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Biased Interpretation of Ambiguous Information in Patients With Chronic Pain: A Systematic Review and Meta-Analysis of Current Studies

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Objective: The aim of this review is to provide a synthesis of studies exploring biased interpretation of ambiguous information in individuals with chronic pain, and to meta-analyze the results of studies comparing individuals with chronic pain to pain-free controls. ***Method:*** Studies were identified via a search of Medline, PsycINFO, Web of Science, CINAHL, and Cochrane Library databases. Search terms were *bias**, *interpretation*, and *ambiguous*, intersected with the term *pain*. ***Results:*** Seven eligible studies (featuring 445 individuals with chronic pain, and 407 pain-free controls including 170 health professionals) using 4 different paradigms (word stem completion task, homographic response task, homophone task, incidental learning task) were identified and included. All 7 studies provided evidence of significantly more frequent pain-related/illness-related interpretations of ambiguous words (which also have possible neutral interpretations) or images (morphed painful and happy facial expressions) in individuals with chronic pain relative to healthy controls. This was confirmed by a significant between-groups difference in a meta-analysis of available data from 4 studies (Hedges' adjusted g effect size = 0.67). ***Conclusions:*** Individuals with chronic pain demonstrate biased interpretation of ambiguous information favoring pain-related/illness-related interpretations. A number of important methodological limitations are apparent however, including potential sources of bias in the classification of participant responses in some paradigms. Further research adopting more rigorous methodology is therefore required. Another area for future research is investigation into how different forms of cognitive bias (i.e., attentional, interpretation, and memory biases) interact with one another in chronic pain patients.

Keywords: chronic pain, interpretation bias, ambiguous information, systematic review, meta-analysis

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Chronic pain disorders are a major health concern (Gureje, Von Korff, Simon, & Gater, 1998; Cimmino, Ferrone, & Cutolo, 2011) estimated to affect approximately 20% of adults (e.g., Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). Chronic pain can profoundly impact individual well-being, and further to pain and discomfort patients frequently experience comorbidities such as anxiety and depressive disorders (Mongini et al., 2006; Miller & Cano, 2009) and insomnia (Morin, Gibson, & Wade, 1998). Negative consequences on social functioning have been reported (e.g., Harris, Morley, & Barton, 2003) along with impairments in cognitive functioning, including those in attention, memory, speed of information processing, and executive functioning (Moriarty, McGuire, & Finn, 2011). Such evidence reflects the currently accepted biopsychosocial view of chronic pain, which states biological, psychological and social factors interact with one another to influence the subjective experience of pain and pain-related disability (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). The biopsychosocial view is essential to the clinical understanding and treatment of chronic pain (Turk & Okifuji, 2002; Rajapakse, Liossi, & Howard, 2014), whereas a purely biomedical view often fails to explain the complex interplay between dysfunction, pain, disability and distress (Nijs, Roussel, van Wilgen, Köke, & Smeets, 2013). Supporting this, psychosocial factors influence the transition of acute to chronic pain (Pincus, Burton, Vogel, & Field, 2002), and are predictive of pain-related disability in chronic pain (e.g., Zale, Lange, Fields, & Ditre, 2013).

Research and theory highlight the important role cognitive factors play in the interpretation of bodily symptoms in general (e.g., Cioffi, 1991; Kolk, Hanewald, Schagen, & Gijsbers van Wijk, 2003), and in the experience of pain specifically (e.g., Eccleston & Crombez, 1999). Indeed, specific cognitive processes, including attention (Legrain et al., 2009) and expectations (Atlas & Wager, 2012), are implicated in pain. Negative interpretation of pain and pain-related outcomes, in the form of individual beliefs, are also associated with poor patient functioning and quality of life (e.g., Lamé, Peters, Vlaeyen, Kleef, & Patijn, 2005; Jackson, Wang, Wang, & Fan, 2014). Furthermore, research has investigated whether cognitive biases for pain-related information exist in patients with chronic pain. Such biases are predicted by theories of emotional processing, which posit biases for information associated with an individual's fears and concerns (e.g., Mogg & Bradley, 1998; Wells & Matthews, 1996; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Schema theory (Beck, 1979; Beck, Emery, & Greenberg, 1985) predicts dysfunc-

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tional schemata result in a selective processing of schema-congruent information, with biases existing across various forms of information processing including attention, memory, and interpretation.

Considering models of chronic pain, the schema enmeshment model of pain (Pincus & Morley, 2001) predicts all patients to demonstrate cognitive biases, including attention, interpretation, and memory biases, for self-referent sensory pain information. The motivational account of attention to pain (Van Damme, Legrain, Vogt, & Crombez, 2010) argues that increased processing of pain and pain-related information will occur in patients prioritizing pain-related goals (e.g., pain management). The misdirected problem solving model (Eccleston & Crombez, 2007) posits that worrying about pain is associated with a hypervigilance for pain and pain-related cues. Based on such accounts, Khatbi and colleagues (Khatibi, Sharpe, Jafari, Gholami, and Dehghani, 2015) argue that interpretation of pain as harmful increases the likelihood that ambiguous stimuli will be interpreted in a pain-related manner. Most recently, the Threat Interpretation Model (Todd et al., 2015) posits that in order for participants to respond to words as pain-related in attentional bias paradigms, these words first have to be categorised as such. As certain words used in this research possess a degree of ambiguity (e.g., *sharp*, *pounding*), an interpretation bias favoring pain-related meanings is necessary, but not sufficient, for attentional bias to be observed. Furthermore, this relationship between interpretation and attention is predicted to be stronger under conditions of high threat.

Two meta-analyses report pain-related attentional biases in chronic pain patients as measured by the visual-probe task (Schoth, Nunes, & Liossi, 2012; Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013). Pincus and Morley (2001) also argue for robust evidence for memory biases from studies using incidental recall of previously presented information, including biases for sensory-pain, illness-related, and health-related words. Researchers have also explored interpretation biases in chronic pain, and recently raised their possible implications (Jones & Sharpe, 2014). Considering this, along with debate that cognitive biases may have a role in the onset and maintenance of pain (Liossi, 2012; Sharpe, 2012; Todd et al., 2015), it is important to summarize current evidence pertaining to pain-/illness-related interpretation biases for ambiguous information in chronic pain. Ambiguity and uncertainty negatively impact adjustment to, and coping with, chronic medical conditions (Mishel, 1990; Johnson Wright, Afari, & Zautra, 2009), and are commonly experienced by patients with chronic pain. For many the underlying cause of their pain remains unknown (Krismer & Van Tulder, 2007), with resulting difficulties and uncertainty in treatment outcomes (Slade, Molloy, & Keating, 2012; Williams, Eccleston, & Morley, 2012).

Although Pincus and Morley in 2001 reviewed the interpretation bias literature, the cognitive bias field has expanded greatly since warranting an updated literature search and systematic review. The purpose of the present review is to provide an updated synthesis of studies exploring biased interpretation of ambiguous information with both pain-/illness-related and neutral/other associations in patients with chronic pain, including a meta-analysis of available data comparing biased interpretations to pain-free controls.

Method

Literature Search

Studies were identified via a search of Medline, PsycINFO, Web of Science, CINAHL, and Cochrane Library databases. Search terms were *bias**, *interpretation*, and *ambiguous*, intersected with the term *pain*. The names of known researchers in the chronic pain cognitive bias field were also used as search terms. Lastly, the reference lists of all obtained articles were inspected. All searches were made from database inception until March 3, 2015.

Inclusion Criteria

For inclusion in the review, each study was required to meet the following criteria:

1. Available in English language until March 3, 2015
2. Explored interpretation bias for ambiguous information that has both pain-related/illness-related associations and neutral/other associations
3. Included a sample of adults (≥18 years old) or children (<18 years old) with chronic pain lasting for 3 months or longer

Search Results

The literature search and study selection process is shown in Figure 1. From an initial identification of 3,437 records, six records including seven individual studies meeting the inclusion criteria were retained for the review (see Table 1 for study characteristics). The two authors performed a quality assessment of each study based on information contained in the reports, with the exception of Griffith, Mclean, and Pearce (1996) which is only available as an abstract. The criteria were based on those used in former attentional bias reviews (Roelofs, Peters, Zeegers, & Vlaeyen, 2002; Schoth et al., 2012; Crombez et al., 2013). In some instances, this assessment is likely to reflect quality of reporting as opposed to quality of methodology. Any disagreements were resolved by discussion, and the results are presented in Supplementary Table 1.

Statistical Procedures: Effect Sizes

Where sufficient data was available, Hedges' adjusted g effect sizes (standardized mean difference) for between-groups comparisons (i.e., interpretation bias scores for chronic pain group vs. healthy control/health professional/acute pain groups) were computed using group means and standard deviations in Review Manager (2014) Version 5.3. In one instance (Pincus, Pearce, & Perrott, 1996) group data was not available, and therefore Cohen's d effect size was computed using the F statistic (Thalheimer & Cook, 2002), which was then subsequently converted to Hedges' g (Rosnow, Rosenthal, & Rubin, 2000). Effect sizes of all eligible comparisons are provided in Supplementary Table 2.

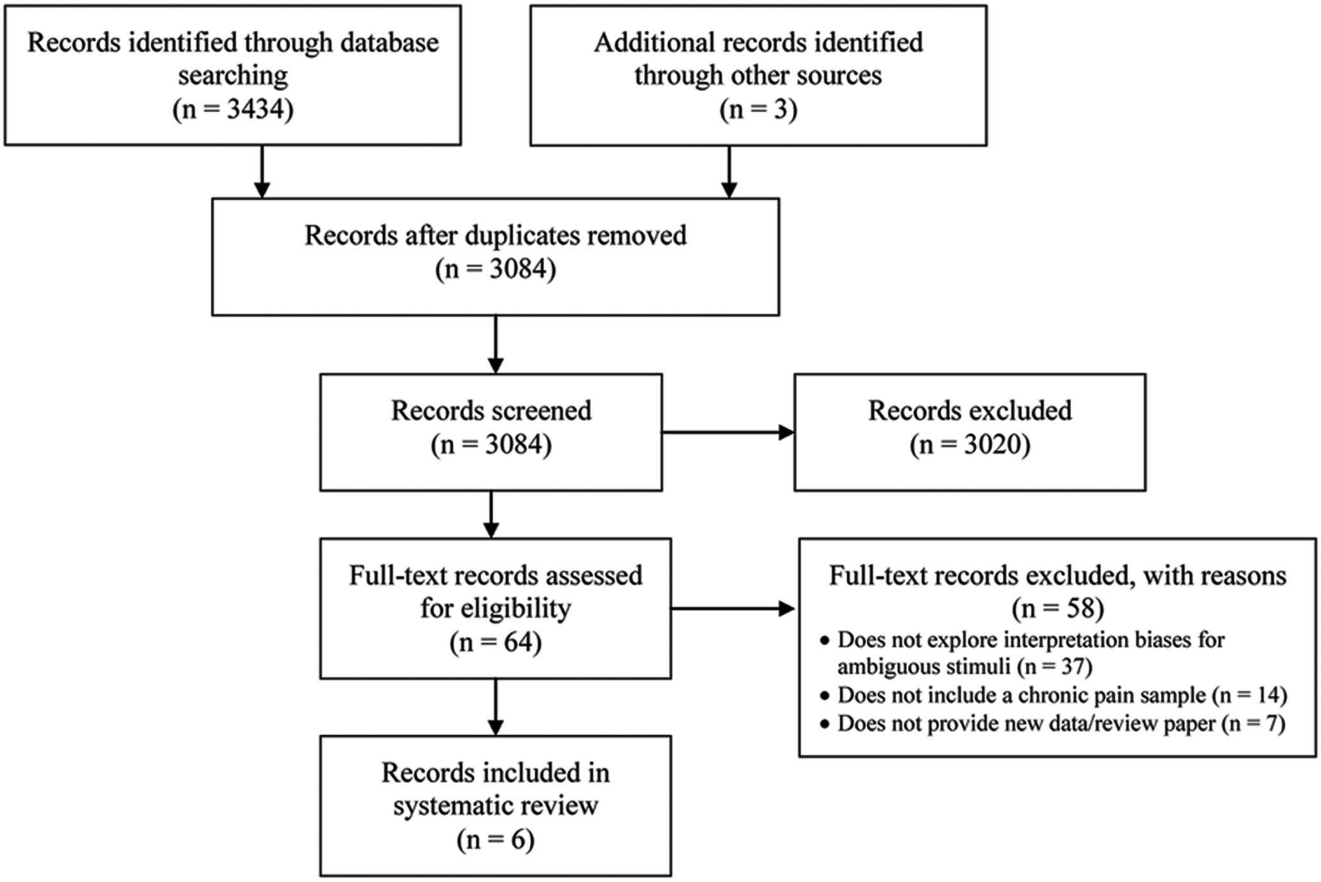

Figure 1. Flow of records for inclusion in the systematic review.

Meta-Analysis Methodological Decisions

Further to the stated inclusion criteria, a number of important methodological decisions were made pertaining to the meta-analysis:

1. In instances where multiple forms of pain-/disability-related interpretation bias data were provided, their respective data and *SD*s were averaged into a single score. Specifically, McKellar, Clark, and Shriner (2003) included pain-related and disability-related homographs, and provided separate data on pain-related and disability-related responses to each (totaling four sets of eligible data). There was some overlap between these stimuli categories however, along with a degree of subjectivity in the classification of participant responses. This data was therefore averaged into a single score representing interpretation bias for homographs with both pain-related/disability-related and neutral associations.

2. The incidental learning task used by Khatibi et al. (2015) allows for the computation of an interpretation bias index based upon mean response times. Negative and positive bias index scores represent painful and happy interpretation of ambiguous expressions respectively. These mean bias indices were multiplied by −1 following specifications provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2011). This ensures that for all studies included in the meta-analysis, higher scores on their respective units of measurement indicate greater evidence of pain-related interpretation bias.

3. Separate data for chronic pain and healthy control groups was required. Study 2 from Pincus, Pearce, McClelland, Farley, and Vogel (1994) featured an osteopath control group including participants with "regular pain" and no pain. As separate untransformed data are not available for these subgroups, data from this osteopath group was excluded.

4. In instances where multiple healthy control groups were recruited, including groups of medical professionals, their respective data and *SD*s were initially averaged into a single score. This decision was made due to the limited number of studies with eligible data for analysis, and enabled us to address the question of whether interpretation of ambiguous information differs between participants with and without chronic pain, regardless of

Table 1
Characteristics of Chronic Pain Interpretation Bias Studies Included in the Systematic Review

Study	Country	Paradigm	Stimuli category	Sample
Edwards & Pearce (1994)	UK	Word stem completion task	Sensory-pain/neutral Affective-pain/neutral Illness-related/neutral	36 Chronic pain 28 Health professionals 38 Healthy controls
Pincus, Pearce, McClelland, Farley, & Vogel (1994)				
Study 1	UK	Homographic response task	Pain-related/neutral	107 Chronic pain 67 Physiotherapists 94 Healthy controls
Study 2	UK	Homographic response task	Pain-related/neutral	47 Chronic pain 25 Healthy controls 26 Pain-free osteopaths 17 Osteopaths reporting regular pain
Griffith, McLean, & Pearce (1996)	UK	Word stem completion task	Pain-related/neutral Illness(threat-related)/neutral	58 Patients with rheumatic disease 47 Patients with chronic back pain, 28 Patients with cancer pain 35 Healthy controls
Pincus, Pearce, & Perrott (1996)	UK	Homophone task	Illness-related/neutral Neutral/neutral	20 Chronic pain 20 Healthy control
McKellar, Clark, & Shriner (2003)	USA	Homographic response task	Sensory-pain Disability Neutral	80 Chronic pain 50 Acute pain 49 Healthy medical staff controls
Khatibi, Sharpe, Jafari, Gholami, & Dehghani (2015)	Iran	Incidental learning task	Painful facial expressions Happy facial expressions	50 Chronic pain 25 Healthy control

whether the latter were medical professionals or not. Subsequently, and in order to address the role of familiarity on interpretation biases, a further analysis was conducted with the exclusion of medical professionals from the healthy control group.

5. Data from acute pain groups were not considered (i.e., McKellar et al., 2003), which do not qualify as healthy controls nor meet criteria for chronic pain.

Statistical Analysis

Data from four studies were available for use in the meta-analysis, which was performed in Review Manager (2014) Version 5.3. A random-effects model was implemented, which assumes the average effect size varies from study to study, and therefore, heterogeneity is to be expected (Field, 2003). While random-effects models have less statistical power than fixed-effects models, the results obtained may be generalized to similar studies not included in the actual analysis (Rosenthal, 1995). The standardized mean difference (Hedges' adjusted g) was used as the studies included in the analysis used different units of measurement. Cochrane's Q and the I^2 statistic were used to assess study heterogeneity. With Cochrane's Q, a significant result is indicative of heterogeneity. With the I^2 statistic, percentages of 25%, 50%, and 75% are indicative of low, medium and high heterogeneity (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). The two authors independently verified the data used in the meta-analysis.

Narrative Review

The majority of studies exploring biased interpretation in chronic pain have used single ambiguous words presented individually to the participant, which are typically either homophones or homographs. Homophones are words which sound the same yet have different spellings and meanings (e.g., pain/pane, sea/see), while homographs are words which have identical spelling yet distinct meanings (e.g., terminal—causing death, airport building; bat—animal, wooden club; Drury, 1969; Gorfein & Weingartner, 2008). While some homographs are also homophones, this is not always the case (e.g., wound—injury, past tense of "to wind").

Edwards and Pearce (1994) recruited 36 patients with chronic pain attending a rheumatology department in a London hospital, 28 health professionals (nurses and physiotherapists working at the hospital), and 38 healthy controls from the general public. Participants performed a word stem completion task, during which they were presented three-letter word stems (e.g., ten__) that they were required to complete with the first two English words that came to mind. Each of the 12 stems had at least one possible pain-related completion (e.g., ten*der*) as well as possible neutral completions (e.g., ten*nis*). Three word type categories were included; four stems could be completed as sensory-pain words (e.g., ten*der*), four completed as affective-pain words (e.g., hor*rible*), and four completed as illness-related words (e.g., dis*ease*). Participants completed the task under the guise of a language experiment, also completing 12 common word endings (e.g., __ed) as a control condition beforehand. Across all three word type categories, the chronic pain group produced significantly more pain-related completions than the healthy control group. Follow-up analysis of a significant group by word type interaction showed the chronic pain group to produce significantly more sensory-pain completions for this category of words than healthy control and health professional groups. The healthy control group produced significantly fewer illness-related completions to illness-related words than chronic pain and health professional groups.

These results provide evidence of a bias for sensory-pain information specifically in chronic pain patients, although should be interpreted with caution as certain responses are homographs with both sensory-pain and positive connotations (i.e., tender-pain, tender-gentleness; sharp-pain, sharp-clever), and it is unknown which interpretation participants were thinking of when producing such words. A further limitation is the scoring method allowed for participants to produce two variants of the same word in response to a word stem (e.g., hur*ting*, hur*tful*), although the authors state there was no evidence this was more likely to occur in the chronic pain group relative to the two other groups. Despite these issues, an advantage of this study was the inclusion of separate sensory-pain, affective-pain, and illness-related categories, enabling investigation into the specificity of biased interpretations. In addition, the recruitment of separate health professional and healthy control groups allowed for exploration into the effects of personal relevance and contextual effects on information processing. It is interesting to note that considering pain-related completions across all three word type categories, health professionals took an intermediate position between chronic pain patients and healthy controls.

Pincus et al. (1994) reported the results of two studies using a homographic response task. In Study 1, 107 patients with chronic pain recruited via a self-help pain organization (type of pain not specified), 94 healthy controls recruited from evening classes, and 67 physiotherapists participated. The homographic response task involved the presentation of 14 ambiguous cues with possible pain-related and neutral associations (e.g., *terminal*—illness, growth, bus, train, airport; *pound*—pain, coin), along with 14 neutral cues. Participants read each cue word, and then wrote down the first word that came to mind, which the researchers determined were either pain-related (i.e., related to pain or suffering) or neutral. The chronic pain group produced significantly more pain-related associations to ambiguous cues than both the healthy control group and the physiotherapist group, even when controlling for group differences in age. For the chronic pain group, pain intensity was found to account for 11% of the variance in scores. The inclusion of both physiotherapist and healthy control groups was a strength. As both groups provided the same proportion of pain-related associations (i.e., 14.1%), the authors argued familiarity effects were unlikely to have influenced the interpretation of ambiguous cues. Measures of anxiety and depression were not collected however, although may have influenced interpretation as has been shown in prior studies exploring interpretation biases in anxious (Matthews, Richards, & Eysenck, 1989) and depressed (Mogg, Bradbury, & Bradley, 2006) samples.

To explore the potential impact of mood, Study 2 repeated the homographic response task with the inclusion of a measure of anxiety and depression. Forty-seven patients with chronic pain recruited from a private session with an osteopath, 25 healthy controls (undergraduate students), and 43 osteopaths (including 26 pain-free osteopaths, and 17 osteopaths reporting regular pain but not seeking treatment) took part. The task was identical to that in Study 1, except for the exclusion of three ambiguous cues deemed to be related more to anxiety than pain (i.e., *shot*, *attack*, *pound*; it is also apparent that two neutral cues were removed, as the total number of cues presented was 23). The groups differed significantly in age and depression (highest in the chronic pain group), which were included as covariates in the analysis. The two pain groups (i.e., chronic pain group, osteopaths with pain) produced significantly more pain-related associations to ambiguous cues than the healthy control group and the pain-free osteopath group. No significant differences were reported between the two pain groups, or between osteopaths who reported regular pain and osteopaths who did not. However, overall osteopaths produced significantly more pain-related associations than healthy controls. Overall, these results suggest the experience of pain to influence interpretation of ambiguous cues as opposed to elevated levels of depression or anxiety. In contrast to Study 1, the results also suggest familiarity effects do influence patterns of bias in medical professionals. Despite the methodological improvements, measures of pain intensity were not collected from the osteopaths reporting regular pain, and therefore could not be compared with the chronic pain group on such measures. Overall, a limitation of both studies is that classification of participant responses to ambiguous cues may themselves reflect a degree of ambiguity. For example, for the cue "plaster," a given example of an accepted pain-related association is "of Paris." While plaster of Paris is used in medicine as a support for broken bones, it also has many other uses unrelated to pain. Similarly, neutral example responses of "rape" and "gun" were provided for "attack" and "shot" cues respectively, although these have negative connotations. Overall, it is clear that results from the homographic response task should be interpreted with caution.

Griffith et al. (1996; presented at the IASP 8th World Congress on Pain), recruited 58 patients with rheumatic disease, 47 patients with chronic back pain, 28 patients with cancer pain, and 35 healthy controls. Participants performed a word stem completion task similar to that used by Edwards and Pearce (1994), which featured 10 word stems that could be completed with pain-related words (e.g., ach*e*) and 10 word stems that could be completed with illness/threat-related words (e.g., dea*th*). All word stems could also be completed with at least three neutral words (e.g., ach*ieve*, dea*r*). The results revealed a differing pattern of interpretation biases across the different groups. Patients with rheumatic disease produced significantly more pain-related completions compared to chronic back pain patients, cancer pain patients, and healthy controls. Patients with rheumatic disease and chronic back pain patients produced significantly more illness completions compared to healthy controls. Chronic back pain patients also produced significantly more illness completions compared to cancer pain patients. No significant differences were found between cancer patients and healthy controls.

Inclusion of three different pain groups allowed for exploration of whether the presence of pain or other characteristics contribute to the patterns of interpretation bias observed. Based on the results, the authors speculate the meaning of a patient's diagnosis, rather than the presence of pain per se, may influence information processing biases. It was speculated that cancer pain patients may produce more illness completions, as their primary concerns may focus on the threatening nature of their illness rather than their pain specifically. Cancer pain patients produced the fewest illness completions of the three pain groups however, which may suggest cognitive avoidance as a coping strategy. Patient coping strategies were not assessed however, and such interpretations can only be speculated. Furthermore, as the study is unpublished it is unknown how well the three groups were matched in terms of characteristics such as pain intensity at time of testing and pain-related disability, which may have contributed to the pattern of results found. Lastly, and as noted above, a general limitation of the word stem completion task is that certain participant responses may themselves be ambiguous.

Pincus et al. (1996) recruited 20 patients with chronic pain (including patients with limb, back and shoulder, and abdominal pain) and 20 healthy controls. Participants completed a homophone task featuring 43 words, including nine ambiguous homophones with illness-related (also referred to in the article as "negative health-related") and neutral meanings (e.g., words which have the same pronunciation but different spellings and meanings, including pain/pane, die/dye, weak/week). Neutral matched words for each interpretation were also included matched on length and frequency. Participants were presented the words auditorily, writing the word down after hearing it. Participants then engaged in a 2-min distraction counting task, and were subsequently asked to recall as many of the words as possible from those they wrote down. Patients with chronic pain, relative to healthy controls, interpreted significantly more ambiguous homophones as illness-related (an average of two words difference between groups). As anxiety and depression were significantly higher in the chronic pain group, these variables were included as covariates in a further analysis, with significant between-groups differences still found. In order to control for awareness of ambiguity, the analysis was repeated minus any homophones participants later identified as ambiguous; once again the same between-groups differences were found. Regression analysis revealed for the chronic pain group, 25% of the variance in their scores was predicted by present pain intensity, 12% of the variance was predicted by pain duration, and 7% of the variance was predicted by worst pain that week. Analysis of responses on the free-recall task showed patients with chronic pain to recall significantly more illness-related homophones than healthy controls.

This study is one of the first to explore multiple forms of cognitive bias in the chronic pain literature, and the only study in the present review. For the chronic pain group, no significant correlation was found between the proportion of illness-related homophones provided in the interpretation task and later recalled in the memory task however. An advantage of using the homophone task, compared to paradigms using homographs, is that participant responses themselves are potentially less ambiguous. That is, it is relatively straightforward to classify responses as threatening or neutral. The notable disadvantage, however, is the greatly reduced number of appropriate homographs available for use, therefore making it difficult to explore pain-related biases specifically. In this study the researchers set out to specifically explore interpretation of a broader set of stimuli reflecting ill-health, although it is notable that a number of the nine ambiguous homophones used may be interpreted in a negative manner albeit with no health-related connotations (i.e., moan/mown, groan/grown, weak/week).

McKellar et al. (2003) recruited 80 individuals with chronic pain (in-patients and outpatients attending a multidisciplinary pain program at a Department of Veterans Affairs hospital), 50 individuals with acute pain (i.e., cardiothoracic postoperative patients), and 49 individuals working as medical staff to serve as healthy controls (all participants were male). Participants completed a homographic response task, which included three categories of words: 40 sensory-pain, 40 disability (also referred to as "illness/disability" words), and 40 neutral words. Each category featured a subset of 30 homographic words (as defined by the authors "words with one or more meanings, i.e., back or fire," p. 30). For each word, participants were instructed to write down the first word which came to mind. Two judges independently rated participant responses as being related unambiguously to pain, to disability, or to neither (referred to as neutral). Preliminary analyses showed participant responses to be unrelated to anxiety, depression, or pain intensity. The results revealed the chronic pain group to produce (a) significantly more pain responses to pain-related homographs than both acute pain and control groups, (b) significantly more pain responses to disability homographs than the control group, (c) significantly more disability responses to disability homographs than the acute pain group, and (d) significantly more disability responses to neutral homographs than the control group.

The recruitment of an acute pain group was a notable strength of this study, which allowed for investigation of whether interpretation biases for pain-related information are specific for individuals with chronic pain only, or whether they are shown by all individuals in pain regardless of duration. The inclusion of a medical staff healthy control group also controlled for potential effects of familiarity with health-related terms. Overall, the results suggest a pain-related interpretation bias in chronic pain, which the authors argue appears to be related to the long-term effects of pain as opposed to exposure to medical environment. While the exploration of bias specificity via the use of separate pain and disability stimuli categories is commendable, there are a number of limitations with the stimuli and procedure adopted. First, there is some apparent overlap between the two stimuli categories; while the majority of pain homographs are sensory descriptors, some reflect a broader dimension of health and could therefore feasibly be included in the disability category (e.g., *doctor*, *joint*). Second, although independent raters of participant responses had a high level of agreement (91% prior to consultation, 100% after consultation), a level of subjectivity is still apparent in the coding of participant responses (e.g., *aspirin* and *pill* were coded as pain-related and disability-related respectively). Third, some of the homographic words appear to have more obvious pain/disability connotations than others (e.g., *terminal*, *growth* compared to *collect*, *ace*). Fourth, many of the nonhomographic words also have multiple meanings, and it is unknown why these were not also included in the analysis (e.g., *splitting, cramp*, *trigger*, *dressing*).

Khatibi et al. (2015) recruited 50 patients with chronic low back pain from physiotherapy clinics, and 25 healthy controls from the community. Participants completed an incidental learning task featuring painful and happy facial expressions (images were in color). During the learning phase of the task, individual facial expressions were presented in the center of the computer screen for 625 ms, and immediately followed by a target either to the left or right of this location. For painful expressions, the target was presented in the right location on 80% of trials, and for happy expressions the target was presented in the left location on 80% of trials. On each trial, participants indicated the location of the target as quickly as possible. Participants are therefore expected to learn an association between facial expression and target location. During the test phase, ambiguous facial expressions were presented, which comprised of morphed painful and happy expressions at a 50%:50% proportion. Targets followed the morphed facial expressions in equal frequency in the left and right locations. This phase also featured a number of original painful and happy facial expressions followed by targets in their associated locations, serving to consolidate participant learning. Participants again were required to indicate the location of the target as quickly as possible during the test phase. An interpretation bias for pain is shown if participants are quicker to respond to targets which, following ambiguous faces, are presented in the associated painful location as opposed to the associated happy location. The results showed that for test phase trials with ambiguous facial expressions, chronic pain patients responded significantly faster to targets in the location predicted by painful expressions than to targets in the location predicted by happy expressions. No significant differences were found for the healthy control group. Participant responses times were also used to compute an interpretation bias index, where a negative score indicates a pain-related interpretation bias, and a positive score a happy interpretation bias. The chronic pain group demonstrated a significantly greater pain-related interpretation bias relative to healthy controls (confirmed via personal communication with the corresponding author). Considering correlations, for chronic pain patients, interpretation bias index scores were negatively correlated with pain intensity, and positively correlated with pain catastrophizing; that is, patients demonstrating greater pain interpretation biases reported lower levels of pain in the previous week, and high levels of pain catastrophizing.

A particular strength of this study is the use of an indirect measure of bias, relying on participant response times instead of written report. Problematic issues pertaining to subjective interpretation of participant responses are therefore avoided. As noted by the authors, a number of limitations may also be raised however. First, the potential influence of familiarity with facial expressions of pain cannot be assessed, as a second control group of medical professionals was not recruited. Second, as only ambiguous painful/happy expressions were included, it remains unknown whether the results obtained reflect a pain-related bias specifically, or rather a general negative interpretative bias. Further research is needed using alternative combinations of stimuli (e.g., ambiguous sad/happy expressions) to address this issue, although this fact does not detract from the importance of this study.

In summary, the methodological quality of the studies varied (Supplementary Table 1). All used appropriate stimuli which were adequately described, and all used appropriate statistical analyses. Four studies provided information on both pain duration and pain intensity at time of testing for the chronic pain group, and two studies reported one of these characteristics. In contrast, only two studies explicitly stated the type of pain experienced by chronic pain patients. Studies were more likely to describe exclusion criteria than specific inclusion criteria. Two studies matched chronic pain and control groups on age and two matched groups on gender. Only three studies assessed and reported data on anxiety and depression, and no study assessed pain-related fear. Two studies reported testing participant groups in the same environment, which were also the only two studies deemed to have adopted response classification/scoring methods free from ambiguity or potential bias. As noted, in some instances this assessment may reflect quality of reporting and not quality of methodology.

Meta-Analytic Results

The majority of comparisons between chronic pain patients and healthy controls revealed medium to large effect sizes (Supplementary Table 2). Across available studies (Pincus et al., 1994, Study 1 and Study 2; McKellar et al., 2003; Khatibi et al., 2015; k = 4 chronic pain n = 284, healthy control n = 260), the mean between-groups effect size was 0.67 (95% confidence interval [CI] [0.50, 0.85]). The test for overall effect was significant (Z = 7.41, $p < .00001$), confirming that chronic pain patients demonstrate significantly more pronounced pain-/illness-related interpretations of ambiguous stimuli relative to healthy controls. This data is presented in a forest plot in Figure 2. No evidence of study heterogeneity was found, as measured by Cochrane's Q (χ^2 = 1.80, p = .62) and the I^2 statistic (I^2 = 0%). However, the power of Cochrane's Q and the I^2 statistic to detect study heterogeneity is reduced when conducting analyses with a small number of studies (Huedo-Medina et al., 2006). The meta-analysis was therefore performed again with the exclusion of Khatibi et al. (2015). This decision was made as Khatibi et al.'s study differed the most from the other investigations, using ambiguous faces, exploring pain-related versus happy interpretations, and assessing interpretation bias via participant response times in the incidental learning task. The results from this subsequent analysis (k = 3 [all using the homographic response task], chronic pain n = 234, healthy control n = 235) revealed very similar results, including a mean between-groups effect size of 0.68 (95% CI [0.49, 0.88]). The test for overall effect remained significant (Z = 7.01, $p <$ 00001), with no evidence of study heterogeneity as measured by Cochrane's Q (χ^2 = 1.71, p = .43) and the I^2 statistic (I^2 = 0%).

	Chronic Pain Group			Healthy Control Group				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Pincus (1994) Study 1	20.3	10.2	107	14.1	8.95	161	50.6%	0.65 [0.40, 0.90]
Pincus (1994) Study 2	1.5	0.42	47	1.1	0.35	25	12.1%	1.00 [0.48, 1.51]
McKellar et al (2003)	4.27	2.24	80	3.01	1.86	49	24.1%	0.60 [0.23, 0.96]
Khatbi et al (2015)	86.9	167.8	50	-5.7	112.5	25	13.2%	0.60 [0.11, 1.09]
Total (95% CI)			**284**			**260**	**100.0%**	**0.67 [0.50, 0.85]**
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 3 (P = 0.62); I² = 0%								
Test for overall effect: Z = 7.41 (P < 0.00001)								

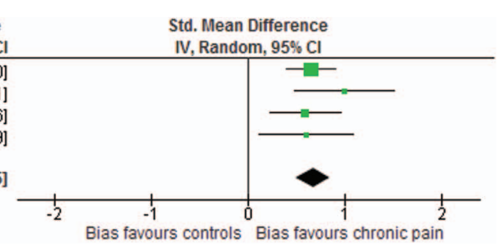

Figure 2. Forest plot of overall effect sizes for individual studies ordered by publication date. See the online article for the color version of this figure.

As familiarity effects can influence patterns of bias, the meta-analysis was repeated once more with the exclusion of medical professionals from the healthy control group (i.e., excluding the study of McKellar et al., 2003 who only recruited healthy medical staff as controls, and also excluding the physiotherapist group from Pincus et al., 1994, Study 1). Across available studies (Pincus et al., 1994, Study 1 and 2; Khatibi et al., 2015; $k = 3$ chronic pain $n = 204$, healthy control $n = 144$), the mean between-groups effect size was 0.71 (95% CI [0.49, 0.93]). The test for overall effect was significant ($Z = 6.27$, $p < .00001$), confirming that chronic pain patients demonstrate significantly more pronounced pain-/illness-related interpretations of ambiguous stimuli relative to healthy controls. No evidence of study heterogeneity was found, as measured by Cochrane's Q ($\chi^2 = 1.51$, $p = .47$) and the I^2 statistic ($I^2 = 0\%$).

Discussion

This review provides a synthesis of research exploring biased interpretation of ambiguous information in patients with chronic pain. Seven experimental studies, using four different paradigms, provided evidence of biased interpretation favoring pain-related or illness-related meanings of ambiguous words and images in patients with chronic pain relative to healthy, pain-free controls. Four studies reported evidence of biased interpretation in chronic pain patients relative to medical professionals specifically, suggesting familiarity with pain-related words is not the sole reason for biases in those with pain. Furthermore, one study showed biases are more pronounced in chronic pain patients than acute pain patients (McKellar et al., 2003), and another revealed patients with rheumatic disease show more pronounced biases than chronic back pain patients (Griffith et al., 1996). These findings suggest both the duration and type of pain also influence patterns of interpretation bias. A meta-analysis of data supports these results, revealing significantly more pronounced interpretations favoring pain- or illness-related meanings in chronic pain patients relative to healthy controls, both with and without the inclusion of medical professionals in the latter group. These results should be considered in relation to an important methodological limitation however; potential ambiguity or bias in the classification of participant responses. Specifically, there are limitations of the classification methods used in word stem completion and homographic response tasks, as participant responses can be ambiguous and subject to interpretation. Despite this caution, these results are supportive of theoretical accounts of emotional processing (e.g., Beck et al., 1985) and models of chronic pain, including the Threat Interpretation Model (Todd et al., 2015).

Of the four paradigms used, the word stem completion task, homographic response task, and homophone task are direct measures of interpretation bias. A possible limitation of direct measures is difficulty ruling out the potential influence of demand characteristics on participant responses (Yoon & Zinbarg, 2007; Khatibi, Schrooten, Vancleef, & Vlaeyen, 2014). Participants may not necessarily provide their initial responses to the ambiguous stimuli, and may be aware of study goals. A number of strategies were used to minimize the impact of demand characteristics however: two studies reported describing the task as a "language" experiment (another was also described as an experiment on "health and language"), one of which also included a control task lending credence to this; four studies also included neutral control words. The incidental learning task used by Khatibi et al. (2015) is an indirect measure of bias, relying on response times instead of written report, and may be less susceptible to effects of study goal awareness and self-presentation biases. In the present review, this was also the only study to report psychometric properties, finding excellent internal consistency for ambiguous test phase trials. Despite differences between the paradigms used, all studies found evidence of biased interpretations, suggesting in patients with chronic pain direct and indirect paradigms produce similar results. Furthermore, the results of the meta-analysis were virtually identical with and without the inclusion of Khatibi et al. (2015). Nevertheless, a study exploring biases in high pain-catastrophizers revealed a different pattern of results between indirect (incidental learning task) and direct (emotion recognition task) measures (Khatibi et al., 2014). To explore this further, future research should use both direct and indirect measures with the same chronic pain sample.

Only one study in the present review explored interpretation biases using pictorial stimuli, an argued advantage of which is increased ecological validity relative to words (Khatibi et al., 2015). The remaining studies used single word stimuli, although limitations include the small number of appropriate pain-related homographs and homophones available. Homophones are also likely to have different frequencies of use; for example, "pain" has a higher written frequency than "pane" (Kucera & Francis, 1967; Wilson, 1988). Between-groups differences may be less likely to emerge when the alternative forms of presented homophones have very different frequencies of use. As "pain" has a higher written frequency than "pane," the majority of participants may interpret this homophone as "pain," regardless of whether they experience chronic pain or not. In contrast, alternative forms of presented homophones with similar frequencies of use may be more ambiguous, and therefore between-groups differences more likely to emerge should they exist. Another consideration is that language changes over time; for example *tablet* can refer to a pharmaceutical pill or a writing medium, but in recent years has also come to mean a handheld computer. Lastly, two of the studies using words explored biased interpretation of sensory-pain words specifically (i.e., Edwards & Pearce, 1994; McKellar et al., 2003), while the remaining word-based investigations included a mixture of sensory-pain and affective-pain/illness-related words within their "pain" category. Meta-analysis has shown significant differences in attentional bias between chronic pain and healthy control groups for sensory- but not affective-pain words (Crombez et al., 2013). Whether differences between sensory and affective dimensions of pain are apparent in interpretation biases remain to be investigated, although an understanding of this will help refine the Threat Interpretation Model (Todd et al., 2015) and allow for stimuli specific predictions.

Considering the limited range of paradigms and experimental stimuli used, a number of methodological recommendations can be made. Ambiguous scenarios have been used to explore interpretation biases in populations other than chronic pain, commonly social phobia (e.g., Stopa & Clark, 2000) and depressed mood (e.g., Berna, Lang, Goodwin, & Holmes, 2011). An advantage of scenarios, compared to single ambiguous words, is the greater range of novel stimuli which can be developed and specifically tailored to the population under study, and which may therefore be more appropriate for exploring specificity of bias (e.g., biases for pain-related interpretations vs. negative interpretations in general). Other possibilities include the use of visual scenes, video clips, or even confederates of the researcher, all of which can be used to present ambiguous behaviors to the participant. Complex stimuli such as these may also be more easily tailored to patients with specific forms of chronic pain, for example depicting behaviors that could be interpreted as being benign or reflecting headache/back pain.

A second recommendation for future research is the incorporation of somatosensory stimuli into experimental designs. Perceptual amplification of both painful and innocuous stimuli have been reported in patients with conditions such as fibromyalgia and chronic myofascial pain (e.g., McDermid, Rollman, & McCain, 1996; Geisser et al., 2003; Hollins et al., 2009), although Van Damme et al. (2015) have recently proposed hypervigilance may be a dynamic process emerging under conditions of sufficient threat (i.e., when the patient is worried about pain and its consequences). Future research should explore whether biased interpretation of ambiguous information is associated with a tendency to perceive moderate but innocuous somatosensory stimuli (e.g., heat, pressure, vibration) as unpleasant or painful. One advantage of somatosensory stimuli is that perceptions of threat are more easily manipulated than they are for symbolic representations of pain, and may therefore offer a more appropriate methodology for testing the Threat Interpretation Model (Todd et al., 2015).

As noted, familiarity effects are not solely responsible for biased pain-related interpretations in patients with chronic pain. Exposure to a medical environment, or frequent use of medical terms, may nevertheless have some impact on participant responses. Three studies in this review included both medical professional and nonmedical professional control groups (Edwards & Pearce, 1994; Pincus et al., 1994, Study 1, Study 2), two of which found evidence of significantly greater bias in the former relative to the latter (Edwards & Pearce, 1994; Pincus et al., 1994, Study 2). It is recommended that future research consider carefully not only the occupation of healthy controls recruited, but also whether they perform a caring role for somebody with pain, as research has also reported evidence of pain-related attentional biases in caregivers of chronic pain patients (e.g., Mohammadi et al., 2012).

Limitations may be highlighted with the meta-analysis. First, due to unavailable data only four of the seven studies identified were included in the analysis. Second, we were not able to explore whether biases are shown for pain-related interpretations specifically, or illness-/disability-related interpretations also. This was due to not only the limited data available, but also the tendency for studies using linguistic stimuli to include a mixture of words in their "pain" category. Furthermore, overlap has been noted in the pain and disability categories used by McKellar et al. (2003). Research is needed to clarify the specificity of interpretation biases, similar to how bias specificity has been explored in attentional bias studies using linguistic (e.g., Liossi, Schoth, Bradley, & Mogg, 2009; Sharpe, Dear, & Schrieber, 2009) and pictorial stimuli (e.g., Schoth & Liossi, 2013; Schoth, Godwin, Liversedge, & Liossi, 2015).

The tendency to show biased interpretation of ambiguous information could potentially, although not necessarily, have clinical implications. Interpreting ambiguous information in a pain-related or threatening manner may maintain or exacerbate emotional distress, as has been argued in anxiety disorders (e.g., Beard, 2011; Mathews, & Mackintosh, 1998). Such biases may also be associated with maladaptive coping strategies such as activity avoidance, which itself plays a role in the maintenance of the pain state (Vlaeyen & Linton, 2000). Considering the cyclical nature of cognitive processes (Neisser, 1967), interpretation biases may encourage increased attentional focus on pain itself, making it more difficult to use distraction-based pain management techniques commonly adopted in pain (Morley, Shapiro, & Biggs, 2004; Johnson, 2005). There is a lack of research exploring these possibilities, and further investigation is needed before clinical implications should be made with any certainty. McKellar et al. (2003) reported no relationship between anxiety, depression, or pain intensity with participants' interpretation bias scores. In contrast, Pincus et al. (1996) reported variance in patient interpretation bias scores to be predicted by present pain intensity, pain duration, and worst pain that week, while Pincus et al. (1994) reported pain intensity to account for 11% of the variance in scores in their first study. As these studies are cross-sectional however, it cannot be argued that these characteristics of pain actually cause interpretation biases, and longitudinal research is needed. Khatibi et al. (2015) found pain-related interpretation bias scores were associated with higher levels of pain catastrophizing and, surprisingly, lower levels of average pain in the prior week. As the ambiguous images featured morphed painful and happy expressions, this latter finding may suggest either an avoidance of pain-related interpretations, or a bias favoring positive interpretations, in those with high pain. Future research clarifying this issue is needed, and the authors warrant caution in interpreting this finding given the retrospective measure of pain used. The remaining investigations included in the present review did not report correlational analyses between interpretation bias scores and pain characteristics.

The combined cognitive bias hypothesis states different forms of bias influence and interact with one another (Hirsch, Clark, & Mathews, 2006). Although some studies have explored memory bias in combination with interpretation bias (e.g., Pincus et al., 1996) or attentional bias (e.g., Pincus, Fraser, & Pearce, 1998), no study to date has explored all three forms of bias in combination in patients with chronic pain. Precisely how different cognitive biases interact in chronic pain, should they interact at all, can only be speculated at present. While the Threat Interpretation Model (Todd et al., 2015) predicts interpretation biases to precede attentional biases, research with depressed samples provides evidence of interpretation bias as a mediating variable between attentional and memory bias (Everaert, Duyck, & Koster 2014; Everaert, Tierens, Uzieblo, & Koster, 2013). Longitudinal research using cognitive bias modification (CBM) techniques is needed to elucidate the precise pathways between different forms of bias. CBM uses modified versions of standard cognitive bias paradigms to either induce biases toward threat, or to train participants to avoid threat (e.g., Salemink, van den Hout, & Kindt, 2009; Jones & Sharpe, 2014). These techniques may be used in several ways to explore combined biases. First, studies training chronic pain patients to make neutral interpretations of ambiguous information will be able to explore subsequent effects on patterns of pain-related attentional and memory biases. Likewise, studies may also train patients to avoid attending to pain-related information, and explore subsequent effects on interpretation and memory. Second, research with healthy individuals without heightened pain-related fears, who presumably do not demonstrate interpretation or attentional biases, can establish whether the induction of one form of bias causes changes to patterns of other forms of bias.

Pain- and health-related interpretation biases have been explored in populations other than chronic pain. Studies using ambiguous morphed facial expressions have found evidence of bias in high pain-catastrophizers (Khatibi et al., 2014) and mothers of children with chronic abdominal pain (Liossi, White, Croome, & Hatira, 2012). Research using ambiguous scenarios has shown biased interpretations in healthy individuals with heightened anxiety sensitivity (Keogh & Cochrane, 2002) and fear of pain (Vancleef, Peters, & De Jong, 2009). Research with ambiguous scenarios has also provided evidence of a mediating effect of negative interpretation bias in the relationship between anxiety sensitivity and chest pain, but in females only (Keogh, Hamid, Hamid, & Ellery, 2004). Research using single ambiguous words has reported illness-related interpretation biases in patients with chronic fatigue syndrome (Moss-Morris & Petrie, 2003), but bias favoring neutral interpretations in patients with irritable bowel syndrome (Chapman & Martin, 2011). Many of these findings remain to be replicated, although highlight the range of research opportunities in this field. The significant results with healthy samples further emphasizes the need to fully assess emotional functioning in participants, as individual differences such as fear of pain and anxiety sensitivity may influence the pattern of results found.

Despite the research possibilities raised, it has yet to be established whether modification of interpretation biases should be attempted in patients with chronic pain for therapeutic purposes. A number of studies support the benefits of attentional bias modification in chronic pain (Carleton, Richter, & Asmundson, 2011; Schoth, Georgallis, & Liossi, 2013; Sharpe et al., 2012), whereby patients are implicitly trained to avoid pain-related information. Research has also shown avoidance of affective-pain information in patients with acute and subacute low-back pain to be predictive of the development of chronic pain at 3- and 6-month follow-up points however (Sharpe, Haggman, Nicholas, Dear, & Refshauge, 2014), highlighting the complexity of this issue. Indeed, Sharpe and colleagues note that training acute pain patients to avoid affective-pain information may not be helpful. CBM for interpretations has shown therapeutic benefits in people with anxiety (Amir & Taylor, 2012) and depression (Lang, Blackwell, Harmer, Davison, & Holmes, 2012), although it is important research is conducted specifically addressing whether interpretation biases have clinical implications in chronic pain. Related to this issue, it is also of importance to determine which specific types of ambiguous information (i.e., words, images, scenarios, somatosensory stimuli) are most likely to be associated with interpretation biases in chronic pain patients. We believe these represent important first steps prior to the running of CBM for interpretations studies in chronic pain.

In conclusion, the seven investigations identified in this systematic review provide evidence for biased pain-related/illness-related interpretations of ambiguous words and images in patients with chronic pain relative to healthy, pain-free individuals. A number of important methodological limitations have been raised with the interpretation bias paradigms used however, warranting further research adopting more rigorous methodology.

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