

Does changing pain-related knowledge reduce pain and improve function through changes in catastrophizing?

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Abstract

Evidence from randomized controlled studies shows that reconceptualizing pain improves patients' knowledge of pain biology, reduces catastrophizing thoughts, and improves pain and function. However, causal relationships between these variables remain untested. It is hypothesized that reductions in catastrophizing could mediate the relationship between improvements in pain knowledge and improvements in pain and function. To test this causal mechanism, we conducted longitudinal mediation analyses on a cohort of 799 patients who were exposed to a pain education intervention. Patients provided responses to the neurophysiology of pain questionnaire, catastrophic thoughts about pain scale, visual analogue pain scale, and the patient specific functional scale, at baseline, 1-month, 6-month, and 12-month follow-up. With adjustment for potential confounding variables, an improvement in pain biology knowledge was significantly associated with a reduction in pain intensity (total effect = -2.20 , 95% confidence interval [CI] = -2.96 to -1.44). However, this effect was not mediated by a reduction in catastrophizing (indirect effect = -0.16 , 95% CI = -0.36 to 0.02). This might be due to a weak, nonsignificant relationship between changes in catastrophizing and pain intensity (path $b = 0.19$, 95% CI = -0.03 to 0.41). Similar trends were found in models with function as the outcome. Our findings indicate that change in catastrophizing did not mediate the effect of pain knowledge acquisition on change in pain or function. The strength of this conclusion is moderated, however, if patient-clinician relational factors are conceptualized as a consequence of catastrophizing, rather than a cause.

Keywords: Pain education, Catastrophizing, Mediation analysis, Pain, Disability

1. Introduction

The process that underpins pain is not simply a direct response to injury or pathology, but is a complex evaluation of nociception and other sensory cues.²⁹ Pain can be conceptualized as an output into consciousness that motivates a person to take protective action to moderate danger or threat.^{28,30} Empirical evidence suggests that a range of factors have a fundamental role in the generation of a painful experience, and manipulating those factors can modulate pain.^{1,33} For example, altering the threat value of a noxious input by changing the meaning that is associated with it can modulate pain. The clinical application of

this is captured in educational interventions that aim to reconceptualize patients' knowledge about pain biology—so called “Explaining pain”—to reduce their pain.³⁴

Evidence from randomized controlled studies shows that explaining pain improves knowledge about pain biology,^{8,27,32} reduces catastrophizing,^{8,27,35} reduces pain,^{32,38,42} and improves function.^{35,36,38} However, evidence to explain *how* changing a patient's knowledge of pain biology might reduce pain and improve function is limited. That is, the mechanisms by which pain reconceptualization results in less pain and better function are unknown.

Catastrophizing is a maladaptive cognitive process, whereby aspects of a painful experience are interpreted as signaling the worst possible outcomes.^{7,48} That is, the threat value of noxious input or perceived danger is magnified or overestimated.⁴⁸ Considering that pain is fundamentally dependent on an evaluation of threat value, catastrophizing is thought to worsen pain by enhancing the efficacy of the neural mechanisms that underpin it.^{52,59,62}

A systematic review of observational studies has shown that catastrophizing *predicts* pain intensity and functional capacity in patients with low back pain⁶⁰; a finding that has also been reported in neuropathic pain,⁵⁰ chronic temporomandibular joint pain,⁵⁷ pain of soft tissue injuries of the shoulder, neck and back,⁵¹ and osteoarthritis.¹⁶ Despite compelling evidence for a predictive effect, there is only preliminary evidence for a *causal* effect of catastrophizing on pain and function.⁵²

Although correlations between pain knowledge, catastrophizing, and pain or function have been found in previous studies,^{22,34,61} no

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study has formally tested the role of catastrophizing on the causal path between knowledge and pain or function. This mechanism by which improvements in pain knowledge lead to reduced pain and better function, through reductions in catastrophizing, can be tested using mediation analyses.¹¹ Understanding this mechanism is important for the development and refinement of educational interventions that aim to reconceptualize patients' knowledge about pain biology.

We hypothesized that change in catastrophizing would mediate the relationship between (1) an initial improvement in pain biology knowledge and subsequent reduction in pain intensity and (2) an initial improvement in pain biology knowledge and subsequent improvement in function.

2. Methods

2.1. Participants and procedures

Data used in this study were collected as part of a clinical audit conducted across Australia, U.S., and United Kingdom between 2001 and 2010. Eleven clinicians (9 physiotherapists and 2 psychologists) from 7 clinics (4 primary access physiotherapy clinics, 2 physiotherapy departments of private hospitals, and 1 physiotherapy department of a multidisciplinary pain unit) were involved in the audit, where each patient was treated by a single clinician (ie, no patient was treated by more than one clinician). Potential participants were either self-referred or referred through primary care general medical practitioners or other departments (orthopedics and rheumatology) of the private hospitals.

We included patients with chronic pain (pain duration greater than 3 months) who could read and write English, and were 18 years of age or older. We excluded patients who had undergone surgery in the preceding 3 months to consultation, had a current diagnosis of cancer, complex regional pain syndrome, phantom limb pain, a psychiatric disorder (not including depression or anxiety), a neurological disorder (multiple sclerosis, Parkinson's disease, dementia, spinal cord injury or stroke), or whose primary complaint was migraine or headache.

All eligible participants received a face-to-face group-based pain education intervention, delivered over 2 to 3 sessions, each session ranging between 30 and 60 minutes in duration. The intervention aimed to reconceptualize the patients' understanding of pain by explaining the biological mechanisms that underpin nociception and pain.⁴ The intervention was delivered between baseline and 1-month follow-up. No formal attempt to standardize the intervention was made, however, all clinicians completed very similar training and were involved in mentoring with the same mentor throughout the data collection period. This mentoring involved discussion of cases and strategies, but there was no formal assessment of aptitude nor standardization of material or performance. Only those

patients who provided complete follow-up data were included in the analyses.

The University of South Australia Human Research Ethics Committee provided ethical approval to access and analyze the deidentified clinical data.

2.2. Measures

Participants were assessed at baseline (T0), 1-month follow-up (T1), 6-month follow-up (T2), and 12-month follow-up (T3). All of the following variables were measured at all 4 time-points (Fig. 1).

2.2.1. Pain biology knowledge

The neurophysiology of pain questionnaire (NPQ) (Appendix 1: <http://links.lww.com/PAIN/A209>)³² was originally designed to assess postgraduate medical students' understanding of pain mechanisms. The language of the original NPQ has been adapted for patients, and is used in clinical practice and research to assess knowledge about the biology of pain. The NPQ includes 9 true and 10 false statements. Patients are required to indicate if each statement is true or false, or if they are unsure. The outcome is calculated by summing the correct responses. The total score ranges from 0 to 19, with higher scores representing better knowledge. The NPQ has acceptable internal consistency (person separation index = 0.84) and good test-retest reliability (intraclass correlation coefficient [ICC] = 0.97) in patients with chronic pain.⁵

2.2.2. Catastrophizing

The catastrophic thoughts about pain scale (CATS) (Appendix 2: <http://links.lww.com/PAIN/A210>; Appendix 3: <http://links.lww.com/PAIN/A211>; Appendix 4: <http://links.lww.com/PAIN/A212>; Appendix 5: <http://links.lww.com/PAIN/A213>) assesses the severity of catastrophizing.²¹ It has 7 items, each scored on an 11-point numeric rating scale. The total score ranges from 0 to 70, with higher scores indicating greater levels of catastrophizing. Preliminary analyses of the psychometric properties of the CATS was undertaken on pilot data collected from 131 people (112 reporting that they suffered from chronic pain) who were attending a public lecture on "understanding pain," in Oxford, United Kingdom. These data suggest that the CATS has high internal consistency (Cronbach's alpha = 0.91) and correlates strongly ($r = 0.80$) with scores on the pain catastrophizing scale (PCS).⁴⁹

2.2.3. Pain intensity

The 100-mm visual analogue scale assesses pain intensity.⁴¹ In response to the following question: "What was your average pain

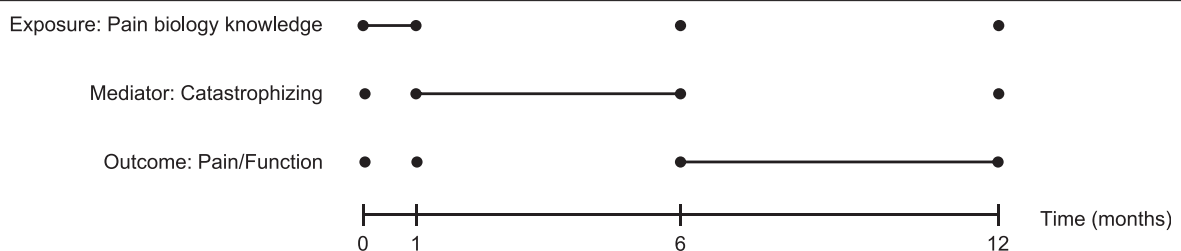


Figure 1. Measurement time-points. Each dot represents the times at which the constructs were measured; each line represents the time periods for which the change scores were calculated for the longitudinal analysis.

level over the last 2 days?”, the patient is asked to place a mark on a 100-mm horizontal line anchored by the statements “no pain” and “pain as bad as it can be.” The distance between the “no pain” anchor and the patient’s mark is measured to determine the score. This scale has high test-retest reliability (ICC = 0.97).²

2.2.4. Function

The patient specific functional scale assesses functional capacity.⁴⁷ Patients are asked on initial assessment to pick 3 to 5 activities they were unable to do or had difficulty with due to their pain. Then they rate their ability to do those tasks on an 11-point numeric rating scale, where 0 = unable to perform activity, and 10 = able to perform activity at the same level as before injury or problem. The score is calculated by summing the scores from each activity, then dividing the sum by the number of activities. The final score is expressed as a percentage of the possible maximum score. This scale has high test-retest reliability (ICC = 0.91),²⁶ and acceptable validity and responsiveness in a range of musculoskeletal pain conditions.¹⁷

2.3. Analysis

To test whether change in catastrophizing mediates the relationship between change in pain biology knowledge and change in pain or function, we conducted longitudinal mediation analyses using change scores (see section 2.3.1). We identified potential confounders by using a theory-driven approach and tested mediation models that were adjusted and unadjusted for selected covariates (see section 2.3.2). To explore the temporal sequence of our hypothesized mechanism, we tested 3 alternative models with alternative temporal sequences of the change in exposure, mediator, and outcome (see section 2.3.3). Separate analyses were conducted for pain and function outcomes.

2.3.1. Longitudinal change score analyses

We calculated change scores (Δ) for pain biology knowledge, catastrophizing, pain, and function, as the difference between measures at 2 selected time points (Fig. 1). We specified an initial change in knowledge ($\Delta T0-T1$) as the exposure, intermediate change in catastrophizing ($\Delta T1-T2$) as the mediator, and late change in pain ($\Delta T2-T3$) as the outcome. This analysis was repeated with late change in function ($\Delta T2-T3$) as the outcome.

In this mediation analysis, the total effect is quantified by the association (correlation coefficient) between an initial change in knowledge ($\Delta T0-T1$) and late change in pain or function ($\Delta T2-T3$). This total effect is decomposed into direct and indirect effects. The indirect effect is the path that is mediated through an intermediate change in catastrophizing ($\Delta T1-T2$), and the direct effect is the total effect minus the indirect effect. The indirect effect is quantified by the product of path a (association between an initial change in knowledge and intermediate change in catastrophizing) and path b (association between an intermediate change in catastrophizing and later change in pain or function, adjusting for the initial change in knowledge).

All mediation analyses were conducted with the PROCESS macro (<http://www.processmacro.org/index.html>) based on ordinary least squares linear regression.⁴⁰ This macro was used to estimate the total, direct, and indirect effects with bias-corrected 95% confidence intervals using 1000 bootstrapped resamples. Associations are reported as unstandardized β coefficients. All analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY).

2.3.2. Identification of potential confounding variables

Potential confounders were identified using directed acyclic graphs (DAGs)⁴³ that represent the hypothesized causal relationships between the variables of interest (Appendices 3 and 4). Directed acyclic graphs are one example of a “structural approach” to causal inference. The following constructs were identified as potential confounders of the indirect, direct, and total effects: pain duration (months), diagnosis, patients’ expectation of outcome (11-point numeric rating scale), and patients’ perception of the clinician (empathy, attentiveness, and expertise—each rated on an 11-point numeric rating scale).^{35,37} In the adjusted models, we statistically controlled for these potential confounders. In the unadjusted models, we did not account for these potential confounders.

2.3.3. Sensitivity analysis for temporal precedence

To rule out the possibility of reversed causal paths, we tested 3 alternative mediation models for each outcome (pain and function). These three alternative models tested whether the change in the mediator precedes the change in the exposure (model 1), change in the outcome precedes the change in the mediator (model 2), and change in the outcome precedes the change in the exposure (model 3). These models are summarized in Table 1. If significant indirect effects were found for any of the 3 alternative models we would conclude that the data supports an alternative temporal sequence. This approach of testing alternative causal sequences to explore the robustness of the primary analyses has been demonstrated in other research areas.^{9,10}

2.3.4. A priori decision plan

We decided a priori to accept the overall hypothesis if the adjusted longitudinal change score analysis showed a significant indirect effect through catastrophizing, and all 3 alternative models showed nonsignificant indirect effects. If the adjusted longitudinal change score analysis indicated a nonsignificant indirect effect, or if at least one of the alternative models indicated a significant indirect effect, we decided to conclude against the overall hypothesis. We published and locked our a priori protocol before commencing the analysis (<http://www.bodyinmind.org/resources/protocols/statistical-analysis/catastrophizing-pain/>).

2.3.5. Post hoc sensitivity analyses

2.3.5.1. Change in catastrophizing from baseline to 1-month as a mediator

It is plausible that the reduction in catastrophizing may have occurred during treatment (ie, earlier than the hypothesized change period—between 1 and 6 months). To explore whether an “early” change in catastrophizing ($\Delta T0-T1$) mediates the

Table 1
Analysis summary.

Model	$\Delta T0-T1$	$\Delta T1-T2$	$\Delta T2-T3$
Longitudinal change score analysis	Knowledge	Catastrophizing	Pain/function
Alternative model 1	Catastrophizing	Knowledge	Pain/function
Alternative model 2	Knowledge	Pain/function	Catastrophizing
Alternative model 3	Pain/function	Catastrophizing	Knowledge

T0, baseline; T1, 1-month follow-up; T2, 6-month follow-up; T3, 12-month follow-up.

relationship between an early change in pain biology knowledge and late change in pain or function, we conducted a separate longitudinal mediation analysis using the same procedure as described in section 2.3.1.

2.3.5.2. Residual change score analysis

Residual change scores express “change” in a variable across 2 time-points, while taking into account the variance in a measure predicted by the baseline measure of the same variable. Because residual change scores also take into account random error, it can yield different results to analyses that use raw change scores. To assess consistency in the mediation models, we repeated the main analysis (section 2.3.1) using residual change scores.

2.3.5.3. The influence of outcome expectancy as a potential confounder

Conceptually, outcome expectancy is closely related to catastrophizing (“a maladaptive cognitive style that focuses on irrational forecasting of future events”⁷). Therefore, adjusting for outcome expectancy could reduce the contribution of catastrophizing to the indirect effect. To explore this, we tested, post hoc, 2 “adjusted” mediation models. The first model included outcome expectancy as a covariate, and the second model did not. All other covariates identified by the DAG were retained in the model.

2.3.5.4. The influence of clinician attributes as a potential confounder

There is some evidence to suggest that interpersonal dimensions of catastrophizing might influence patient-therapist relational factors such as perceived empathy, expertise, and attentiveness of the clinician.¹⁸ Therefore, adjusting for clinician attributes could reduce the contribution of catastrophizing to the indirect effect. To explore this possibility, we tested post hoc, 2 “adjusted” mediation models. The first model included clinician attributes (empathy, expertise, and attentiveness) as covariates, and the

second model did not include these factors. All other covariates identified by the DAG were kept in the model.

3. Results

3.1. Participants

Participant flow is presented in **Figure 2**. From a total sample of 867 potential participants, 799 cases were included in the final analysis. Participants’ ages ranged from 18 to 70 years (mean = 43.07, SD = 10.98) and 63% were female. All participants were diagnosed with a chronic pain condition that lasted for longer than 3 months (52% were diagnosed with spinal pain with or without neuropathic pain; 22% with neuropathic pain only; 17% with fibromyalgia or general widespread pain; and 9% with upper-limb pain). Pain duration ranged from 3 to 143 months (mean = 54.83, SD = 29.60) (**Table 2**).

3.2. Change scores

Initial ($\Delta T0-T1$), intermediate ($\Delta T1-T2$), and late ($\Delta T2-T3$) change indices for pain biology knowledge, catastrophizing, pain, and function are presented in **Table 3**, and visually represented in **Figure 3**.

3.3. Mediation analyses

3.3.1. Pain as the outcome variable

In the unadjusted model, an initial improvement in pain biology knowledge was significantly associated with later reduction in pain intensity (total effect = -1.34 , 95% confidence interval [CI] = -2.12 to -0.55). 32% of this total effect was mediated by a reduction in catastrophizing (indirect effect = -0.43 , 95% CI = -0.67 to -0.24) (**Table 4**). Reported parameters are unstandardized β coefficients.

In the adjusted model, an initial improvement in pain biology knowledge was significantly associated with later reduction in

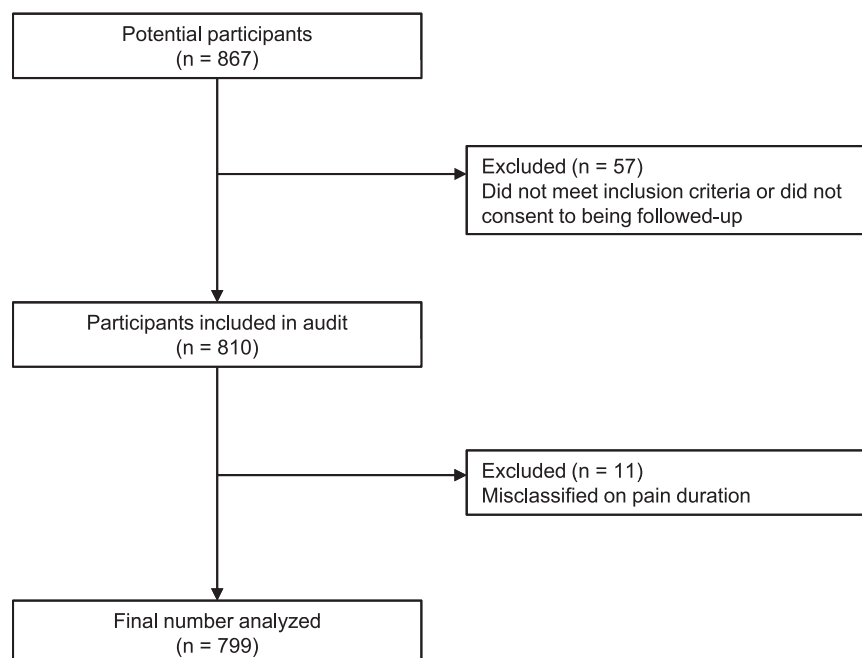


Figure 2. Participant flow.

Table 2
Summary of patients' baseline characteristics (n = 799).

Characteristic	Frequency (%)	Mean (SD)	Range
Gender			
Female	503 (63)		
Male	296 (37)		
Age (y)		43.07 (10.98)	18-70
Pain duration (mo)		54.83 (29.60)	3-143
Diagnosis			
Spinal pain	416 (52)		
Neuropathic pain	175 (22)		
Fibromyalgia	137 (17)		
Upper-limb pain	71 (9)		
Pain biology knowledge*		3.86 (1.93)	0-10
Catastrophizing†		39.25 (8.59)	19-61
Pain intensity‡		50.47 (15.62)	8-95
Function§		2.22 (2.03)	0-10

* Neurophysiology of pain questionnaire (possible range: 0-19).

† Catastrophic thoughts about pain scale (possible range: 0-70).

‡ 100-mm visual analogue scale (possible range: 0-100).

§ Patient-specific functional scale (possible range: 0-100).

pain intensity (total effect = -2.20 , 95% CI = -2.96 to -1.44). This effect was not mediated by a reduction in catastrophizing (indirect effect = -0.16 , 95% CI = -0.36 to 0.02). This is likely due to a nonsignificant relationship between changes in catastrophizing and pain intensity (path b = 0.19 , 95% CI = -0.03 to 0.41).

3.3.2. Function as the outcome variable

In the unadjusted model, an initial improvement in pain biology knowledge was significantly associated with later improvement in function (total effect = 1.70 , 95% CI = 1.25 - 2.15). This effect was not mediated by a reduction in catastrophizing (indirect effect = 0.09 , 95% CI = -0.01 to 0.21). This is likely due to a nonsignificant relationship between changes in catastrophizing and function (path b = -0.11 , 95% CI = -0.22 to 0.01) (Table 4).

In the adjusted model, an initial improvement in pain biology knowledge was significantly associated with later improvement in function (total effect = 2.29 , 95% CI = 1.84 - 2.73). This effect was not mediated by a reduction in catastrophizing (indirect effect = -0.01 , 95% CI = -0.11 to 0.11). This is likely due to a nonsignificant relationship between changes in catastrophizing and function (path b = 0.01 , 95% CI = -0.13 to 0.12).

Table 3
Change scores.

Variable	Change period (months)	Mean (SD)	Range
Pain biology knowledge*	0-1	4.51 (1.64)	0 to 9
	1-6	0.50 (0.82)	-1 to 2
	6-12	0.29 (0.75)	-1 to 2
Catastrophizing†	0-1	0.09 (3.65)	-6 to 6
	1-6	-13.33 (6.32)	-30 to 6
	6-12	-1.90 (2.62)	-6 to 2
Pain intensity‡	0-1	0.14 (9.08)	-58 to 57
	1-6	-8.91 (15.63)	-75 to 67
	6-12	-25.41 (18.70)	-95 to 34
Function§	0-1	10.81 (6.28)	0 to 21
	1-6	17.22 (20.59)	-21 to 81
	6-12	33.07 (10.97)	1 to 59

* Neurophysiology of pain questionnaire (possible range: 0-19).

† Catastrophic thoughts about pain scale (possible range: 0-70).

‡ 100-mm visual analogue scale (possible range: 0-100).

§ Patient-specific functional scale (possible range: 0-100).

3.3.3. A priori sensitivity analysis for temporal precedence

The total effect, direct effect, indirect effect, path a, and path b for the alternative models are presented in Table 5. None of the 3 alternative models for each outcome (pain and function) showed significant indirect effects.

3.4. Post hoc sensitivity analyses

3.4.1. Change in catastrophizing from baseline to 1-month as a mediator

Both unadjusted and adjusted models showed that an early change in catastrophizing does not mediate the relationship between an early change in pain biology knowledge and late change in pain or function (Appendix 6.1: <http://links.lww.com/PAIN/A214>).

3.4.2. Residual change score analysis

The residual change score analysis yielded similar results to the raw change analysis. The results are reported in Appendix 6.2.

3.4.3. The influence of outcome expectancy as a potential confounder

Removing outcome expectancy as a potential confounder did not influence the indirect effects in the adjusted models for pain or function (Appendix 6.3).

3.4.4. The influence of clinician attributes as a potential confounder

With changes in pain as the outcome, the inclusion of clinician attributes as a covariate reduced the magnitude of the indirect effect through catastrophizing such that it was no longer significant (indirect effect = -0.16 , 95% CI = -0.36 to 0.02). However, when clinician attributes were not included as covariates, the indirect effect through catastrophizing reduced, but still remained significant (indirect effect = -0.36 , 95% CI = -0.60 to -0.13). With function as the outcome, removal of clinician attributes as a covariate did not influence the indirect effect (Appendix 6.4).

4. Discussion

4.1. Main findings

Changes in catastrophizing did not mediate the relationship between improved pain biology knowledge and improved pain or function in the adjusted models. The adjusted models showed that an initial improvement in pain biology knowledge led to a reduction in pain, an improvement in function (total effects), and a reduction in catastrophizing (path a). However, the reduction in catastrophizing neither led to a reduction in pain, nor an improvement in function (path b). This resulted in a small and nonsignificant indirect effect through changes in catastrophizing.

Interestingly, our first hypothesis (that changes in catastrophizing would mediate the relationship between changes in pain biology knowledge and pain) was supported by the unadjusted model, but was not supported by the adjusted model. One possible explanation for the discrepancy in the results from the unadjusted and adjusted models could be due to the effects of confounding variables. Because consideration of confounding is critical for causal inference from observational data, we adjusted for selected covariates to ensure that any indirect effects

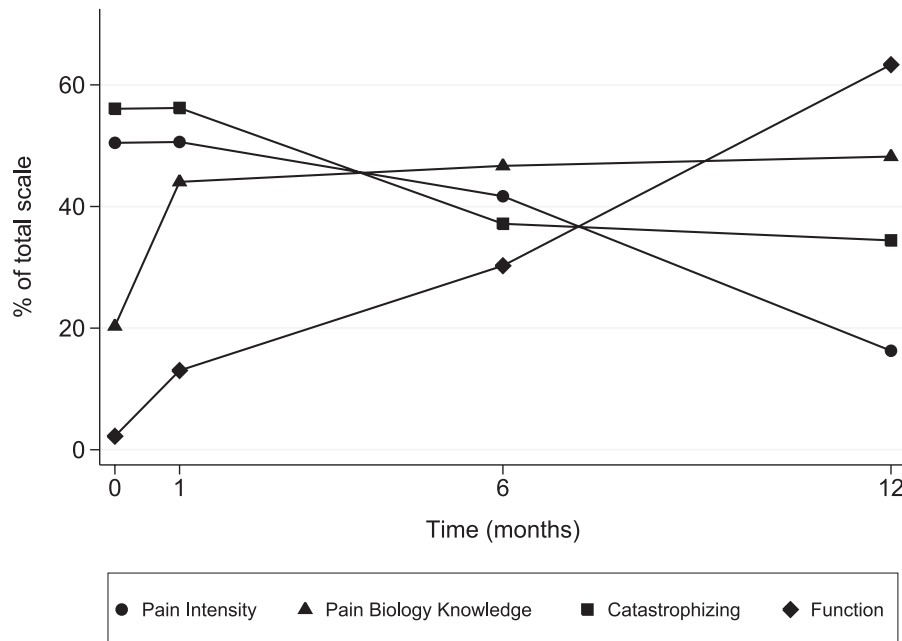


Figure 3. Mean % of total score for pain biology knowledge, catastrophizing, pain and function plotted across time.

identified were actually associated with the mediator of interest, and not a confounder. Recent methodological developments have demonstrated that traditional methods for covariate selection based on statistical associations can introduce, rather than eliminate, bias.¹² Therefore, we used a theory-driven approach to hypothesize a causal structure for the relationships between the variables, and identified potential confounders using DAGs.⁴³ Adjusting for covariates in mediation models can affect the total, direct, and indirect effects in opposing directions.^{23,54} We found this to be the case in our mediation models; statistical adjustment increased the total and direct effects, but reduced the indirect effect (Table 4).

Our first post hoc sensitivity analysis (section 2.3.5.1) showed that an early change in catastrophizing did not mediate the relationship between changes in pain biology knowledge and changes in pain or function. This finding seems reasonable considering that most of the change in catastrophizing occurred between 1 and 6 months, and that pain and function started improving after the 1-month time-point (Fig. 3). The residual change score analysis (section 2.3.5.2) showed similar results to raw change score analyses. Both of the adjusted models for change in pain and function as the outcome showed negligible indirect effects. Although the adjusted indirect effect for change in pain (as the outcome) might be interpreted as statistically significant,

the close proximity of the bounds of the 95% CI (−0.04 to −0.01) to zero suggest that this indirect effect is negligible. The reduction of the indirect effect from the unadjusted to adjusted models is consistent with the trend observed in the raw change score analysis. The third post hoc sensitivity analysis (section 2.3.5.3) shows that adjusting for outcome expectancy did not mask the relationship between changes in catastrophizing and changes in pain or function. The fourth post hoc sensitivity analysis (section 2.3.5.4) suggests that the inclusion of clinician attributes influenced the mediation effect through catastrophizing. We conceptualized clinician attributes as potential confounders because of their effects on key pain outcomes and psychological constructs.^{3,6,46,55} For example, if a patient perceived their clinician to lack empathy or have poor expertise, then this might lead to increases in catastrophizing, limit knowledge uptake, and influence changes in pain and function. However, clinician attributes (relational factors) are sometimes conceptualized as a consequence of catastrophizing. For example, Lackner and Gurtman¹⁸ suggest that people who score high on measures of catastrophizing have personality characteristics that might impact interpersonal perception. This means that adjusting for clinician attributes could have removed the variance in the outcomes that is contributed by a likely consequence of catastrophizing. However, in our study, clinician attributes were

Table 4
Longitudinal raw change score analyses.

	Total effect	Direct effect	Indirect effect*	Path a	Path b
Pain					
Unadjusted	−1.34 (−2.12 to −0.55)†	−0.91 (−1.71 to −0.12)†	−0.43 (−0.67 to −0.24)†	−0.85 (−1.11 to −0.59)†	0.50 (0.29 to 0.71)†
Adjusted	−2.20 (−2.96 to −1.44)†	−2.04 (−2.82 to −1.25)†	−0.16 (−0.36 to 0.02)	−0.87 (−1.11 to −0.63)†	0.19 (−0.03 to 0.41)
Function					
Unadjusted	1.70 (1.25 to 2.15)†	1.61 (1.15 to 2.07)†	0.09 (−0.01 to 0.21)	−0.85 (−1.11 to −0.59)†	−0.11 (−0.22 to 0.01)
Adjusted	2.29 (1.84 to 2.73)†	2.28 (1.82 to 2.74)†	−0.01 (−0.11 to 0.11)	−0.87 (−1.11 to −0.63)†	0.01 (−0.13 to 0.12)

Adjusted and unadjusted coefficients with their 95% confidence intervals.

* The indirect effect quantifies how much two cases that differ by one unit on the exposure (knowledge) are estimated to differ on the outcome (pain/function) in result of the effect of the exposure (knowledge) on the mediator (catastrophizing), which in turn affects the outcome (pain/function).

† Indicates a 95% confidence interval that does not include 0.

Table 5
Sensitivity analyses for temporal precedence.

	Total effect	Direct effect	Indirect effect	Path a	Path b
Pain					
1	0.06 (−0.42 to 0.29)	0.05 (−0.41 to 0.30)	−0.01 (−0.05 to 0.01)	0.01 (−0.01 to 0.02)	−1.00 (−2.60 to 0.59)
2	−0.02 (−0.09 to 0.13)	−0.02 (−0.09 to 0.13)	−0.00 (−0.01 to 0.00)	−0.05 (−0.71 to 0.62)	0.01 (−0.01 to 0.02)
3	−0.00 (−0.01 to 0.00)	−0.00 (−0.01 to 0.00)	0.00 (−0.00 to 0.00)	−0.01 (−0.06 to 0.03)	0.00 (−0.01 to 0.01)
Function					
1	−0.15 (−0.06 to 0.36)	−0.15 (−0.06 to 0.36)	0.00 (−0.02 to 0.01)	0.01 (−0.01 to 0.02)	−0.20 (−1.14 to 0.73)
2	−0.02 (−0.09 to 0.13)	−0.01 (−0.10 to 0.12)	0.01 (−0.01 to 0.03)	0.58 (−0.29 to 1.45)	0.02 (0.01 to 0.03)*
3	−0.00 (−0.01 to 0.01)	−0.00 (−0.01 to 0.01)	0.00 (−0.00 to 0.00)	0.06 (−0.01 to 0.13)	0.00 (−0.01 to 0.01)

Adjusted coefficients with 95% confidence intervals.

* Indicates a 95% confidence interval that does not include 0.

measured at baseline, and are therefore more likely to be a precursor to our hypothesized mediator (change in catastrophizing between T1 and T2), rather than a consequence of it.

The different conceptions about the role of clinician attributes on the mediating effect of catastrophizing raises an interesting question as to how relational factors might confound the relationship between catastrophizing and pain outcomes, and how much relational factors are themselves dependent on catastrophizing. If one chooses to conceptualize relational factors as a potential confounder (ie, relational factors influencing changes in catastrophizing), the results would suggest that changes in catastrophizing is unlikely to mediate the relationship between knowledge uptake and pain outcomes. However, if one accepts that the variability in patients' perceptions of clinicians is a consequence of catastrophizing, it is then plausible to conclude that changes in catastrophizing is a mediator. Further work in this area could provide a more detailed conceptualization of the role of relational factors on the mechanistic role of catastrophizing.

4.2. Relevance to existing literature

This study is the first to test a possible mechanism that might underlie the relationship between pain biology knowledge and pain or function. The selection of our exposure and mediator variables was guided by previous work that demonstrated causal effects of pain education interventions in improving patients' pain biology knowledge^{8,27,31} and reducing catastrophizing.^{8,27,35} Our study advances the existing evidence by demonstrating that knowledge uptake causes a reduction in catastrophizing, but that changes in catastrophizing do not lead to improvements in pain or function. That we observed a direct relationship between knowledge uptake and clinically relevant changes in the outcomes (34% improvement in pain and 61% improvement in function), clearly suggests that there are other indirect pathways that have yet to be identified.

Our results seem contrary to previous investigations of catastrophizing as a mediator of pain and functional improvements.^{25,60} However, most studies did not eliminate the effects of confounding. It is likely that estimates of path b (catastrophizing→pain or function) in previous studies could have been confounded as they were based on simple statistical associations without adjustment for potential covariates.^{20,24,45,56} Only one study⁴⁴ adjusted for age, gender, baseline values of the outcome and mediator, treatment center, and disability duration. However, even that work did not use an explicit, theoretical approach to select their covariates, introducing the risk of missing important confounders, or erroneously adjusting for variables that lie on the causal path.^{14,43} This inconsistency in the literature suggests that, although catastrophizing might be correlated with severity of pain and

disability, it would seem prudent now, in light of the development of the field, to question the role of catastrophizing as a cause of these outcomes. That is, recent developments in mediation analysis state that, for causal interpretation of mediation effects, careful consideration for potential confounders is required to satisfy the “no unmeasured confounding” assumption.^{39,58} We further explored this inconsistent finding by testing our theoretical assumptions for the selection of 2 proposed confounders—expectancy (section 2.3.5.3) and clinician attributes (section 2.3.5.4). We found that adjusting for expectancy did not influence the adjusted indirect effects, but clinician attributes did. Without adjustment for clinician attributes, the indirect effect through catastrophizing was significant (section 3.4.4). One could interpret this more consistent finding by suggesting that relational factors such as perceived clinician attributes are part of the interpersonal dimensions of a catastrophizing individual which influences interpersonal relations. Recent work by Trost et al.⁵³ also suggests that catastrophizing is a heritable trait, which might determine interpersonal perceptions. Another possible explanation for the discrepancy between our findings and previous work is that in comparison to more commonly used measures of catastrophizing (eg, PCS), the CATS contains items that might also reflect “worry.” Yet, “worry” is an item in the PCS, and the PCS has shown to be strongly correlated with CATS ($r = 0.80$). Thus, the findings of this study may suggest that only aspects of catastrophizing that reflect “worry” do not mediate the relationship between improvements in pain knowledge and improvements in pain or function.

4.3. Strengths and limitations

Strengths of this study include our theoretical approach to identifying confounding variables (with post hoc tests of our selection of potential confounders), and the temporal sensitivity analyses to test alternative causal directions of our proposed mechanism. Our mediation models and its surrounding causal structure was informed by theory and empirical evidence from laboratory and clinical studies. These attributes fulfill key methodological quality criteria for observational mediation studies (Appendix 5).^{19,25} We also prespecified a transparent analysis plan and did not deviate from our original protocol. This study also has limitations. The cohort was a selected sample of patients who were exposed to a reasonably standardized pain biology education intervention. This limits the generalizability of our findings to those who undergo similar interventions. We therefore limit the interpretation of our results to explain the mechanism underlying the association between knowledge uptake and changes in outcomes (pain and function), and cannot fully attribute these effects to pain biology education. We selected potential confounders based on a theory-driven approach that is

in line with contemporary standards in epidemiological methodology.^{13,43} However, this approach comes with assumptions. To confidently rule out all sources of confounding, all potential confounders need to be identified and be measured without error.¹⁵ Our DAG specified one potential variable (prior beliefs about pain) that could have exerted further confounding effects, and there is uncertainty around the measurement properties of clinician attributes and outcome expectancy.

5. Conclusion

Our findings show that change in catastrophizing did not mediate the effect of pain knowledge acquisition on change in pain or function. The strength of this conclusion is moderated, however, if patient-clinician relational factors are conceptualized as a consequence of catastrophizing, rather than a cause.

Conflict of interest statement

H. Lee: grants (National Health & Medical Research Council of Australia), J. H. McAuley: grants (National Health & Medical Research Council of Australia), S. J. Kamper: consultancy (AO Spine: providing methodological advice for research projects); Employment (National Health & Medical Research Council of Australia), A. C. Traeger: grants (National Health & Medical Research Council of Australia), G. L. Moseley: consultancy (Grunenthal, Pfizer, Australian Institute of Sport); grants (National Health & Medical Research Council of Australia); payment for lectures including service on speakers bureaus (lectures for various companies on pain); royalties (Explain Pain, Painful Yarns, Graded motor imagery handbook, Noigroup publications), and M. Hübscher has no conflicts of interest to declare.

Appendices. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at <http://links.lww.com/PAIN/A209>, <http://links.lww.com/PAIN/A210>, <http://links.lww.com/PAIN/A211>, <http://links.lww.com/PAIN/A212>, <http://links.lww.com/PAIN/A213>, and <http://links.lww.com/PAIN/A214>.

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References

- [1] Arntz A, Claassens L. The meaning of pain influences its experienced intensity. *PAIN* 2004;109:20–5.
- [2] Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med* 2001;8:1153–7.
- [3] Blasi Z, Di Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. *Lancet* 2001;357:757–62.
- [4] Butler DS, Moseley GL. *Explain pain*. Adelaide: NOI Group Publishing, 2003.
- [5] Catley MJ, O'Connell NE, Moseley GL. How good is the neurophysiology of pain questionnaire? A Rasch analysis of psychometric properties. *J Pain* 2013;14:818–27.
- [6] Derksen F, Bensing J, Lagro-Janssen A. Effectiveness of empathy in general practice: a systematic review. *Br J Gen Pract* 2013;63:76–84.
- [7] Ellis A. *Reason and emotion in psychotherapy*. New York: Lyle Stuart, 1962.
- [8] Gallagher L, McAuley J, Moseley GL. A randomized-controlled trial of using a book of metaphors to reconceptualize pain and decrease catastrophizing in people with chronic pain. *Clin J Pain* 2012;29:1.

- [9] Greitemeyer T, McLatchie N. Denying humanness to others: a newly discovered mechanism by which violent video games increase aggressive behavior. *Psychol Sci* 2011;22:659–65.
- [10] Guendelman MD, Cheryan S, Monin B. Fitting in but getting fat: identity threat and dietary choices among U.S. immigrant groups. *Psychol Sci* 2011;22:959–67.
- [11] Hayes AF. Beyond Baron and Kenny: statistical mediation analysis in the new millennium. *Commun Monogr* 2009;76:408–20.
- [12] Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol* 2002;155:176–84.
- [13] Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health* 2006;60:578–86.
- [14] Hernández-Díaz S, Wilcox AJ, Schisterman EF, Hernán MA. From causal diagrams to birth weight-specific curves of infant mortality. *Eur J Epidemiol* 2008;23:163–6.
- [15] Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ* 2010;340:c2289.
- [16] Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *PAIN* 2000;87:325–34.
- [17] Kowalchuk-Horn K, Jennings S, Richardson G, VanVliet D, Hefford C, Abbott JH. The patient-specific functional scale: psychometrics, clinimetrics, and application as a clinical outcome measure. *J Orthop Sports Phys Ther* 2011;42:30–40.
- [18] Lackner JMA, Gurtman MBB. Pain catastrophizing and interpersonal problems: a circumplex analysis of the communal coping model. *PAIN* 2004;110:597–604.
- [19] Lee H, Hübscher M, Moseley GL, Kamper SJ, Traeger AC, Mansell G, McAuley JH. How does pain lead to disability? A systematic review and meta-analysis of mediation studies in people with back and neck pain. *PAIN* 2015;156:988–97.
- [20] Leeuw M, Goossens MEJB, van Breukelen GJP, de Jong JR, Heuts PHTG, Smeets RJEM, Köke AJA, Vlaeyen JWS. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *PAIN* 2008;138:192–207.
- [21] Lefebvre J, Keefe F, Caldwell D, Waters S, Ulrich A. The development of the catastrophizing-state (CATS) scale in a clinical sample. Presented at: 10th World Congress on Pain; August 22, 2002; San Diego.
- [22] Louw A, Diener I, Butler DS, Puenteadura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil* 2011;92:2041–56.
- [23] MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. *Prev Sci* 2000;1:173–81.
- [24] Mannion AF, Mu M, Taimela S, Dvorak J. A randomized clinical trial of three active therapies for chronic. *Spine (Phila Pa 1976)* 1999;24:2435–48.
- [25] Mansell G, Kamper SJ, Kent P. Why and how back pain interventions work: what can we do to find out? *Best Pract Res Clin Rheumatol* 2013;27:685–97.
- [26] Maughan EF, Lewis JS. Outcome measures in chronic low back pain. *Eur Spine J* 2010;19:1484–94.
- [27] Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijens S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil* 2010;91:1153–9.
- [28] Melzack R, Wall PD. *Textbook of pain*. Churchill Livingstone, London, United Kingdom; 1999.
- [29] Merskey H, Bogduk N. *Classification of chronic pain, IASP task force on taxonomy*. Seattle: Int Assoc Study Pain Press, 1994. Available at: www.iasp-pain.org. Accessed 10 August 2015.
- [30] Moseley G. A pain neuromatrix approach to patients with chronic pain. *Man Ther* 2003;8:130–40.
- [31] Moseley GL. Joining forces—combining cognition-targeted motor control training with group or individual pain physiology education: a successful treatment for chronic low back pain. *J Man Manip Ther* 2003;11:88–94.
- [32] Moseley GL. Unraveling the barriers to reconceptualization of the problem in chronic pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. *J Pain* 2003;4:184–9.
- [33] Moseley GL, Arntz A. The context of a noxious stimulus affects the pain it evokes. *PAIN* 2007;133:64–71.
- [34] Moseley GL, Butler DS. 15 years of explaining pain—the past, present and future. *J Pain* 2015;16:807–13.
- [35] Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain* 2004;20:324–30.
- [36] Moseley L. Combined physiotherapy and education is efficacious for chronic low back pain. *Aust J Physiother* 2002;48:297–302.

- [37] Nicholas MK, Wilson PH, Goyen J. Operant-behavioural and cognitive-behavioural treatment for chronic low back pain. *Behav Res Ther* 1991; 29:225–38.
- [38] Van Oosterwijck J, Nijs J, Meeus M, Truijen S, Craps J, Van den Keybus N, Paul L. Pain neurophysiology education improves cognitions, pain thresholds, and movement performance in people with chronic whiplash: a pilot study. *J Rehabil Res Dev* 2011;48:43–58.
- [39] Pearl J. Interpretation and identification of causal mediation. *Psychol Methods* 2014;19:459–81.
- [40] Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res Methods Instrum Comput* 2004;36:717–31.
- [41] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *PAIN* 1983;17:45–56.
- [42] Ryan CG, Gray HG, Newton M, Granat MH. Pain biology education and exercise classes compared to pain biology education alone for individuals with chronic low back pain: a pilot randomised controlled trial. *Man Ther* 2010;15:382–7.
- [43] Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;8:70.
- [44] Smeets RJE, Vlaeyen JWS, Kester ADM, Knottnerus JA. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. *J Pain* 2006;7:261–71.
- [45] Spinhoven P, Ter Kuile M, Kole-Snijders AMJ, Hutten Mansfeld M, Den Ouden DJ, Vlaeyen JWS. Catastrophizing and internal pain control as mediators of outcome in the multidisciplinary treatment of chronic low back pain. *Eur J Pain* 2004;8:211–9.
- [46] Stewart M. Effective physician-patient communication and health outcomes: a review. *Can Med Assoc J* 1995;152:1423–33.
- [47] Stratford P, Gill C, Westaway M, Binkley J. Assessing disability and change on individual patients: a report of a patient specific measure. *Physiother Can* 1995;47:258–63.
- [48] Sullivan M, Thorn B, Haythornthwaite J, Keefe F, Martin M, Bradley L, Lefebvre J. Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain* 2001;17:52–64.
- [49] Sullivan MJL, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7:524–32.
- [50] Sullivan MJL, Lynch ME, Clark AJ. Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. *PAIN* 2005;113:310–15.
- [51] Sullivan MJL, Stanish W, Waite H, Sullivan M, Tripp DA. Catastrophizing, pain, and disability in patients with soft-tissue injuries. *PAIN* 1998;77: 253–60.
- [52] Terry EL, Thompson KA, Rhudy JL. Experimental reduction of pain catastrophizing modulates pain report but not spinal nociception as verified by mediation analyses. *PAIN* 2015;156:1477–88.
- [53] Trost Z, Strachan E, Sullivan M, Vervoort T, Avery AR, Afari N. Heritability of pain catastrophizing and associations with experimental pain outcomes: a twin study. *PAIN* 2015;156:514–20.
- [54] Tu YK, Gunnell D, Gilthorpe MS. Simpson's Paradox, Lord's Paradox, and Suppression Effects are the same phenomenon—the reversal paradox. *Emerg Themes Epidemiol* 2008;5:2.
- [55] Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *J Am Med Assoc* 1994;271:1609–14.
- [56] Turner JA, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *PAIN* 2007;127:276–86.
- [57] Turner JA, Mancl L, Aaron LA. Pain-related catastrophizing: a daily process study. *PAIN* 2004;110:103–11.
- [58] VanderWeele TJ. A three-way decomposition of a total effect into direct, indirect, and interactive effects. *Epidemiology* 2013;24:224–32.
- [59] Wallin M, Liedberg G, Börsbo B, Gerde B. Thermal detection and pain thresholds but not pressure pain thresholds are correlated with psychological factors in women with chronic whiplash-associated pain. *Clin J Pain* 2012;28:211–21.
- [60] Wertli MM, Burgstaller JM, Weiser S, Steurer J, Kofmehl R, Held U. Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review. *Spine (Phila Pa 1976)* 2013;39:263–73.
- [61] Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing—a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine J* 2014;14:2639–57.
- [62] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *PAIN* 2011;152:S2–15.