of S1 with bilateral cuneus, occipital cortex, left thalamus, precuneus, cerebellum and IFG showed positive association with post-treatment ↓ PCS scores (all Z statistics were above 3.26)
Gracely[31]	fMRI - Task based: 12 pressure pain conditions and 12 resting conditions	Weak	• ↑ catastrophizing scores showed positive correlation with ↑ brain activity in ipsilateral claustrum (r=0.51), cerebellum (r=0.43), medial frontal gyrus (r=0.47), postcentral gyrus (r=0.41) and middle frontal gyrus (r =0.40) • Catastrophizing was positively correlated to activation in anterior and medial/posterior part of the ACC (r=0.43 and r=0.41, respectively), medial frontal gyrus (r=0.40) and lentiform nucleus (r=0.40) • Contralateral rostral ACC and contralateral lentiform nucleus only activated in the high catastrophizing group

(*Continued*)

Table 3 (Continued).

Study	Brain analysis methods or events/tasks	Risk of bias	Main findings
Seminowicz[79]	fMRI - Task based: TENS evoked mild or moderate electric pain	Weak	• PCS showed positive correlation with activity in aINS, rostral ACC, PCC, DLPFC and mPFC, premotor cortex, parietal cortex, superior temporal cortex, hippocampus, putamen and thalamus (all correlational coefficients were above 0.52) in the mild pain condition (pain intensity=20/100) • PCS showed negative correlation with DLPFC, mPFC, inferior and superior temporal cortex, superior and inferior parietal cortex including the S1 and amygdala (all correlational coefficients were above 0.46) in the moderate pain condition (pain intensity=60/100)
Lloyd[75]	fMRI - Task based: low back electric stimulation and resting periods	Weak	• Negative correlation was found between catastrophizing scores and brain activation in midline retrospenial cingulate cortex and inferior parietal cortex in the low/no pain behavior group (r=−0.43) (The authors did not report whether pain catastrophizing had any relation with brain activity in the high pain behavior group)
Burgmer[71]	fMRI – Task based: pressure pain task with or without prior notification of the pain intensity	Strong	• The activation of left posterior parietal cortex correlated with state pain catastrophizing negatively (r=−0.76) among FM patients in trials without any prior notice of pain intensity but not among controls
Lin[74]	fMRI – Task based: electric stimuli on the upper right incisor in 2 conditions: 1) predictable pain, 2) unpredictable (moderate or milder)	Moderate	• Positive correlation between PCS and right posterior hippocampal activation in the unpredictable pain condition (when participants did not know the incoming pain's intensity – correlational coefficients are not reported)
Hiramatsu[72]	fMRI – Task based: pain task with electrical stimulation (moderate pain and mild discomfort conditions)	Weak	• Positive correlation was found between PCS magnification and activation in the right DLPFC (r=0.43) in the moderate pain (4/10) vs mild discomfort (1/10) condition in all subjects
Hubbard[73]	fMRI – Task based: attention network test	Moderate	• Brain areas involved in attentional alerting – aMCC and right aINS – correlated with catastrophizing scores positively (r=0.32 and r=0.47, respectively) • While activity of brain areas involved in orienting (IFJ and SMA) correlated negatively with PCS scores (r=−0.41 and r=−0.40, respectively) in the patient group. • Two areas in the executive attention control system – thalamus and dmPFC - had different association with PCS scores (r=−0.42 and r=0.55, respectively)

(*Continued*)

Table 3 (Continued).

Study	Brain analysis methods or events/tasks	Risk of bias	Main findings
Lloyd[76]	fMRI – Task based: Pain task (lifting the leg causes pain) in 3 conditions: 3 colours to signify the expectation of movement thus the level of pain: green - the leg will be moved, yellow - the leg may be moved, red - the leg will definitely not be moved	Moderate	• In the predictable vs unpredictable pain condition PCS rumination scores as a covariate in group differences analysis correlated with brain activation in the left superior parietal lobe/precuneus, bilateral superior part of the lateral occipital cortex and intracalcarine cortex • In the predictable pain vs baseline condition PCS rumination covaried positively with group differences in the right premotor cortex, right superior parietal lobe/precunesus, left S2, left hippocampus • In the predictable vs no pain condition PCS rumination scores covaried positively with activation in the right premotor cortex, right supramarginal gyrus, right sensorimotor cortex and cuneal cortex
Loggia[77]	fMRI – Task based: cuff pressure pain stimuli preceded by visual cues	Moderate	• ↑ PCS scores correlated with ↓ brain activation in the VLPFC (r=−0.47), superior parietal cortex and precuneus to visual cues preceded pain cuff pressure • anticipatory brain activity in right anterior/VLPFC mediated the relationship between PCS and hyperalgesia indexed by the cuff pressure needed to achieve the target pain intensity rating
Kim[80]	Functional connectivity analysis in rest and pain: changes from rest to pain in S1	Weak	• ↑ connectivity from rest to pain between S1-aINS (r=0.44) and S1-middle frontal gyrus (r was not reported) showed positive correlation with catastrophizing in FM patients • no correlations found in controls between pain catastrophizing and changes in S1 connectivity from rest to pain phase
Mathur[78]	fMRI – Task based mild, moderate and non-painful thermal stimuli	Weak	• In the painful vs non-painful condition PCS scores negatively correlated with brain activation in the right mPFC, left caudate and left PCC/precuneus and positively correlated with bilateral aINS in the patient group (correlational coefficients were not reported in the paper)

Abbreviations: ns, non-significant; ACC, anterior cingulate cortex; aINS, anterior insula; aMCC, anterior midcingulate cortex; CBF, cerebral blood flow; CBT, cognitive behavioral therapy; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; FM, fibromyalgia; fMRI, functional magnetic resonance imaging; GM, gray matter; GMV, gray matter volume; ICA, independent component analysis; IFG, inferior frontal gyrus; IFJ, inferior frontal junction; INS, insula; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PCS, pain catastrophizing scale; pINS, posterior insula; PPC, posterior parietal cortex; PVG, periventricular gray; qASL, quantitative arterial spin labelling; rsFC, resting state functional connectivity; S1, primary somatosensory area; S2, secondary somatosensory area; SMA, supplementary motor area; TDM, temporomandibular disorder; TENS, transcutaneous electrical nerve stimulations; VBM, voxel based morphometry; VLPFC, ventrolateral prefrontal cortex.

Table 4 Studies using an experimental pain task fMRI design

	Sample	Type	Modality	System	Side	Body part	NRS	Pain ratings during fMRI session	Control variable
Gracely[31]	N=29 FM patients (19 F, 10 M)	Pressure	Mechanical	Cutaneous	Left	Thumbnail	Mild pain: 7.5/21 slightly intense pain: 13.5/21	No	Current mood
Seminowicz[79]	N=22 healthy control (12 F, 10 M)	Electric stimuli	Electrical	Transcutaneous	Left	Median nerve (upper limb)	Mild: 20/100 moderate: 60/100	No	Neuroticism, pain intensity
Hiramatsu[72]	N=12 OA patients (3 M, 9 F) and 11 controls (3 M, 8 F)	Electric stimuli	Electrical	Cutaneous	Right	Knee	Mild discomfort: 1/10 moderate pain: 4/10	No (but explicit instruction to concentrate on pain)	
Mathur[78]	N=14 migraine patients and 14 controls (3 F, 11 M in both groups)	Heat stimuli	Thermal	Cutaneous	Left	Volar forearm	No pain: 37 °C mild pain: P2-1°C moderate (P2) pain: 5 or 6/10	No	
Lin[74]	N=15 healthy controls (6 M, 9 F)	Electric stimuli	Electrical	Cutaneous	Right	Upper central incisor	Mild-moderate: 3/10 strong: 6/10	Yes	
Lloyd[75]	N=28 chronic low back pain patients (16 M and 14 F in the original sample, the ratio is not clear after excluding 2 participants) and 17 healthy controls (8 M, 9 F)	Tactile stimuli	Electrical	Muscular	Middle	Low back	Target pain intensity rating: 7/10 (maximum 14.5 mA)	No (but explicit instructions to focus on the pain)	
Lloyd[76]	N=29 nonspecific low-back pain patients (16 M, 13 F)	Lifting the leg	Mechanical	Muscular	Right or left (depending on subjective discomfort)	Leg	Moderate: 7/10	No	Fear of pain beliefs, depression and anxiety sumscore in group comparison

(*Continued*)

Table 4 (Continued).

	Sample	Type	Modality	System	Side	Body part	NRS	Pain ratings during fMRI session	Control variable
Loggia[77]	N=31 FM patients (4 M, 27 F)	Cuff pressure pain	Mechanical	Muscular	Right	Calf	Target pain intensity rating: 50/100	Yes	
Burgmer[71]	N=12 FM patients and 14 healthy controls (all F)	Pressure pain	Mechanical	Cutaneous	Left	Thumbnail	Moderate: 2/10 medium: 5/10 severe: 8/10	Yes	Depression and anxiety sumscore in group comparison
Henderson[67]	N=34 healthy controls (16 M, 18 F)	hypertonic saline infusion	mechanical	intra muscular	right	masseter muscle	5/10	Yes	age and gender as nuisance variables

Abbreviations: FM, fibromyalgia; OA, osteoarthritis; F, female; M, male; NRS, Numeric Rating Scale.

healthy controls with chronic pain patients.[71,72,75,78] We also discuss Hubbard et al's work[73] in this section. Although they used an attention paradigm instead of painful stimuli, they explored the effects of chronic pain and pain catastrophizing on brain activation both in controls and chronic pain patients.

Most of the studies used mechanical pain stimuli, whether it was pressure pain,[31,71,77] saline infusion[67] or the patient's own pain.[76] Four studies used electric stimuli[72,74,75,79] and one used heat as painful stimulus.[78]

Although the studies used different stimuli, the most commonly associated areas with pain catastrophizing were the DLPFC,[67,72,79] the insula,[67,73,78] the ACC,[31,70,74] the PCC[78,79] and parts of the supplementary motor area (SMA).[73,76,79]

In six studies, the participants were instructed to concentrate on the painful stimuli[71,72,74,75,77,78] and in three cases[71,74,77] they also had to rate the pain intensity immediately after they received the stimuli.

Comparing the studies along the pain intensity is difficult, as different authors used different scales and values to measure the intensity of the painful stimuli (for more information, see the NRS column in Table 4, where it can be seen that eg, "moderate pain" can range from 2 to 7 on a 10-point visual analog scale, depending on the study), but it cannot be ignored either. For instance, in three studies[67,72,79] when the intensity of the stimulus was low (20/100 or 4/10) a positive relationship, and when the intensity of the stimulus was moderate (5/10 or 60/100) a negative relationship emerged between blood oxygenation level dependent (BOLD) activity in DLPFC and catastrophizing, which may suggest that the intensity of the stimulus may moderate the relationship between catastrophizing and brain activity.

The anticipatory phase was investigated by Loggia et al[77] and by Burgmer et al.[71] In these studies, the anticipatory activity in anterior/ventrolateral prefrontal cortex (VLPFC) and posterior parietal cortex was associated with pain catastrophizing, respectively.

We found that only four studies[31,71,76,79] controlled for the confounding effects of other variables. Six of the studies here had low/weak level of evidence,[31,67,72,75,79] three had moderate,[74,76,77] and in only one case was the level of evidence strong.[71]

Discussion

Pain catastrophizing is consistently associated with increased pain reports; therefore, we expected that

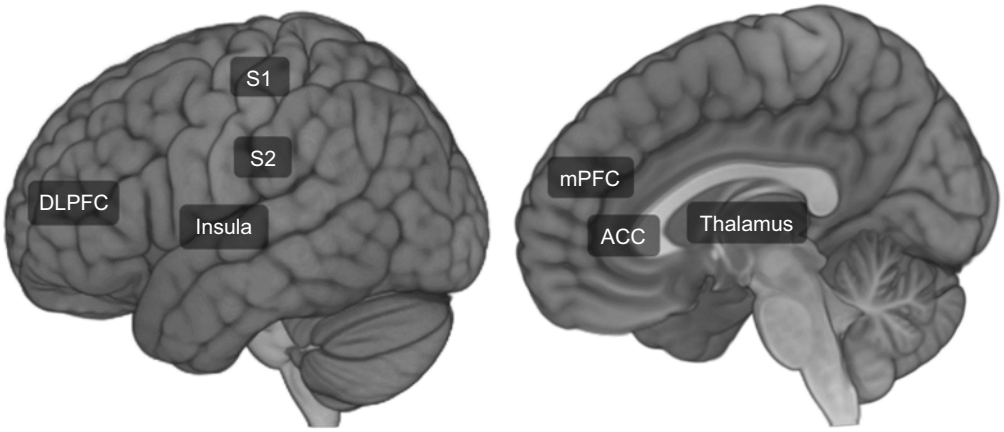

Figure 2 Most commonly reported areas in relation to pain catastrophizing in the reviewed studies.
Abbreviations: S1, primary somatosensory area; S2, secondary somatosensory area; DLPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex.

structural and/or functional characteristics of brain areas involved in pain perception, including the S1 and S2, ACC and MCC, insula, the PFC, the thalamus, the motor cortex, the SMA and also the brainstem,[32,82–84] may be associated with increased tendency to pain catastrophizing.

Some of the areas contributing to pain perception, primarily the S1, S2, thalamus, INS and ACC, have been proposed to be involved mainly in the sensory-discriminative and affective components of conscious pain experience.[92] We found that many studies reviewed here reported a connection between pain catastrophizing and these areas (see Table 3 and Figure 2 for the main findings). GMV of these areas seems to correlate with pain catastrophizing negatively, at least among patients. For instance, higher pain catastrophizing was related to smaller GMV of ACC/MCC and S1 and GMV of aINS[64] and the increase of GMV in S1 and S2 and ACC after CBT was related to decrease in pain catastrophizing[66] in patients. Connectivity and task-based fMRI results suggest that increased activity of areas involved in pain processing and increased functional connectivity between them are associated with higher pain catastrophizing scores. For instance, increased connectivity between S1 and insula from rest to pain[80] correlated pain catastrophizing positively or decrease in connectivity between S1 and insula from pre-treatment to post-treatment[70] were related to decrease in pain catastrophizing. The activity of S2[31,76] also showed positive correlation to pain catastrophizing in studies using experimental pain. We found that among chronic pain patients, increased connectivity of thalamus with aINS as a seed,[64] and with mPFC as a seed[69] was associated with increased tendency to catastrophizing pain, and connectivity of the somatosensory cortex for leg with the thalamus changed with changes in pain catastrophizing after CBT.[70] There was also a positive association between activity of aINS,[67,73,78,79] and activity of ACC[31,67,73,79] with pain catastrophizing in task-based studies (except in Henderson et al's study).

Based on these results, pain catastrophizing might be associated with the affective and intensity-related components of pain. Though the level of evidence in these studies was moderate to weak, it is reasonable to suggest that one of the mechanisms underlying catastrophizing cognitions is that they "make" the painful stimuli more salient and parallel, subjectively more intense, which is in line with the results of questionnaire studies.[5–19]

We also expected DLPFC as a key correlate of trait pain catastrophizing based on its role in attentional and pain modulatory functioning, thus contributing to the cognitive aspect of pain processing. Results of some studies reviewed here supported our expectations. GMV of DLPFC correlated with PCS scores negatively among IBS[62] and migraine patients.[64] Three studies, using experimental pain, reported results on the connections between activity of DLPFC and pain catastrophizing;[67,72,79] however, the results were not conclusive. Two of these studies, using an acute pain experimental design with healthy participants, only found a negative relationship between pain catastrophizing and cerebral blood flow (CBF) in right DLPFC during acute moderate pain (5/10)[67] and BOLD activity of bilateral DLPFC during acute moderate pain (60/100).[79] When the pain was only mild (20/100) in that latter study, the relationship was the opposite: positive correlation with pain catastrophizing,[79] similarly to

a mixed sample (patients + controls) study, in which participants were investigated during moderate pain (4/10) vs mild discomfort (1/10).[72] Direct comparison of these results is not easy since labelling pain intensity and the used numeric rating scales varied from study to study (see Table 4). In addition, methodological quality of fMRI studies that provided an association between the activation of DLPFC in task-based studies and pain catastrophizing was weak, thus it is hard to come to a definite conclusion on the potential role of DPLFC in catastrophizing.

We also aimed to review the neural correlates of pain catastrophizing in pain patients and pain-free controls. Concerning DLPFC, two studies[62,64] found opposite association between GM density of DLPFC and pain catastrophizing in patients and healthy controls. They found that decreased DLPFC GM density is associated with increased tendency to catastrophize pain in patients (IBS and migraine patients). As the DLPFC is part of the descending pain modulation system, which can modify the pain experience, the decreased amount of DLPFC GM might explain the increased amount of pain perception in chronic pain.[84,85] However, in the control groups a positive association was found between GMV density of DLPFC and pain catastrophizing. Those who had higher pain catastrophizing scores had higher GM density in DLPFC, suggesting different mechanisms underlying pain catastrophizing among controls and pain patients. This idea is supported by other results: one study[64] in our review found that relationship between catastrophizing and GMV of other brain regions – such as inferior frontal gyrus (IFG), S1, aMCC, mPFC – also had an opposite relationship in controls and in (migraine) patients. However, it is not clear whether these results can be generalizable to other pain conditions compared to controls.

Differences between healthy subjects and pain patients might suggest that structural and functional brain alterations related to pain catastrophizing may depend on prior and/or relatively stable/constant pain experience. It is worth noting that pain conditions (such as fibromyalgia, IBS, migraine, TMD, and low back pain) investigated in studies selected for our review may differ in some specific structural and functional brain alterations, but may share similar alterations within regions involved in pain processing and pain modulation, such as the INS, ACC, PFC (for a review see the work of Davis[85] or Bushnell[86]). Chronic pain related neural reorganization in GM, white matter or brain connectivity is hypothesized to be accompanied by a shift in the salience of the pain.[87] When chronic pain develops, painful stimuli are no longer just external threats but an inherent part of the everyday experience of patients. According to our review, regardless of the type of the chronic pain, neural correlates and mechanisms of pain catastrophizing might be similar across disorders: catastrophizing might be associated with enhanced intensity and affective processing, along with increased attentional processes towards painful stimuli and/or weakened modulation of pain.

Limitations and future recommendations

One major limitation of the reviewed studies is that most of the participants were females. One explanation to this might be that the prevalence of chronic pain is slightly higher in women than in men.[88] Another limitation would be the different age the reviewed studies reported. In most cases, the mean age of the patient group was well above 30. While in most of the studies, the authors used an age matched control group, generally the healthy participants are younger.

Although the average number of participants was above twelve in line with the findings of Desmond[54] and David[81], they also say that for reliable results, one needs at least twice this many in each group. In addition, quality of the reviewed studies was moderate to weak. This might be one of the reasons we could not find similar results in the reviewed studies.

It has been proposed that GM alterations in chronic pain are at least partially due to chronic pain itself,[87,89,90] therefore duration of the disease should be controlled for; however, only one study controlled for pain duration,[63] and many studies did not check confounding variables at all in the analyses.

It is also worth mentioning that in some studies that compared two groups – pain-free control group vs patient group – the results on pain catastrophizing of the healthy participants are not explicitly published, which makes the comparison nearly impossible. Our intention to compare neural correlates of pain catastrophizing in patient and in pain free participants sheds light on another shortcoming of pain catastrophizing studies: PCS asks about general pain-related thoughts which, for a chronic pain patient, might be the actual clinical pain, while a healthy participant might recall a distant memory of a painful event. In relation to this, studies reviewed here did not evaluate the interaction

between the actual spontaneous pain in chronic pain patients and the acute painful stimuli that were administered. In addition, generalizability of findings on neural correlates of pain catastrophizing among chronic pain patients still remained in question, since only some types of chronic pain were explored in the studies we found. More than half of the studies (10 from 16 involving chronic pain patient samples) observed fibromyalgia, irritable bowel syndrome and migraine, while in the rest mainly muscolosceletal pain was addressed.

Only one study in our review evaluated the effect of current (state) pain catastrophic thoughts which emerged during experimental pain.[71] Thus we have no information about how state and trait pain catastrophizing might interact in processing or anticipating painful stimuli.

In this review, we saw that fMRI studies using a pain task to observe connection between pain catastrophizing and brain activation applied different scales to rate pain intensity. In addition, labels (eg, "moderate") for pain intensity varied from study to study, therefore direct comparison of these results was challenged.

Besides pain perception, anticipatory processes could be interesting in relation to pain catastrophizing, but only two studies investigated this relationship.[71,77] Cues signalling subsequent painful stimuli may differ in their level of pain predictability. We found only two studies that tested predictable and unpredictable painful stimuli, but they did not analyze brain response to cues related to predictable and unpredictable pain in relation to pain catastrophizing.[74,76]

Another limitation could be our risk of bias tool. Although we based our tool on frequently used and accepted ones, we added some MRI specific items such as statistical threshold corrected for multiple testing.

For better understanding of the effect of pain catastrophizing, direct manipulation of pain catastrophic thoughts, while anticipating and perceiving pain, could be a useful way to investigate the mechanisms underlying catastrophizing. Difficulties in attentional disengagement from pain-related information have been hypothesized as a key process underlying pain catastrophizing.[27–30] However, the design of fMRI studies with pain tasks we reviewed here does not allow any conclusions to be drawn about that. If catastrophizing can be conceptualized as an expectation,[91] studies on anticipation of pain would deserve more attention in relation to pain catastrophizing. In addition, induction of catastrophic thoughts during anticipation or perception of painful stimuli could help to explore whether the correlates of catastrophizing are similar or different across pain-free and chronic pain samples. The use of a unified rating scale is advised for future catastrophizing and pain-task studies for easier comparison. It is important to mention that the DLPFC – identified as a hypothesized key area in our introduction – is not an anatomical region, but rather a functional one, thus a meta-analytic approach would identify more precisely which particular areas of DLPFC (or any other regions) are related to pain catastrophizing if more studies with strong evidence would be available.

Conclusions

Based on the results reviewed here, we can conclude that pain catastrophizing might be related to salience detection, pain processing, and top-down attentional processes. We found this association across a range of brain imaging modalities; thus, our review highlights the complex and moderate to weak association between pain catastrophizing and the activity or morphology/connectivity of brain areas relating to these processes.

Our results also point out that these processes in relation to pain catastrophizing are more pronounced in chronic pain patients. In addition, some of the results reviewed here suggest different correlates (and perhaps mechanisms) underlying pain catastrophizing among controls and pain patients. However, it is not obvious whether the presence or experience of chronic pain is associated with structural and functional changes or instead methodological issues (namely that the measured pain catastrophizing is related to a distant memory, as in healthy controls, or a current disturbing painful disorder, as in the chronic pain patients) are responsible for these differences. To improve prevention and treatment of painful conditions, longitudinal studies of healthy subjects with high pain catastrophizing would be required to understand which pain catastrophizing related brain mechanisms contribute to the transformation of acute pain states into chronic pain syndromes.

Abbreviation list

ACC, anterior cingulate cortex; aINS, anterior insula; aMCC, anterior midcingulate cortex; BOLD, blood oxygenation level dependent; CBF, cerebral blood flow; CBT, cognitive behavioral therapy; CEN, cognitive executive network; CSQ, Coping Strategies Questionnaire; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; dmPFC, dorsomedial prefrontal cortex; FC, functional connectivity; FDR, false discovery rate; FM, fibromyalgia; (f)MRI,

(functional) magnetic resonance imaging; FWE, family wise error; GMV, gray matter volume; IBS, irritable bowel syndrome; IFG, inferior frontal gyrus; LPVD, localized provoked vulvodynia; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; NFR, nociceptive flexion reflex; OA, osteoarthritis; PAG, periaqueductal gray; PCC, posterior cingulate cortex; PCS, Pain Catastrophizing Scale; pgACC, pregenual anterior cingulate cortex; pINS, posterior insula; PPC, posterior parietal cortex; PVD, provoked vestibulodynia; PVG, periventricular gray; qASL, quantitative arterial spin labeling; rsFC, resting state functional connectivity; S1, primary somatosensory area; S2, secondary somatosensory area; SMA, supplementary motor area; TMD, temporomandibular disorder; TMJD, temporomandibular muscle and joint disorders; VBM, voxel based morphometry; VLPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

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Disclosure

The authors declare that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Materials

Appendix S1 Studies found and left out from the systematic review

	Author	Reason
1	Brown[92]	Used electroencephalography (EEG) to measure brain activation
2	Castelnuovo[93]	Review
3	Cathcart[93]	Review
4	Chen[95]	Used DTI to measure structural connectivity
5	Cottam[96]	Did not examine neural changes connected directly to PCS, only controlled for PCS scores
6	Edwards[97]	Review
7	Fayed[98]	Mainly brain metabolites and not brain activity
8	Goldenberg[99]	Review
9	Gorczyca[100]	Review
10	Goswami[101]	The number of participants is below 12
11	Jensen[102]	Used EEG to measure brain activation
12	Kawamichi[103]	Not relevant in our research (since we looked for potential mechanisms underlying catastrophizing)
13	Knudsen[104]	Review
14	Leung[105]	Review
15	Lieberman[106]	Used DTI to measure structural connectivity
16	Lunn[107]	No fMRI in the study
17	Morris[108]	Only published a study protocol
18	Morris[109]	Did not examine neural changes connected directly to PCS
19	Piché[110]	Did not examine neural changes connected directly to PCS, only controlled for PCS scores
20	Quartana[53]	Review
21	Schmidt[111]	Did not examine neural changes connected directly to PCS
22	Simons[112]	Review
23	Shimada[113]	Used EEG to measure brain activation
24	Vase[22]	Used EEG to measure brain activation
25	Wieser[114]	Used EEG to measure brain activation
26	Youssef[115]	Did not examine neural changes connected directly to PCS

Abbreviations: EEG, electroencephalography; PCS, pain catastrophizing scale; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging.

Appendix S2 Risk of bias appraisal (based on data from[56-58])

Selection bias: • Was the sampling method appropriate? Were cases consecutive or randomly selected? If it was not explicitly stated, the study was rated as having an unclear risk of bias • Was the percentage of the response rate reported?
Study design: • Was the study design mentioned? What type did they use? Did they choose a method appropriate for the study's aim? (We preferred this question instead of evaluating the study design per se (using the hierarchy of evidence)).
Detection bias: • Was the patient group diagnosed according to criteria? • Did the authors ensure that the controls did not have the patient's condition? (yes if the study uses the same diagnostic tool on the controls too, or describes the control group as " pain-free" or "free of neurological disorders" N/A if there is no control group) • Did they use matched groups (in race, gender, age, SES, etc.)? • Were baseline characteristics (age, gender, etc.) clearly described?
Data collection and quality check: • Were the acquisition techniques clearly described (scanner type, repetition time, voxel sizes, fov, etc.)? • Was the task design clearly reported? Were the participants give and instructions? Was the task inside the scanner appropriate? Was the session length appropriate? Were there any the pain ratings? • Was the task design clearly reported? Were the participants give and instructions? Was the task inside the scanner appropriate? Was the session length appropriate? Were there any the pain ratings?
Drop-out rate described • Was the drop-out rate mentioned? (based on the reported numbers, a study was marked as weak if the drop-out rate was more than 40%)
Confounding variables controlled for • Were confounding variables controlled for and reported? • A study was marked as weak if the authors did not report anything, moderate if the authors controlled for either task [eg, age for gray matter studies] or catastrophizing [eg, depression, neuroticism] relevant variables and strong if the authors controlled for both task and catastrophizing relevant variables
Reporting bias: • Did the authors reported the thresholds they used? (was *p*-value uncorrected or FWE/FDR corrected? Did they use small volume correction at ROIs? etc.) • Were the results clearly reported (with *r* or *z* scores)? • Were all outcomes and groups reported on? (was the result of the study in line with the aims?) • Studies were marked as weak if they reported uncorrected results or no correction, moderate if they reported FDR/FWE correction but did not report z scores or all outcomes

Abbreviations: SES, socioeconomic status; FWE, family wise error; FDR, false discovery rate; FOV, field of view; ROI, region of interest.