NOVA

University of Newcastle Research Online

nova.newcastle.edu.au

Lee, Hopin; Hübscher, Markus; Moseley, G. Lorimer; Kamper, Steven J.; Traeger, Adrian C.; Skinner, Ian W.; Williams, Christopher M.; McAuley, James H. "An embedded randomised controlled trial of a Teaser Campaign to optimise recruitment in primary care", Published in *Clinical Trials* Vol. 14, Issue 2, p. 162-169. (2017)

Available from: <http://dx.doi.org/10.1177/1740774516683921>

Copyright © 2017 The Authors. Reprinted by permission of SAGE Publications.

This is the author's final accepted manuscript version. Published version title appears as 'An embedded randomised controlled trial of a Teaser Campaign to optimise recruitment in primary care'.

Accessed from: <http://hdl.handle.net/1959.13/1350411>

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

Authors: Hopin Lee^{a,b}, James H. McAuley^{a,b}, Markus Hübscher^{a,b}, Steven J. Kamper^{c,d}, Adrian C. Traeger^{a,b}, G. Lorimer Moseley^{a,e}

Affiliations:

- a. Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia
- b. Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia
- c. EMGO+ Institute, VU University Medical Centre, Amsterdam, Netherlands
- d. The George Institute for Global Health, University of Sydney, Sydney, NSW, Australia
- e. Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia

Corresponding Author:

Hopin Lee
Neuroscience Research Australia, Barker Street, Randwick, NSW 2031, Australia
E-mail: h.lee@neura.edu.au
Telephone: +61093991049
Institutional URL: www.neura.edu.au

Key words: pain education; catastrophizing; mediation analysis; pain; disability

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 theorized that reductions in catastrophizing could mediate the relationship between improvements in pain knowledge and improvements in pain/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% 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, non-significant 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 catastrophizing does not mediate the relationship between pain biology knowledge and pain/function. It remains possible that other psychosocial factors could mediate this relationship.

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 [27]. Pain can be conceptualized as an output into consciousness that motivates a person to take protective action to moderate the danger or threat [26,28]. Empirical evidence suggests a range of factors have a fundamental role in the generation of a painful experience and manipulating those factors can modulate pain [1,32]. 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' - in order to reduce their pain [33].

Evidence from randomized controlled studies shows that explaining pain improves knowledge about pain biology [7,25,31], reduces catastrophizing [7,25,35], reduces pain [31,38,42], 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 [6,47]. That is, the threat value of noxious input or perceived danger is magnified or overestimated [47]. 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 [51,56,60].

A systematic review of observational studies has shown that catastrophizing *predicts* pain intensity and functional capacity in patients with low back pain [57]; a finding that has also been reported in neuropathic pain [49], chronic temporomandibular joint pain [53], pain of

soft tissue injuries of the shoulder, neck and back [50], and osteoarthritis [15]. Despite compelling evidence for a predictive effect, there is only preliminary evidence for a *causal* effect of catastrophizing on pain and function [51].

Although correlations between pain knowledge, catastrophizing, and pain/function have been found in previous studies [20,33,58]; no study has formally tested the role of catastrophizing on the causal path between knowledge and pain/function. This mechanism by which improvements in pain knowledge lead to reduced pain and better function, via reductions in catastrophizing, can be tested using mediation analyses [10]. 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 a 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, USA, and the UK 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. Potential participants were either self-referred or referred via 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, 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, 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 to 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. 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 de-identified 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 (**Figure 1**).

2.2.1 Pain biology knowledge

The Neurophysiology of Pain Questionnaire (NPQ) (**Appendix 1**) [31] 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 whether 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 (ICC = 0.97) in patients with chronic pain [5].

2.2.2 Catastrophizing

The Catastrophic Thoughts about Pain Scale (CATS) (**Appendix 2**) assesses the severity of catastrophizing [19]. 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, UK. Those 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 [48].

2.2.3 Pain intensity

The 100mm visual analogue scale assesses pain intensity [41]. In response to the following question: “What was your average pain level over the last two days?”, the patient is asked to place a mark on a 100mm 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) [3].

2.2.4 Function

The Patient Specific Functional Scale assesses functional capacity [46]. 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) [24]; and acceptable validity and responsiveness in a range of musculoskeletal pain conditions [16].

2.3 Analysis

To test whether catastrophizing mediates the relationship between pain biology knowledge and pain/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 three alternative models with alternative temporal sequences of the 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 two selected time points (**Figure 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/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/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. Armonk, NY: IBM Corp.

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**). DAGs 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, diagnosis, patients' expectation of outcome, patients' perception of the clinician (empathy, attentiveness, and expertise). 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 three 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 three 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 [8,9].

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 three alternative models showed non-significant indirect effects. If the adjusted longitudinal change score analysis indicated a non-significant 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 locked and published our *a priori* protocol prior to commencing analysis (<http://www.bodyinmind.org/resources/protocols/statistical-analysis/catastrophizing-pain/>).

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 three 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).

3.2 Mediation analyses

3.2.1 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% 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 3**). Reported parameters are unstandardized β coefficients.

In the adjusted model, an initial improvement in pain biology knowledge was significantly associated with later reduction in 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 non-significant relationship between changes in catastrophizing and pain intensity (path b = 0.19, 95% CI = -0.03 to 0.41).

3.2.2 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 to 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 non-significant relationship between changes in catastrophizing and function (path b = -0.11, 95% CI = -0.22 to 0.01) (**Table 3**).

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 to 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 non-significant relationship between changes in catastrophizing and function (path b = 0.01, 95% CI = -0.13 to 0.12).

3.2.3 Alternative models

The total effect, direct effect, indirect effect, path a, and path b for the alternative models are presented in **Table 4**. None of the three alternative models for each outcome (pain and function) showed significant indirect effects.

4. DISCUSSION

Main findings

Catastrophizing was not a mediator of the relationship between improved pain biology knowledge and improved pain and 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 did not lead to a reduction in pain, nor an improvement in function (path b). This resulted in a small and non-significant indirect effect through catastrophizing.

Interestingly, our first hypothesis (catastrophizing mediates the relationship between pain biology knowledge and pain) was supported by the unadjusted model, but was not supported by the adjusted model. A likely explanation for the discrepancy in the results from the unadjusted and adjusted models could be due 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 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 [11].

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 [21,52]. 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 3**).

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/function. The selection of our exposure and mediator variables was guided by previous work that demonstrated causal effects of pain education interventions on improving patients' pain biology knowledge [7,25,30] and reducing catastrophizing [7,25,35]. Our study advances existing evidence by demonstrating that knowledge uptake causes a reduction in catastrophizing, but that catastrophizing does not lead to improvements in pain or function. That we observed a direct causal relationship between knowledge uptake and our outcomes (pain and 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 [23,57]. However, most studies did not eliminate the effects of confounding. It is likely that estimates of path b (catastrophizing → pain/function) in previous studies could have been confounded as they were based on simple statistical associations without adjustment for potential covariates [18,22,45,54]. Only one study [44] 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 [13,43]. 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 explicitly state that for causal interpretation of mediation effects, careful consideration for potential confounders is required to satisfy the 'no unmeasured confounding' assumption [39,55]. Our approach to the selection and adjustment of covariates [12,43] leaves us confident that the adjusted effects we observed are less likely to include spurious associations induced by confounding variables. Although the discrepancy

between our findings and previous work may simply reflect that previous work did not look at shifts in catastrophizing associated with improved pain-related knowledge, it is also possible the reported significant mediating effects of catastrophizing in previous studies is influenced by confounding.

What then, might be the mediating pathway by which change in pain biology knowledge results in reduced pain and improved function? Perhaps the most obvious candidate is an indirect effect through an alternative understanding of the meaning and the causes of one's pain [29]. Primary objectives of pain education are to shift one's understanding of pain from an indicator of tissue damage or pathology, to that of a protective mechanism, and to provide an understanding of the increased protective buffer that is afforded by sensitization of nociceptive pathways [33]. That perception of pain depends on meaning is well established [1,32,59] and explaining pain aims to change pain's meaning [4,33,34]. Catastrophizing, on the other hand, focuses on the cognitive responses to pain – 'What if I can't control the pain', and the likelihood of recovery – 'What if the pain doesn't go away'. As such, although both altered conceptualization of the biology of pain and decreased pain-related catastrophizing may arguably reduce pain; that they appear to do so via different mechanistic pathways is perhaps not surprising. Educating patients with information about the biological underpinnings of pain may also motivate patients to change behavior by improving their confidence in carrying out daily activities [2,37]. Self-efficacy has been shown to mediate the development of disability [17] and has also been identified as a mediator for psychological interventions on pain outcomes [23]. Thus, it is worth speculating whether self-efficacy explains a part of the total effect of pain biology knowledge on pain and function.

Strengths and limitations

Strengths of this study include our rigorous approach to identifying confounding variables 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. We also pre-specified a transparent analysis plan and did not deviate from our original protocol. These attributes fulfil key methodological quality criteria for observational mediation studies (**Appendix 5**) [17,23]. 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). We selected potential confounders based on a theory-driven approach that is in line with contemporary standards in epidemiological methodology [12,43]. 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 [14]. Our DAG specified one potential variable (prior beliefs about pain) that could have exerted further confounding effects. However, the adjustment for other covariates (e.g. outcome expectancies and clinicians' attributes) makes our findings more robust, in comparison to previous work that did not explicitly consider confounding effects.

5. CONCLUSION

Our findings show that catastrophizing does not mediate the effect of pain biology knowledge on pain and function. It remains possible that other factors could mediate this relationship.

Acknowledgements and conflicts of interest statement

- Hopin Lee: Grants (National Health & Medical Research Council of Australia)
- James H. McAuley: Grants (National Health & Medical Research Council of Australia)
- Markus Hübscher: None
- Steven J. Kamper: Consultancy (AO Spine: providing methodological advice for research projects); Employment (National Health & Medical Research Council of Australia)
- Adrian C. Traeger: Grants (National Health & Medical Research Council of Australia)
- G. Lorimer 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)

REFERENCES

- [1] Arntz A, Claassens L. The meaning of pain influences its experienced intensity. *Pain* 2004;109:20–25.
- [2] Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev* 1977;84:191.
- [3] Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med* 2001;8:1153–1157.
- [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] Ellis A. *Reason and emotion in psychotherapy*. New York: Lyle Stuart, 1962.
- [7] 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.
- [8] Greitemeyer T, McLatchie N. Denying humanness to others: a newly discovered mechanism by which violent video games increase aggressive behavior. *Psychol Sci* 2011;22:659–665.
- [9] Guendelman MD, Cheryan S, Monin B. Fitting in but getting fat: identity threat and dietary choices among U.S. immigrant groups. *Psychol Sci* 2011;22:959–967.
- [10] Hayes AF. Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Commun Monogr* 2009;76:408–420.

- [11] 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;155:176–184.
- [12] Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health* 2006;60:578–586.
- [13] Hernández-Díaz S, Wilcox AJ, Schisterman EF, Hernán M a. From causal diagrams to birth weight-specific curves of infant mortality. *Eur J Epidemiol* 2008;23:163–166.
- [14] Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *BMJ* 2010;340.
- [15] 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;87:325–334.
- [16] 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.
- [17] 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;156:988–997.
- [18] Leeuw M, Goossens MEJB, van Breukelen GJP, de Jong JR, Heuts PHTG, Smeets RJEM, Köke AJ a, 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.

- [19] Lefebvre J, Keefe F, Caldwell D, Waters S, Ulrich A. The development of the catastrophizing-state (CATS) scale in a clinical sample. 10th World Congress on Pain. San Diego, 2002.
- [20] Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Arch Phys Med Rehabil* 2011;92:2041–56.
- [21] MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. *Prev Sci* 2000;1:173–81.
- [22] Mannion AF, Mu M, Taimela S, Dvorak J. A Randomized Clinical Trial of Three Active Therapies for Chronic. *Spine (Phila Pa 1976)* 1999;24:2435–2448.
- [23] 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.
- [24] Maughan EF, Lewis JS. Outcome measures in chronic low back pain. *Eur Spine J* 2010;19:1484–1494.
- [25] Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen 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.
- [26] Melzack R, Wall PD. Textbook of pain. Churchill Livingstone, 1999.
- [27] Merskey H, Bogduk N. Classification of chronic pain, IASP Task Force on Taxonomy. Seattle, WA Int Assoc Study Pain Press (available online www.iasp-pain.org) 1994.
- [28] Moseley G. A pain neuromatrix approach to patients with chronic pain. *Man Ther* 2003;8:130–140.

- [29] Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain* 2004;8:39–45.
- [30] 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.
- [31] 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;4:184–189.
- [32] Moseley GL, Arntz A. The context of a noxious stimulus affects the pain it evokes. *Pain* 2007;133:64–71.
- [33] Moseley GL, Butler DS. 15 Years of Explaining Pain - The Past, Present and Future. *J Pain* 2015;16(9):807-813.
- [34] Moseley GL, Butler DS. *The Explain Pain Handbook: Protectometer*. Adelaide: Noigroup Publications, 2015.
- [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. The pain self-efficacy questionnaire: Taking pain into account. *Eur J Pain* 2007;11:153–163.
- [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(4):459-81
- [40] Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behav Res methods instruments 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 RJEM, 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 D-J, 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] Stratford P, Gill C, Westaway M, Binkley J. Assessing Disability and Change on Individual Patients: A Report of a Patient Specific Measure. *Physiother Canada* 1995.

- [47] 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.
- [48] Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychol Assess* 1995;7:524–532.
- [49] Sullivan MJL, Lynch ME, Clark a. J. Dimensions of catastrophic thinking associated with pain experience and disability in patients with neuropathic pain conditions. *Pain* 2005;113:310–315.
- [50] Sullivan MJL, Stanish W, Waite H, Sullivan M, Tripp D a. Catastrophizing, pain, and disability in patients with soft-tissue injuries. *Pain* 1998;77:253–260.
- [51] 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;156:1477–1488.
- [52] Tu Y-K, 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.
- [53] Turner JA., Mancl L, Aaron LA. Pain-related catastrophizing: A daily process study. *Pain* 2004;110:103–111.
- [54] Turner J, Holtzman S, Mancl L. Mediators, moderators, and predictors of therapeutic change in cognitive-behavioral therapy for chronic pain. *Pain* 2007;127:276–86.
- [55] VanderWeele TJ. A three-way decomposition of a total effect into direct, indirect, and interactive effects. *Epidemiology* 2013;24:224–32.

- [56] Wallin M, Liedberg G, Börsbo B, Gerdle 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;28:211–221.
- [57] 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.
- [58] 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.
- [59] Wiech K, Lin C, Brodersen KH, Bingel U, Ploner M, Tracey I. Anterior insula integrates information about salience into perceptual decisions about pain. *J Neurosci* 2010;30:16324–16331.
- [60] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2011;152:S2–15.

FIGURE CAPTIONS

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.

Figure 2. Participant flow