Are individual levels of pain anxiety related to negative interpretation bias?

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Are individual levels of pain anxiety related to negative interpretation bias? An examination using an ambiguous word priming task

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Abstract

Background: Cognitive processes like attentional and interpretation biases have been suggested to play a vital role in the onset and exacerbation of chronic pain. Research consistently supports the occurrence of interpretation bias (IB) in pain patients and healthy individuals high in pain anxiety. Nevertheless, studies on the indirect assessment of IB or the relation between IB and responses to pain are limited. The present studies examined the association between indirect assessed IB and pain anxiety, while Study 2 additionally examined IB as a mediator in the relation between pain anxiety and pain responses.
Method: In Study 1 ($N = 125$) and Study 2 ($N = 73$), anxiety sensitivity, injury/illness sensitivity (IS) and pain catastrophizing were assessed with questionnaires. IB was indirectly derived from performance on an ambiguous word priming task. In Study 2, an experimental heat pain induction was used to assess pain responses (i.e. tolerance and subjective pain experience).
Results: Results showed a positive correlation between pain anxiety and IB, albeit that the strength of the observed associations differed between both studies. Furthermore, IB was inversely related to pain tolerance, and found to mediate the relation between IS and pain tolerance in Study 2.
Conclusions: Current findings underscore the importance of interpretational processes in the context of physical health threat. Furthermore, the ambiguous word priming task is proposed as a suitable paradigm for further research on the indirect assessment of IB. Nevertheless, further research is warranted to deepen our understanding of IB and its contribution to the experience of (chronic) pain.

1. Introduction

Contrasting the extensive body of research on attentional bias in the domain of pain (Schoth et al., 2012; Crombez et al., 2013), studies on interpretation bias (IB) are considerably less numerous. Nevertheless, these few studies consistently demonstrated the occurrence of IB in pain patients (e.g. Edwards and Pearce, 1994; Pincus et al., 1994, 1996). Pain-directed IB has been reported to be specific to the state of pain, and independent of levels of broad negative emotionality like neuroticism or trait anxiety (Pincus et al., 1994, 1996). However, paralleling the vital role of IB in the onset and maintenance of anxiety disorders (Mathews and Mackintosh, 1998; Hertel and Mathews, 2011), IB might be suggested to play a steering role in pain, rather than being a byproduct of the state of pain only. One way to examine this is by studying IB in function of specific pain anxiety

What's already known about this topic?
- Pain patients and pain anxious individuals show negative interpretation bias for pain-related ambiguity.
- Interpretational processes are considered to guide emotional and behavioural responses to pain.

What does this study add?
- Pain anxiety is associated with the *automatized* tendency to make negative, health threatening interpretations, as assessed with an ambiguous word priming paradigm.
- Negative interpretation bias is associated with *lower tolerance* for unfamiliar pain.

constructs known to hold vulnerability for pain (i.e. anxiety sensitivity (AS), injury/illness sensitivity (IS), pain catastrophizing (PC) (e.g. Keogh and Asmundson, 2004). In pain patients, Khatibi et al. (2015) recently reported a positive association between pain-directed IB and levels of pain catastrophizing and fear of pain. In nonclinical populations, positive associations between IB and pain anxiety have been frequently reported (Keogh and Cochrane, 2002; Keogh et al., 2004; Vancleef and Peters, 2008; Khatibi et al., 2014a,b). Moreover, Keogh and colleagues (Keogh and Cochrane 2002; Keogh et al. 2004) identified IB as a mediator in the relation between AS and pain tolerance, suggesting that IB could be an explanatory mechanism for the link between pain anxiety and pain outcomes.

Studies on IB in the domain of pain merely relied on direct assessment methods like vignette questionnaires or paper-and-pencil association tasks (e.g. Edwards and Pearce, 1994; Keogh and Cochrane, 2002; Vancleef and Peters, 2008). Besides drawbacks of social desirability and response bias, the typical non-time constrained nature of these measures makes them less suitable to tap into spontaneous interpretations as made immediately upon confrontation with ambiguity (Richards and French, 1992; Mathews and MacLeod, 1994). Indirect measures of IB, like the homograph priming task (Richards and French, 1992), are proposed to overcome these limitations. In this computerized task, lexical decisions are required to targets following ambiguous prime words. IB is then derived from facilitated responses to concern-congruent over neutrally related word targets. Richards and French (1992) demonstrated this task to be sensitive to assess anxiety-related IB in high anxious individuals.

We modified the homograph priming task for the assessment of IB in the context of pain and physical health threat in a nonclinical population. Study 1 examined the hypothesis that pain anxiety levels (i.e. AS, IS and pain catastrophizing) are positively associated with IB. Study 2 additionally examined the direct relation between IB and responses to experimentally induced pain, and the mediating role of IB in the relation between pain anxiety and pain responses (i.e. pain tolerance, experienced intensity, unpleasantness and fear of pain).

2. Study 1

2.1 Method

2.1.1 Participants

125 healthy participants (44 male; 81 female) with a mean age of 25.41 years (SD = 8.88) were recruited at Maastricht's University local community to participate in the study. Inclusion criteria stated (1) being natively Dutch speaking and (2) being free from pain complaints at the moment of testing. Dyslexia was formulated as an exclusion criterion because the IB assessment required fast lexical decision responses to briefly presented ambiguous words. To ensure compliance with these criteria, they were stated on recruitment folders, and were verbally queried at the moment of scheduling a test appointment by telephone or email. A final check for compliance with in- and exclusion criteria was done at the moment that participants came for their test appointment and did not result in exclusion of participants at that point anymore. Participants took part in the study in exchange for course credits or a gift voucher. The study protocol was approved by the local ethical board of the Faculty of Psychology and Neuroscience, Maastricht University, the Netherlands.

2.2 Material and measures

2.2.1 Self-report measures

Anxiety sensitivity was assessed with the Anxiety Sensitivity Index (ASI; Peterson and Heilbronner, 1987). The ASI contains 16 statements that assert the negative consequences of experiencing anxiety (e.g. 'It scares me when my heart beats rapidly'). The ASI has good psychometric properties (e.g.

Peterson and Heilbronner, 1987; Zinbarg and Barlow, 1996; Vancleef et al., 2006). Internal consistency in the current study was good with Cronbach's $\alpha = 0.80$.

The Illness/injury Sensitivity Index-revised (ISI-R; Carleton et al., 2006) was administered to assess fear of injury and illness. The ISI-R contains nine items (e.g. 'The thought of injury terrifies me') that are scored on a 5-point Likert-Scale (0 = not at all agree; 4 = totally agree). Total scores are commonly used to assess a general fear of physical harm (Carleton et al., 2006). The ISI-R has good psychometric qualities (Carleton et al., 2006; Vancleef et al., 2006). In the current study, the ISI-R had good internal consistency with Cronbach's $\alpha = 0.87$.

Pain catastrophizing was assessed with the Pain Catastrophizing Scale (PCS; Sullivan et al., 1995). Keeping painful situations in mind, participants indicate on a 5-point Likert Scale (0 = not at all; 4 = all the time) to what extent they experience each of 13 feelings and thoughts when in pain (e.g. 'I feel as if I can't take this anymore'). The PCS has proven to be a reliable and valid measure and was found suitable to measure pain catastrophizing in both healthy and clinical populations (Sullivan et al., 1995; Severeijns et al., 2002; Van Damme et al., 2002). Cronbach's alpha in the present study was excellent with (Cronbach's $\alpha = 0.89$).

2.2.2 Ambiguous word priming task

IB was assessed with an ambiguous word priming task that we modelled after the homograph priming paradigm by Richards and French (1992). The task consists of 84 trials (i.e. prime-target pairs) in which the prime is always an ambiguous word and the target is either a word or a non-word. In case of word targets, 50% are related to the word prime and the remainder are unrelated to the ambiguous prime. Each trial starts with the presentation of a central fixation cross (250 ms), followed by the presentation of the ambiguous prime word. After 500 ms, the prime word is briefly replaced by a blank screen (250 ms) followed by the presentation of the target word centrally on screen. The target word remains on screen until a response is provided or 5000 ms have past. Participants are instructed to make a lexical decision to the target (i.e. word or nonword) fast and accurately as possible. It is assumed that responses are facilitated (i.e. faster and more accurate) for target words that are in accordance with the meaning that was activated by the preceding prime word.

Within the task, *critical* trials are included for which the ambiguous prime word can have both a health threatening and a non-health related meaning (e.g. needle). Each prime word is then followed by either (1) a target word that is semantically related to the health threatening meaning of the prime word (i.e. wound) or (2) a target word that is semantically related to the non-health threatening meaning of the prime word (i.e. embroidery) or (3) a target word that is semantically unrelated to the potential meanings of the prime word (i.e. chair). Critical ambiguous prime words ($N = 15$)1 were selected from a word rating pilot conducted in 39 healthy volunteers, in which 45 ambiguous words were presented in combination with potential target words (health threatening and non-health threatening). Respondents indicated the relatedness of each target word to the ambiguous prime word (0–100%). As a general rule, word pairs were selected as eligible for incorporation in the task when the relatedness percentage was higher than 60% for both the health threatening and a non-health threatening related target word. In addition, word pairs on which either respondents or members of the research group commented that one of the words was infrequently used in Dutch language were not incorporated in the task. Furthermore, we aimed to include word pairs for which relatedness percentage for both target words did not deviate more than 15% from one another. These criteria were set to ensure that selected ambiguous words were paired with targets that were both commonly associated to the prime word, while one word meaning was not highly dominant over the other target word meaning. Stimulus words and corresponding word pilot ratings are presented in Table S1.

Unrelated target words were assigned to the ambiguous primes by hand to ensure that the target word was not related to the prime. After selecting the critical word pairs, these pairs were distributed over three wordlists. Because each ambiguous prime was presented only once to participants, target words were as a category counterbalanced over the three word lists such that each list consisted of five health threatening prime-target pairs, five non-health threatening prime-target pairs and five unrelated prime-target pairs. To illustrate, the prime 'needle' was followed by the health threatening target 'Wound' for 1/3 of all participants, by the target 'embroidery' for 1/3 of participants and by the word 'chair' for one-third of participants.

Additional prime target pairs were added to the task to ensure methodological soundness of the task.

To make sure that the task was not transparent with respect to its goal to assess reactions to health threat related ambiguity, neutral filler pairs were incorporated that consisted of a neutral ambiguous prime words followed by a neutral target word or an unrelated target word. The proportion of word targets was kept equal to the proportion of non-word targets by adding neutral ambiguous word primes followed by a non-word (Bisson and Sears, 2007). All target words were categorically matched on word length. Except for the critical prime-target trials, all other trials were identical in all three conditions. In total, the task consisted of 84 trials (prime-target word pairs), meaning that 168 words were presented to participants. Split-half reliability (intraclass correlation coefficients) as calculated over the *ambiguous critical word* trials (first and second test half) indicated satisfactory reliability with $r = 0.64$. Split half reliability as calculated over target categories within the critical ambiguous word pairs (health threatening, neutral, non-related) also indicated satisfactory split-half reliability, ranging from $r = 0.54$ to 0.71. Split-half reliability as calculated over IB Index scores was low, however, with $r = 0.05$. Please note that the latter calculations include a few trials only (2–3 trials per test half), which negatively affects the split-half coefficient.

2.3 Procedure

Participants were tested in a sound attenuated laboratory in the university building. After providing informed consent, participants were seated behind the PC at a seating distance of approximately 60 cm. Task instructions for the ambiguous word priming task appeared on screen. The task started with a practice phase (8 non-health related ambiguous prime words and targets), to get participants acquainted with the response procedure. Upon completion of the interpretation task, participants completed the ASI. The ISI-R and the PCS.

2.4 Statistical analyses

Prior to data analysis, individual reaction times (RT) that deviated more than 3SDs from the general RT or below 300 ms (Richards and French, 1992) were removed from the datafile (300 ms < RT < 1532 ms; 0.02% of all trials). One participant showed an error percentage score (35.5%) which deviated more than 3SD from the general error percentage (mean = 5.51, SD = 4.83). Data of this participant were therefore excluded from all further analyses. Mean error percentage was 5.33, SD = 4.03. For the homograph priming task, analyses were conducted on RT scores for correct lexical decision responses only (Richards and French, 1992).

First, several independent samples *t*-tests were conducted to test task assumptions of semantic priming in the task by testing whether responses were faster to word over non-word trials, and to related over unrelated word trials. The latter assumption was tested in the filler word trials only, as responses to critical word trials are hypothesized to be influenced by interpretational tendencies.

Next, an IB Index was calculated by subtracting RT on the health threatening resolutions of ambiguity from RT on the non-health threatening resolutions of ambiguity. Positive scores are then indicative of prioritizing the health threatening over the neutral meaning of the ambiguous prime word (i.e. negative interpretation bias), while negative scores indicate prioritizing the positive over the negative interpretation of ambiguity.

The relation between IB and the pain anxiety constructs (AS, IS, PC) was examined with Pearson correlation coefficients. Scatterplots, including fitted linear regression line are presented to aid interpretation of the correlation analyses.

Effect sizes and 95% confidence intervals (CI) are added to illustrate strength of observed effects (Lakens, 2013).

2.5 Results

Descriptive statistics for the pain anxiety measures are presented in Table 1. Inspection of Table 1 shows relatively low scores on both the ASI and PCS given the possible range 0–64 and 0–52, respectively.

Overall mean RT in the ambiguous word priming task was 627.34 ms (SD = 133.06). The check of task assumptions demonstrated that, irrespective of target category, responses were faster to word (597.62 ms, SD = 134.51) than to non-word trials (653.48 ms, SD = 139.49), with $t(123) = 9.78$, $p < 0.001$; 95% CI (−67.15, −0.36), Hedges $g_{av} = 0.41$. Furthermore, responses to related targets (573.42 ms,

Table 1 Descriptive statistics (mean, standard deviation, minimum, maximum) and Pearson correlation coefficients for the pain anxiety measures ($N = 125$).

Measure	M	SD	Min	Max	2	3
1. ASI	10.78	5.93	3	29	0.58**	0.54**
2. ISI-R	7.60	5.80	0	29		0.61**
3. PCS	10.51	6.91	1	35		

ASI, Anxiety Sensitivity Index; ISI-R, Injury/Illness Sensitivity Index revised; PCS, Pain Catastrophizing Scale.
**$p \leq 0.01$.

SD = 135.54) were faster than responses to unrelated targets (585.08 ms, SD = 129.63) in the filler trials with $t(123) = 2.04$, $p < 0.05$, 95% CI (−24.93, −0.36), Hedges $g_{av} = 0.09$.

Mean IB Index was −26.24 ms (SD = 103.49). Pearson correlations showed a positive significant correlation between the IB Index and AS ($r = 0.24$, $p = 0.008$, Fig. 1a), IS ($r = 0.24$ $p = 0.006$, Fig. 1b), and PC ($r = 0.23$, $p = 0.008$, Fig. 1c), respectively.

3. Study 2

Results of Study 1 demonstrated a positive association between IB as measured with an ambiguous word priming paradigm and AS, IS and PC.

In addition to replicating findings of Study 1, Study 2 aims to examine the relation between IB and responses to experimentally induced heat pain. Cognitive appraisal and interpretation of pain have been put forward as important predictors of the emotional and behavioural responses that individuals show to pain (Pincus and Morley, 2001; Gatchel et al., 2007). Likewise, information processing theories and dual processing theories postulate that concern congruent cognitive biases steer further behavioural responding, thereby exercising a crucial role within the maintenance of psychopathology (Riemann and McNally, 1995; Mathews and Mackintosh, 1998; Fazio and Olson, 2003). Notwithstanding these theoretical postulations, only few empirical studies have moved beyond the goal of examining the occurrence of IB in the domain of pain to study its relation with relevant pain outcomes. Some tentative evidence for a relation between IB and pain responses (i.e. pain tolerance) stems from studies by Keogh and colleagues (Keogh and Cochrane 2002; Keogh et al. 2004), who demonstrated IB to mediated the relation between AS and tolerance for cold pressor pain. Recently, causal effects of IB on pain avoidance behaviour were reported (Jones and Sharpe, 2014). Further examination of the relation between IB and pain outcomes is especially relevant in the light of recent advances in the field of cognitive bias modification where alterations in cognitive bias are assumed to exert beneficial effects on emotional and behavioural outcomes (Hertel and Mathews, 2011; Jones and Sharpe, 2014).

In Study 2, the following hypotheses were formulated: (1) elevated levels of pain anxiety (i.e. AS, IS, PC) are associated with IB towards health threat (replication study 1), (2) elevated levels of pain anxiety are associated with responses to an experimentally induced heat pain stimulus (i.e. tolerance, subjective ratings of pain intensity, pain unpleasantness and fear of pain), (3) IB mediates the relation between pain anxiety and pain responses. To increase ecological validity of the pain stimulus, a physical sensory stimulus was used that entailed a certain degree of uncertainty and ambiguity for participants. More specifically, participants were

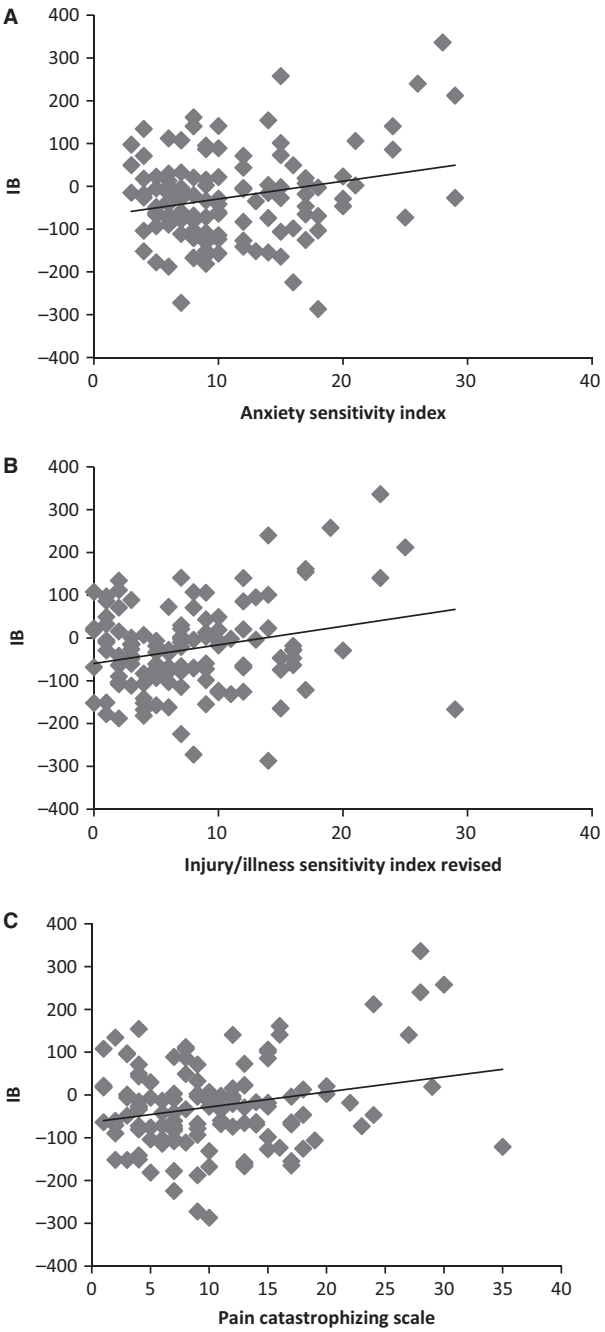

Figure 1 Scatterplots depicting Pearson correlation coefficients and linear fitted regression lines for the Interpretation Bias Index (IB) and anxiety sensitivity (a), Injury/Illness Sensitivity Index (b) and pain catastrophizing (c).

exposed to a heat pain stimulus that they had never experienced before, which was introduced to participants as a 'warmth sensation with the potential of becoming painful' (see Method section).

3.1 Method

3.1.1 Participants

Participants were recruited at Maastricht's University local community. The following exclusion criteria were set in addition to the inclusion and exclusion criteria of Study 1: (1) participation in Study 1; (2) presence of any of the following conditions: pregnancy, (history of) cardiovascular and neurological problems (e.g. thrombosis, epilepsy), current injury on the non-dominant arm, (3) no prior experience with the experimental heat pain induction. 74 participants agreed to participate. However, as the pain induction procedure failed for one of the participants due to technical difficulties, a total of 73 participants (11 male; 62 female) with a mean age of 24.5 years (SD = 8.35) were included in the data file. The study protocol was approved by the ethical board of the Faculty of Psychology and Neuroscience, Maastricht University, The Netherlands.

3.2 Materials and measures

Pain anxiety measures (ASI, ISI-R, PCS) and IB task (ambiguous word priming task) were identical to Study 1.

3.2.1 Pain induction: Heat pain

The heat stimulus was applied on the volar forearm of the non-dominant arm through a 30 mm × 30 mm contact thermode (MEDOC-ATS, Ltd Advanced Medical System, Ramat Yishai, Israel).Via the limits procedure, a stimulus was administered that started at baseline temperature (32 °C) and that gradually increased in temperature (rate = 1 °C/s) until tolerance was reached or the pre-set maximum temperature of 51 °C was reached. When the stimulus was broken off by the participant, or when the maximum temperature of 51 °C was reached, stimulus temperature instantaneously decreased (rate = 8 °C/s) to baseline temperature.

3.2.2 Pain intensity, pain unpleasantness and fear of pain

Experienced pain intensity, experienced pain unpleasantness and experienced fear of pain were assessed on a 100 mm Visual Analogue Scale (VAS) that was anchored with 'not at all painful/not at all unpleasant/not all afraid' at the left extreme and 'extremely painful/extremely unpleasant/extremely afraid' at the right extreme. Each VAS referred explicitly to the moment at which participants decided to break off the stimulus (e.g. for pain intensity: 'How painful was the warmth stimulus at the moment that you decided to break it off?').

3.3 Procedure

The procedure was identical to that of Study 1 up until finishing the ambiguous word priming task. Next, the pain induction procedure was started. Participants were informed that the stimulus would gradually increase in temperature and could progress from feeling 'pleasantly warm' to 'painfully hot'. They were informed that the warmth stimulus would not result in tissue damage or burn wounds. The experimenter explained and demonstrated how participants could break off the stimulus instantaneously by pushing a response button that they held in their dominant hand during the induction. Participants were explicitly instructed to break off the warmth stimulus 'at the moment that they felt they could not bear it any longer'. Next the probe was attached to the volar forearm of the non-dominant arm. The experimenter ensured that the participant was seated comfortably during the induction procedure; the arm stretched out and resting on an armchair, and the stop button in the dominant hand. The stimulus started after a verbal signal of the experimenter. After termination of the warmth stimulus the temperature returned to baseline temperature and the thermode was removed. Participants next completed VAS ratings for experienced pain intensity, unpleasantness and fear of the warmth stimulus. Next, they completed the self-report measures (i.e. ASI, ISI-R, PCS).

3.4 Statistical analyses

RT data were handled as in Study 1. Individual RT that deviated more than 3SDs from the general RT or that were below 300 ms were deleted from the datafile (300 ms < RT < 1204.26 ms; 0.02% of all trials).

IB Index was calculated as in Study 1. Pearson correlation coefficients were calculated to explore associations between (1) pain anxiety (AS, IS, PC) and IB; (2) pain anxiety and pain outcome measures (i.e. pain intensity, pain unpleasantness, fear of heat

pain, heat pain tolerance); (3) IB and pain outcome measures. As subjective pain ratings are confounded by tolerance (higher tolerance means longer exposure to and higher temperature of the heat stimulus), pain tolerance was controlled for in all analyses were the pain ratings (intensity, unpleasantness, fear) were incorporated. Scatterplots, including fitted linear regression line are presented to aid interpretation of the correlation analyses.

Effect sizes and 95% CI are added to illustrate strength of observed effects (Lakens, 2013).

Next, IB was examined as a mediator in the relation between pain anxiety (AS, IS, PC, respectively) and the pain outcome measures (tolerance for heat pain, pain intensity, pain unpleasantness, fear of pain). Direct and indirect effects of pain anxiety constructs via IB to the pain outcome measures were estimated and a bootstrapping procedure was used to decide on mediation (Hayes, 2009, 2013). Mediation was decided on when zero fell outside the 95% bias-corrected CI that was calculated around the indirect effect (with 5000 bootstrap samples) (Preacher and Hayes, 2008; Hayes, 2009). Pain tolerance was entered as a covariate in all models where pain intensity, pain unpleasantness or fear of pain were dependent variables. Note that, in contrast with former mediation testing methods (i.e. Baron and Kenny, 1986), a significant association between independent and dependent variable is not considered a prerequisite for mediational testing in the current approach (Hayes, 2009).

3.5 Results

Overall mean RT in the interpretation task was 583.09 ms (SD = 96.05). Mean error percentage was 3.87%, SD = 3.07. *T*-tests were conducted to check task assumptions and showed that in general, responses were faster to word (558.62 ms; SD = 92.78) than to non-word trials (604.64 ms; SD = 98.94) with $t(72) = -8.32$, $p < 0.001$; 95% CI (−57.03; −34.98), Hedges $g_{av} = 0.48$; and to related (541.14 ms; SD = 92.61) than to unrelated to targets (552.73; SD = 96.04) with $t(72) = -1.99$, $p = 0.05$, 95% CI (−23.17, 0.004), Hedges $g_{av} = 0.12$, within the filler trials.

Table 2 presents descriptive statistics for the main variables. Pearson correlations (Table 2; Fig. 2) between the IB Index and the pain anxiety measures showed a marginally significant correlation between IB Index and ISI-R only, with $r = 0.23$, $p = 0.05$ (Fig. 2b). Furthermore, enhanced levels of pain directed IB were found to be significantly associated with lower tolerance for the heat pain stimulus. Fear of pain, but none of the other subjective pain ratings, was found to be significantly associated with AS, IS and PC. Four participants were able to tolerate the heat stimulus until the predefined maximal temperature was reached and did thus not reach pain tolerance. When analyses were repeated in the sample excluding these four participants ($N = 69$), a similar pattern of results was observed.

We next proceeded with testing the direct and indirect effects of pain anxiety on the pain outcome measures via IB, or in other words, the mediational effect of IB. Note that the correlation analysis (Table 2) showed the relation between pain anxiety and pain outcome variables to be significant for fear of pain only. Nevertheless, we tested the mediating role of IB for all pain anxiety-pain outcome relations. As advocated by (Hayes, 2009) a significant relation between predictor and outcome variable is not a prerequisite for indirect effects to occur (*see*

Table 2 Mean (M), standard deviation (SD), minimum score (Min.), maximum score (Max.) and correlation coefficients (zero order and partial correlation coefficients) for pain anxiety, Interpretation Bias Index and pain outcome measures ($N = 73$).

Measure	M	SD	Min	Max	2.	3.	4.	5.	6.	7.	8.
1. ASI	10.64	5.74	0	27	0.43**	0.58**	0.04	0.06	−0.17[a]	0.09[a]	0.36**,[a]
2. ISI-R	6.43	5.06	0	26		0.53**	0.23*	0.06	−0.15[a]	0.09[a]	0.45**,[a]
3. PCS	11.85	8.12	1	38			0.06	0.12[a]	−0.13[a]	−0.03[a]	0.25*,[a]
4. IB Index	−27.96	82.37	−265.20	140.25				−0.25*	−0.07[a]	0.15[a]	0.16[a]
5. Tolerance	47.56	2.65	37.6	51.1					0.31**	0.29*	0.03
6. Pain intensity	54.27	24.36	1	92						0.66**,[a]	0.13[a]
7. Pain unpleasantness	49.59	25.47	9	97							0.41**,[a]
8. Fear of pain	32.58	24.58	0	84							

ASI, Anxiety Sensitivity Index; ISI-R, Injury/Illness Sensitivity Index revised; PCS, Pain Catastrophizing Scale; IB-Index, Interpretation Bias Index.
*$p \leq 0.05$.
**$p \leq 0.01$.
[a]Partial correlation coefficients controlled for pain tolerance.

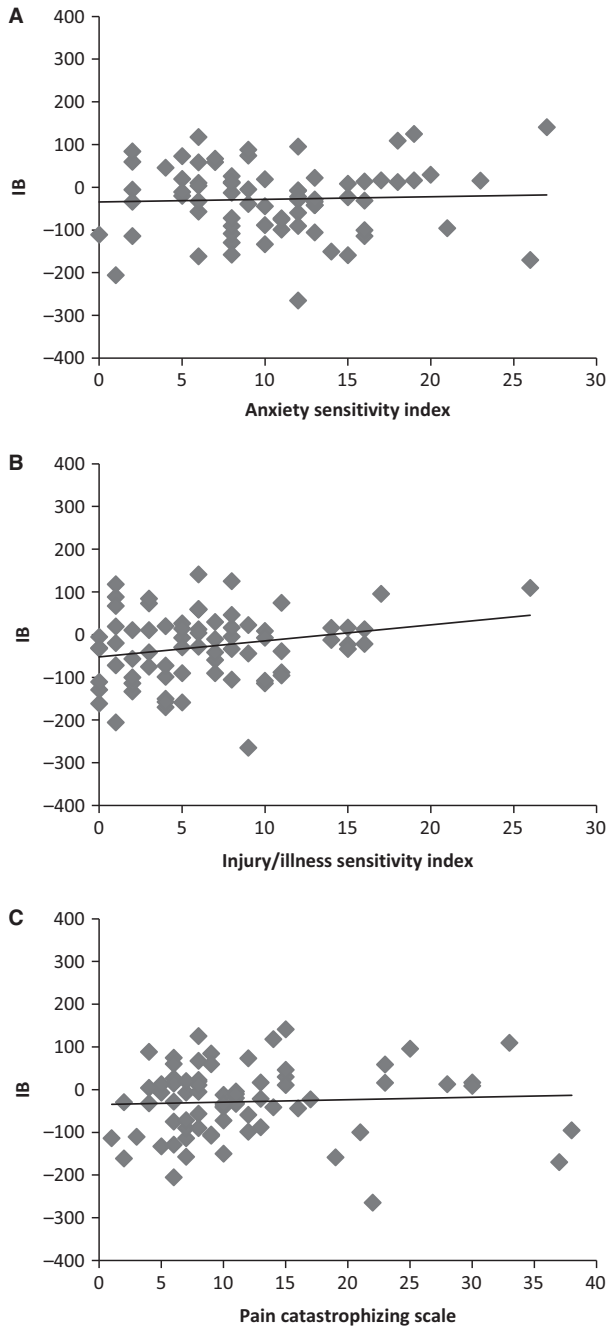

Figure 2 Scatterplots depicting Pearson correlation coefficients and linear fitted regression lines for the Interpretation Bias Index (IB) and anxiety sensitivity (a), Injury/Illness Sensitivity Index (b) and pain catastrophizing (c).

Hayes, 2009 for a detailed discussion). In Table 3, unstandardized coefficients of direct and indirect effects can be found. Furthermore, Table 3 displays the 95% CI for the indirect effect in all mediational models that were tested. IB could be identified as a mediator in the relation between IS and pain tolerance only, with 95% CI (−0.963; −0.0018) (see Fig. 3). All other mediational analyses did not yield significant indirect effects.

3.6 Overall analyses

As results of Study 1 regarding the associations between pain anxiety and IB were only partially replicated in Study 2, we additionally pooled the data of both studies together ($N = 197$). First, we conducted a series of linear regression analyses, with IB Index as dependent variable, and one of the pain anxiety constructs (ASI, ISI-R, PCS respectively; all centred), 'Study' (1 vs. 2; dummy coded), and the interaction between 'study' and pain anxiety (product term) as predictor variables (Table 4). The relation between pain anxiety and IB Index was not found to be significantly influenced by 'study'. We next calculated Pearson correlation coefficients within the pooled data set, resulting in moderate positive correlations between IB and AS ($r = 0.18$, $p = 0.01$), IB and ISI-R ($r = 0.24$, $p = 0.001$), and IB and PCS ($r = 0.17$, $p = 0.02$).

4. Discussion and conclusions

In two studies, an ambiguous word priming paradigm was used to examine whether elevated levels of pain anxiety in healthy participants are associated with the tendency to make negative interpretations of health related ambiguity, and whether IB is associated with responses to experimentally induced pain, thereby mediating the relation between pain anxiety and pain responses. Results demonstrate a positive association between IB and elevated levels of IS, AS and PC. Furthermore, IB was found to be negatively related to pain tolerance, and to mediate the relation between IS and pain tolerance.

Current findings offer support for the idea that individual levels of pain anxiety are associated with IB (Keogh and Cochrane, 2002; Keogh et al., 2004; Vancleef and Peters, 2008; Khatibi et al., 2014a,b). Although Study 2 only showed a significant correlation between IS and IB, Study 1 as well as the pooled data of both studies showed significant positive relations between all three pain anxiety levels and IB.

Differences in study procedure might underlie divergent findings between both studies. For example, the fact that persons are aware of upcoming pain in a controlled lab environment in Study 2 might have superimposed on effects of pain anxiety.

Table 3 Results of mediational analyses with IB as mediator (M) in the relation between the pain anxiety constructs (IV's) and the pain outcome measures (DV's); point estimates of direct and indirect effects and upper (ULLCI) and lower limit (LLCI) confidence intervals for the indirect effect.

Dependent variable (DV)	Independent variable (IV)	Effect of IV on M	Effect of M on DV	Direct effect (c')	Indirect effect (a * b)	Total effect (c)	LLCI	ULCI
Tolerance	AS	0.6031	−0.0082 *	0.0317	−0.0050	0.0267	−0.0488	0.0252
	IS	3.730*	−0.0091	0.0664	−0.0339	0.0325	−0.0963	−0.0018
	PC	0.5600	−0.0084*	0.0436	−0.0047	0.0389	−0.0413	0.0156
Pain intensity[a]	AS	0.8169	−0.0174	−0.6518	−0.0142	−0.6660	−0.2958	0.1027
	IS	4.005*	−0.0099	−0.6322	−0.0398	−0.6720	−0.3755	0.3262
	PC	0.8794	−0.0168	−0.3675	−0.0148	−0.3823	−0.2471	0.0678
Pain unpleasantness[a]	AS	0.8169	0.0449	0.3297	0.0367	0.3664	−0.1137	0.4406
	IS	4.005*	0.0429	0.2151	0.1717	0.3868	−0.0917	0.7706
	PC	0.8794	0.0474	−0.1220	−0.0417	−0.0803	−0.0624	0.4191
Fear of pain[a]	AS	0.8169	0.0432	1.485**	0.0353	1.520**	−0.1101	0.4118
	IS	4.005*	0.0155	2.109**	0.0622	2.171**	−0.1624	0.5060
	PC	0.8794	0.0431	0.7058*	0.0379	0.7438*	−0.0528	0.3374

AS, anxiety sensitivity; IS, injury/illness sensitivity; PC, pain catastrophizing.
Point estimate significant with *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
[a]Analyses statistically controlled for pain tolerance (covariate).

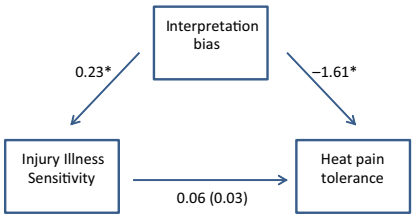

Figure 3 Standardized regression coefficient for the mediational effect of interpretation bias (IB) in the relation between injury/illness sensitivity (IS) and heat pain tolerance. Standardized regression coefficient for the direct effect of IS on heat tolerance, controlled for effect of IB, presented between parentheses.

Table 4 Results of Linear regression analyses with the pain anxiety constructs (AS, IS, PC; centred), Study (Study 1 vs. Study 2; Dummy coded) and their interaction (product term) entered as predictor variables and IB Index score as dependent variable ($N = 197$).

Predictor variable	*B*	*SE B*	β	*t*	*p*
AS	4.17	1.44	0.25	2.90	0.004
Study	−1.38	13.97	−0.01	−0.10	0.921
AS × Study	−3.56	2.42	−0.13	−1.47	.142
$R^2 = 0.04$, $F(3,193) = 2.83$, $p = 0.04$					
IS	4.36	1.46	0.25	2.99	0.003
Study	3.10	13.97	0.02	0.22	0.824
IS × Study	−0.63	2.63	−0.02	−0.24	0.812
$R^2 = 0.06$, $F(3,193) = 3.95$, $p = 0.009$					
PC	3.53	1.24	0.27	2.85	0.005
Study	−3.82	14.03	−0.02	−0.27	0.786
PCS × Study	−2.97	1.85	−0.15	−1.61	0.110
$R^2 = 0.04$, $F(3,193) = 2.77$, $p = 0.04$					

AS, anxiety sensitivity; IS, injury/illness sensitivity; PC, pain catastrophizing.

Furthermore, results of Study 2 and the pooled data indicate a robust relation between IS and IB specifically. This might be explained by the content-specificity of the IB measure (Vancleef and Peters, 2008). Because the self-referential nature of stimuli is an important factor in cognitive bias assessment (Dear et al., 2011), critical ambiguous prime words were chosen after a word pilot study conducted in a population comparable to our study population. Selected ambiguous words reflect general health-threat predominantly. IS defined as specific fearfulness of signals of physical harm or illness (Carleton et al., 2006), is presumably most sensitive to these ambiguous critical prime words. A content-specific relation between pain anxiety and IB has been demonstrated before (Vancleef and Peters, 2008). Moreover, positive associations between pain-directed IB and pain catastrophizing have been reported when less content-specific stimuli were used (i.e. ambiguous facial expressions) (Khatibi et al., 2014a,b, 2015).

Along the lines of our hypotheses, IB was found to be directly associated with tolerance for heat pain, and to mediate the relation between IS and pain tolerance. This finding tentatively adds to the sparse amount of literature demonstrating a direct relation between IB and pain responses (Keogh and Cochrane, 2002; Keogh et al., 2004). Nevertheless, observed relations were modest in strength only, and no association was found between IB and the subjective pain ratings. Further research aimed at substantiating the link between IB and pain outcomes seems especially relevant in the light of recent cognitive

bias modification research, where alterations in cognitive biases are hypothesized to yield positive emotional and behavioural outcomes (Hertel and Mathews, 2011; Jones and Sharpe, 2014). One might argue that in examining the relation between IB and pain, it would have been more interesting to use a more 'ambiguous' sensory stimulus. It is important to note, though, that participants did not have prior experience with the heat pain stimulus before the tolerance assessment and that the stimulus was administered only once. Hence, results indicate that the extent to which one is willing to tolerate an unfamiliar and potentially painful physical sensation is inversely associated with the tendency to make negative interpretations of health related ambiguity. Nevertheless, an intriguing question for future research concerns the relation between IB and the tendency to label ambiguous sensory stimuli as 'painful'. In addition to contextual factors (e.g. threat value), cognitive factors like IB might help explain individual decisions about painfulness and its meaning to the pain sufferer (Arntz and Claassens, 2004; Moseley and Arntz, 2007; Wiech et al., 2010).

Somewhat surprisingly, pain anxiety levels were found to be unrelated to tolerance for the heat stimulus. However, note again that the pain stimulus was only administered once and could be stopped by participants whenever they wanted. It is likely that this specific procedure was too mild to induce the type of intolerable and uncontrollable pain that is often aimed at in experimental pain induction procedures. Indeed, relatively low pain intensity and unpleasantness ratings were reported here (mean VAS scores around 50). Tolerance was found associated with pain intensity and pain unpleasantness though, thereby supporting the general principle that longer exposure to pain also yields higher intensity and unpleasantness reports. Furthermore, fear of pain was be highly associated with pain anxiety (Vlaeyen and Linton, 2000; Leeuw et al., 2007).

An overall goal of this study was to test the ambiguous word priming task as a suitable paradigm for the indirect, fast and reliable assessment of IB in the context of pain. The merit of the homograph priming task was already demonstrated by Richards and French (1992) and the current study confirms its potential to become a more widely adopted paradigm for the indirect assessment of IB. The paradigm is sensitive to differentiate words from non-words, and more importantly, to differentiate related from unrelated target words following ambiguous primes. Nonetheless, a number of issues need consideration to improve the paradigm further. First, because we were the first to modify this paradigm for use in the domain of pain and physical health threat in a Dutch-speaking population, we designed and selected the stimuli for the task ourselves. Based upon a small word pilot study, 15 critical prime target pairs were ultimately selected to be eligible for incorporation in the task. However, some of these critical prime-target pairs did not fully meet the criteria for stimuli selection and might therefore be suboptimal in the light of the goals of this task (see Method section and Supporting Information Table S1). An extended word pilot study is warranted to improve stimulus selection. Second, the paradigm would benefit from the inclusion of more critical trials from which IB score can be derived, amongst others to overcome the problem of low reliability of IB scores as observed in the current study. Third, two related and one unrelated target word were presented per ambiguous word prime in the current paradigm. However, because the unrelated target was not split up in a threatening a nonthreatening target (e.g. Richards and French, 1992; Bisson and Sears, 2007), we were only able to make a direct comparison between related interpretations of ambiguity, without accounting for the unrelated emotional targets, resulting in a less sensitive measure.

It should be noted that creating a paradigm for IB assessment in the domain of health and pain is inherently bothered by several challenges. First, establishing health-related ambiguity is a difficult endeavour given the high alarming value of health threat and the evolutionary determined adaptive function that early detection of such threat has (Ohman and Mineka, 2001). Furthermore, the presence of non-ambiguous health threatening stimuli within the paradigm (here: health threatening target words) may cause an undesirable general priming effect towards interpretations within a health threatening scheme (Vancleef et al., 2009). The effect of the presence of other stimuli on the interpretation of ambiguity was also illustrated by the finding that healthy participants are more inclined to categorize ambiguous facial expressions as painful in case the pictures are preceded by negative words for example (Yamada and Decety, 2009). A third challenge lies in objectifying and thereby controlling for the ambiguous nature of stimuli, as the extent to which something is ambiguous, is determined by several factors, including the context in which the stimulus is presented and personal experiences of respondents.

Apart from shortcomings on the level of stimulus construction and selection, other drawbacks might hinder interpretation of current results. First, the use

of word stimuli might affect the ecological validity and thereby generalizability of findings. In the context of pain, ambiguity often lies in the experience of unexplainable somatosensory sensations. Hence, it might be more appropriate to rely on study paradigms that assess responses to ambiguous physical sensations (e.g. Witthöft et al., 2011) or ambiguous facial expressions of pain (e.g. Khatibi et al., 2015) rather than verbal descriptive stimuli. Second, low to modest anxiety levels were observed in both study samples. Future research should include a preselected participant sample, as having both extremes (high and low anxiety) represented in the study sample (Richards and French, 1992) has been argued to be crucial for detecting effects of IB in function of anxiety.

Notwithstanding the aforementioned shortcomings, the current study demonstrates (health-threat oriented) IB to be associated with individual levels of pain anxiety and to mediate responses to experimentally induced pain. These results contribute to the sparse amount of literature currently available on the study of IB in the domain of pain and health threat and offer tentative support for the suggestion that IB constitutes a latent vulnerability mechanism to consider in the development of chronic pain.

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Author contributions

L.M.G.V. was responsible for conception and design of the study, data acquisition, data analysis and drafting the manuscript. L.M.G.V., M.M.H. and M.L.P. contributed to the design of the study, the interpretation of the data, and critically revising the manuscript for intellectual content. All authors discussed results of the study and commented on the manuscript.

Note

[1] Initially, 21 critical prime words were incorporated in the task. However, while data collection for Study 2 was ongoing, the pilot ratings were critically reviewed for purposes of word selection for another study. In this process, it was decided that six prime words did not show >60% relatedness for both targets and/or were not frequently used within Dutch language. Two of the remaining critical word target pairs were not in agreement with the <15% relatedness difference. However, these were kept in the task to maintain an acceptable amount of critical trials and allowing an equal division over the three critical target categories (five health threatening, five neutral, five unrelated). Statistical analyses that were conducted post-hoc indicated that removal of these six words did not affect the general pattern of results for Study 1 and Study 2.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Words and target words (translated) as incorporated in the ambiguous word priming task. Mean relatedness ratings and difference % for health threatening and non-health threatening target words as incorporated in the ambiguous word priming paradigm.