Painful memories:
An investigation into the effect of memory on pain perception

A thesis submitted to The University of Manchester for the degree of Doctor of Clinical Psychology (ClinPsyD) in the faculty of Medical and Human Sciences

2014

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ABSTRACT OF THESIS

The University of Manchester

Ellen Rachel Swannell
Doctor of Clinical Psychology (ClinPsyD)

Painful memories: An investigation into the effect of memory on pain perception

2014

This thesis, which has been prepared in paper format, is an exploration of how memory affects pain perception.

Paper 1, prepared according to guidelines for the journal Pain, is a systematic review of the literature on how memory affects pain perception. Twenty-nine articles satisfied inclusion criteria for the review. Studies were critically appraised and a narrative synthesis was used to make sense of findings. Two types of study were identified; priming and expectancy. Overall, there is good evidence that memory affects pain perception, however, methodological quality of reviewed studies was variable and this limited the conclusions that could be drawn. The findings are discussed in relation to current theoretical models of memory and pain and suggestions for the future direction of studies in the area are made.

Paper 2, also prepared according to guidelines for the journal Pain, reports an experiment that was conducted in order to test a cognitive model of how memory can affect pain perception (Brown, 2004). Twenty-seven participants were subliminally presented with words that shared either a low or high degree of association with the word ‘pain’ (low versus high associates). Shortly after, randomised laser heat stimuli was delivered at one of three intensity levels (low, moderate, high). Behavioural ratings of pain were taken and physiological responses were measured using electroencephalogram. Pain ratings were higher after the presentation of a high associate than they were after a low associate for the moderate and high intensity conditions only. These effects remained when various measures of mood, anxiety and symptom reporting were controlled for. Similar effects in physiological data are reported with larger amplitudes in both stimulus preceding negativity and the N2 component of the laser evoked potential after presentation of a high associate relative to a low associate. Data are discussed in relation to activation-based theories of memory and pain.

Paper 3, a critical reflection, considers additional issues that have arisen throughout Papers 1 and 2. The systematic review process, as it was applied in Paper 1 is critically appraised and methodological, theoretical and clinical implications of Paper 2 are discussed.
DECLARATION

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Firstly, I’d like to thank my supervisors Dr Richard Brown, Dr Chris Brown and Prof Anthony Jones for their unwavering guidance and support. Your expertise has helped me produce a thesis that I am very proud of. Special thanks to Tim Rainey for supporting me with the almost impossible task of getting the software and equipment working perfectly in tandem!

The last few years have been incredibly challenging for me but somehow I’ve managed to keep going, not least because of the love and support of my family; in particular my amazing husband Paul and my mum and her partner David who have all kept me smiling and laughing.

Finally, this thesis is dedicated to my beautiful daughters Heidi and Karina. You will probably never read this big book that took up so much of my time but thank you for not letting it become the centre of our universe x
THE AUTHOR

The author completed her BSc (hons) in Psychology at Lancaster University in 2001. She then worked clinically for 2 years in hospital and residential settings before completing an MSc in Psychological Research Methods, also at Lancaster University. After two Research Associate posts, working at Lancaster and Manchester Universities on a variety of projects in Cognitive Psychology, she commenced a PhD at Lancaster University in 2006. This ESRC funded project was entitled Developmental trends in semantic and phonological false memory: An investigation using the Deese-Roediger-McDermott paradigm. The author started her Clinical Psychology doctorate at The University of Manchester in 2010.
PAPER 1

The effect of activating schemata on pain: A systematic literature review

The following paper has been prepared for submission to *Pain*. The author information pack is provided in Appendix I. Specific guidelines for systematic reviews can be found in Appendix II. Tables and figures are given in-text to aid understanding in this thesis.

**Word count**

Total: 7985

Total (excluding figures and tables): 5591

Abstract: 243
The effect of activating schemata on pain: A systematic review

Abstract
Both theory and literature suggest a strong association between cognitive functions and pain perception. Memory is a cognitive function that is hypothesized to play a crucial role in the development and maintenance of chronic pain conditions. However, previous reviews have focussed on the effect pain has on memory performance. The aim of this review was to systematically evaluate and critically appraise literature on the effect of activating schemata on pain. Database searches were performed in PsychINFO, Embase and Medline for papers including relevant keyword terms up to January, 2014. Out of 7915 potential articles, 29 were identified as eligible for inclusion and assessed for quality using rating scales that were adapted from the Critical Appraisal Skills Programme. Articles were then subject to a narrative synthesis. Two types of study were identified according to the memory manipulations they utilised: priming and expectancy. Data from expectancy studies were most consistent and showed that high expectancy cues increased pain ratings relative to low expectancy cues. These effects were mirrored in physiological measures of pain perception, using EEG and fMRI. Data from priming studies showed that priming with negative and/or health-related materials increased pain ratings but this effect was more consistent for pictures than for words. Quality was found to be variable, particularly for priming studies and this may explain anomalous data in this group of studies. This review discusses findings in relation to current theoretical models of memory and pain and recommendations for future research are made.

1. Introduction
Traditionally, pain has been viewed as a purely physiological state. However, more recent accounts indicate that pain is influenced by various psychological factors such as mental well-being, beliefs about illness and the self, and cognitive functions. It has been shown that these play an important role in both subjective pain experience and physical disability [20,44,45].

Cognitive functions are crucial determinants of pain experience, not only at the behavioural level but also at the physiological level [e.g. 6,7,74] and memory is a
cognitive function that has been theorised to play an important role in the perception of pain, as well as the development and maintenance of chronic pain conditions [18,32,53,61].

1.1. Relationships between pain and memory

Although many cognitive models of pain and memory provide a basis for an association between pain and memory, few have addressed this directly. More recent cognitive models have attempted to be more explicit about how memory and pain. For example, Brown [9] proposes that symptoms such as pain can result from the chronic over-activation of pain-related schemata in memory that are present in all individuals but may be more active in those who have experienced pain, illness, or health anxiety. More recently, Noel et al. [57] outlined a preliminary cognitive model of memory development for acute pain. They too highlighted the importance of schemata that may lead to negative memory biases, particularly in anxious children. These then predict future pain experiences. Noel et al. argue that encoding within an individual’s environment (e.g., via familial beliefs and experiences) contributes to the formation of pain-related schemata.

Much experimental research has focussed on how pain impacts on memory processes. Clearly this is an important issue given that many people are living with painful conditions and memory is a cognitive process that is central to everyday functioning, as well as higher-level perceptions such as identity. Generally, studies have found poor explicit memory performance in pain patients relative to controls, with automatic processes remaining relatively intact [25,28,43,75]. Others have looked at the accuracy and quality of memory for pain-related material. For example, pain patients have been found to demonstrate a memorial bias for pain-related information [19,59,61] and they also tend to overestimate the intensity of a painful stimulus when compared with controls [e.g. 21], particularly if in a state of high pain during recall [e.g. 70]. Other factors such as catastrophising, anxiety and mood have been found to mediate the effect of pain on memory [35,41,65,77].

Whilst there is a sizable amount of work on the effect of pain on memory as well as summary and review papers in the area, it is only in recent years that there has been an increasing focus on the effect of memory on pain. The nature of the
relationship is likely to be complex and difficult to elucidate given that both pain and memory are multi-faceted. Moreover, whilst pain is relatively easy to measure in a laboratory setting, in the form of in-the-moment intensity or unpleasantness ratings, memories, particularly autobiographical ones, are not. Such memories are formed over a lifetime and contribute to our conscious identity and yet theory suggests they can impact on behaviour unconsciously, in the form of schemata for example. One way of assessing these memories in the laboratory is to activate schemata by presenting relevant information. There is a large literature looking at how activation of schemata, either consciously or unconsciously can affect behavioural responses generally [e.g. 2,5,12,56]. More recent studies have looked at how activation of pain-related schemata in memory, either by presenting information that is broadly related to pain or information about the nature of ensuing pain, can impact on both subjective and physiological measures of pain perception. However, it is unclear what conclusions may be drawn from such studies, or indeed what the quality of that research is. Moreover, at the time of writing, no summary or review papers have addressed this topic, hence the need for the current review.

1.2. A focus of review

The goal of this systematic review was to identify, summarise and critically appraise research on the effect of memory on pain, with a view to improving our understanding of i. whether activating schemata in memory affects pain; ii. the nature of any such effect; and iii. future directions for research.

1.3. Defining ‘memory’

Whilst there is a commonly accepted definition of pain laid out by the International Association for the Study of Pain; i.e. “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [31], the term ‘memory’ encompasses a wide range of constructs along with various definitions that are beyond the scope of this paper (see Schacter & Tulving [68] for a review). At the simplest level, memory may be thought of as the encoding, storage and retrieval of information. It was therefore decided that studies describing the effect of encoding or retrieving information on pain experience
would be included in this review. This broad definition encompasses many different forms of memory, including declarative and procedural memory, working memory, semantic, episodic and autobiographical memory, amongst others. We were particularly interested in how internally held schemata and expectations about pain impact on pain perception.

2. Method

2.1. Search strategy

To identify publications on the effect of memory on pain, a systematic review was conducted using principles from the Centre for Reviews and Dissemination [10]. In order to identify keywords that would capture relevant articles, a survey of keywords used in highly relevant articles and theories was conducted. On this basis, the following key terms were selected: pain, memory, schema, priming and expectation.

The search was performed in PsychINFO, Embase and Medline databases for records published up to January, 2014 using the five selected keywords combined as follows: Pain AND (memory OR schema OR priming OR expectation). The search was limited to the English language, peer reviewed journals and human participants.

2.2. Inclusion and exclusion criteria

Articles were selected for further inspection by ES from the initial pool of 7906 according to information provided in the titles and abstracts. Sixty-six such articles were identified because they appeared to address the effect of memory on pain. Inspection of reference sections for these 66 articles identified nine additional articles that were also deemed relevant for further inspection. The method section of these 75 articles was then scrutinised for possible inclusion in the review, using the following criteria:
Inclusion:

- Articles describing experimental research addressing the effect of a memory manipulation prior to pain exposure on subsequent pain measures. All types of memory were permissible but memory tasks had to involve the encoding and/or retrieval of information that was meaningful to the experience of pain, for example, affectively-valenced words.
- Pain was a dependent variable and assessed using either a subjective (e.g., self-reported unpleasantness) or behavioural measure (e.g. tolerance).
- For clinical populations, a baseline measure of pain had to be established (pain levels in non-clinical populations were assumed to be at floor level at baseline).

Exclusion:

- Studies reporting only physiological (e.g., neuroimaging) pain data.
- Studies involving the encoding of information that was irrelevant to pain.
- Studies investigating the placebo/nocebo effect on pain, which have been reviewed extensively elsewhere [see 13,22,47,60,63].

All 75 articles were independently assessed by both authors. Agreement concerning inclusion was reached independently for 63 of the articles identified. Disagreements for the remaining 12 were successfully resolved through discussion so that the authors were in 100% agreement. Twenty-nine articles met the above criteria. See Figure 1 for a flow diagram of the review process.

2.3. Assessment of methodological quality

Included articles were read fully by ES before being assessed against criteria laid out by the Critical Appraisal Skills Programme (CASP) [14]. According to the Scottish Intercollegiate Guidelines Network algorithm for classifying study design [69], the majority of articles under scrutiny could be described as reporting either randomised or non-randomised controlled trials. However, given the heterogeneity of articles under review and the lack of guidelines for assessing the quality of non-clinical experimental studies, questions from a number of CASP methodology
checklists were combined to form a new checklist. This checklist included questions on the appropriateness of recruitment, methodology and analyses, as well as questions relating to the results of the study and the value of those results in light of the assumptions and assertions made by the authors. Possible answers to each question were ‘yes’, ‘insufficient information to judge’, or ‘no’ and corresponding values (1, 0.5, 0) were assigned to each outcome so that studies could be readily compared. Although subjective, this approach at least provided a systematic and transparent method for judging the quality of the research.

3. Results

Given the heterogeneity in theoretical foundation and methods amongst studies, narrative synthesis was deemed the most appropriate way of making sense of the selected information. Studies were divided into groups based on the types of memory they targeted. Two such groups were identified: priming studies and expectancy studies.

3.1. Priming studies

3.1.1. Study characteristics

An overview of the methods and results of the 16 studies in this area is provided in Table 1. Priming involves the presentation of information that is designed to activate related material in memory. For example, on perceiving the word *sleep*, related words such as *dream* and *tired* might be primed or ‘activated’ in memory. The memory material is then thought to influence behavioural responses, for example, a faster reaction time to *dream* on a subsequent problem solving task. In the reviewed studies, pain-related and/or emotionally valenced information was presented in various formats before participants were exposed to a pain stimulus. Priming materials did not give information about what the pain stimulus would be (see expectancy studies). In some studies, priming materials were presented both before the pain tasks and during pain tasks. Where this was the case, only data for materials presented before pain tasks are considered in this review.
Figure 1. Flow-diagram outlining the process for article inclusion.

Potentially eligible articles identified by electronic database search
\[ N = 7906 \]

Additional articles identified from reference lists of eligible publications
\[ N = 9 \]

Articles included in the review
\[ n = 29 \]

Articles excluded
\[ N = 7840 \]

Articles identified as potentially eligible based on title and abstract
\[ N = 75 \]

Articles excluded
\[ N = 46 \]
- Non-experimental: \[ N = 9 \]
- Did not meet memory manipulation criteria: \[ N = 16 \]
- Pain not treated as dependent variable: \[ N = 19 \]
3.1.2. Methodological quality

Quality ratings for each of the studies are presented in Table 2. The mean quality rating for priming studies was 8.44 and the standard deviation, 1.78 (range 4 – 10). Priming studies clearly vary with respect to quality. The best quality studies controlled for a variety of extraneous variables that are known to effect pain experiences such as mental and physical health, situational mood and anxiety, pain catastrophizing, symptom reporting and use of analgesics. Some studies excluded participants on the basis of one or more of these variables [e.g. 49,50,51], others included them as covariates in their analyses [e.g. 1]. However, a large proportion of studies did not adequately control for these variables, meaning that conclusions from these studies should be treated with caution.

Studies also varied according to the controls and checks they adopted for memory manipulations. Higher quality studies utilised priming materials that had been previously published [16,23,34,48,52] and others implemented checks to determine whether prime manipulations had been effective [e.g. 51,66].

With respect to the delivery of pain, studies were generally well controlled. Studies published before 2001 did not hold water temperature constant during the CPT. However, later studies have either kept water at a constant temperature [16], circulated water to prevent warm water building up around the hand [48,49,50,51] or both [66]. Only one study did not introduce controls to keep water temperature constant [23]. Studies using laser or electrical stimulation individually calibrated participants’ pain thresholds thereby increasing precision. These studies, as well as those applying heat stimuli, also comprised multiple trials thus increasing the number of data points collected and reducing the risk of error.

3.1.3. Results

In 6 of the 8 studies that used picture priming, participants reported higher levels of pain after viewing unpleasant and/or pain-related pictures than they did after viewing pleasant or neutral pictures. Interestingly, De Wied and Verbaten [16] compared unpleasant pictures with and without pain-related information. They
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Total number of participants</th>
<th>Design</th>
<th>Memory manipulation</th>
<th>Source of pain</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminabadi et al. [1]</td>
<td>Healthy children aged 6 – 7 years</td>
<td>80</td>
<td>RCT, between</td>
<td>Encoding a story about going to the dentist (the situation in which pain was administered; test condition) or a story about going to the hairdressers (control condition)</td>
<td>Dental injection of local anaesthetic agent</td>
<td>Significantly lower levels of reported pain intensity and situational anxiety in the test group compared to the control group.</td>
</tr>
<tr>
<td>De Wied &amp; Verbaten [16]</td>
<td>Healthy adults</td>
<td>65 (exp. 1) 39 (exp. 2)</td>
<td>RCT, between</td>
<td>Priming with either positive, negative or neutral pictures (exp. 1); priming with negative pictures either related or not related to pain (exp. 2)</td>
<td>CPT (exp. 1 &amp; 2)</td>
<td>Significantly higher pain tolerance in the positive condition relative to the negative condition, difference between positive and neutral conditions approaching significance (positive &gt; neutral). No significant differences in reported pain intensity between conditions (exp. 1). Significantly higher pain tolerance in the pain-related condition relative to the negative condition. No significant differences in reported pain intensity between conditions (exp. 2)</td>
</tr>
<tr>
<td>Fowler et al. [23]</td>
<td>Healthy adults</td>
<td>89</td>
<td>RCT, between</td>
<td>Priming of feminine or masculine gender role or neutral event via retrieval of autobiographical memory</td>
<td>CPT</td>
<td>For those primed with feminine gender role, significantly less pain reported in men than in women. No significant differences in pain between men and women when primed with masculine gender role or neutral event.</td>
</tr>
<tr>
<td>Greenstein [26]</td>
<td>Healthy adults</td>
<td>60</td>
<td>RCT, between</td>
<td>Priming with pleasant or unpleasant slides crossed with recall vs. no recall conditions or control (no slides, no recall)</td>
<td>CPT</td>
<td>Significantly higher pain tolerance after viewing unpleasant slides relative to control and pleasant slide conditions. No significant effects of recall.</td>
</tr>
<tr>
<td>Grimm &amp; Kanfer [27]</td>
<td>Healthy adults</td>
<td>48</td>
<td>CT, between</td>
<td>Reading material on physical adaption to pain (relative to CPT)</td>
<td>CPT</td>
<td>No significant effect of inter-trial reading material</td>
</tr>
</tbody>
</table>

Study design: RCT – Randomised controlled trial; CT – Controlled trial; CC – Case control  
Pain manipulation: CPT – Cold pressor task; LS – Laser stimulation  
Main findings: EEG - Electroencephalography
Table 1. An overview of priming studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Total number of participants</th>
<th>Design</th>
<th>Memory manipulation</th>
<th>Source of pain</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenntner-Mabiala &amp; Pauli</td>
<td>Healthy adults</td>
<td>30</td>
<td>CT, within</td>
<td>neutral reading material) given between 2 trials of CPT pain Priming with unpleasant, pleasant or neutral slides</td>
<td>Electrical stimulation either during or post picture presentation</td>
<td>Pain ratings lower for positive pictures relative to negative and neutral pictures on trials where pain stimulus given during picture presentation. Pain ratings lower for positive pictures relative to both negative and neutral pictures and lower for neutral relative to negative pictures where pain stimulus given after picture presentation. Event-related potentials elicited by pain stimulus differed according to picture type. Priming with pain-related images led to a significant increase in hit rate and false alarm rate for both pain and heat relative to priming with neutral images. Significantly lower pain intensity threshold in fear and disgust groups relative to neutral groups. Significantly lower pain tolerance in fear group relative to neutral group (exp. 1). Significantly higher pain intensity threshold in males in erotic group relative to males in nurturant or neutral groups. Significantly higher pain unpleasantness thresholds in erotic group relative to both nurturant and neutral groups (males and females) (exp. 2)</td>
</tr>
<tr>
<td>Kirwilliam &amp; Derbyshire</td>
<td>Healthy adults</td>
<td>50</td>
<td>RCT, between</td>
<td>Priming with either pain-related or neutral images</td>
<td>Heat detection task using stimuli from circular thermode</td>
<td></td>
</tr>
<tr>
<td>Meagher et al. [48]</td>
<td>Healthy adults</td>
<td>50 (exp. 1) 70 (exp. 2)</td>
<td>RCT, between</td>
<td>Priming with pictures depicting either fear, disgust or neutral images (exp. 1); erotic, nurturant or neutral images (exp. 2)</td>
<td>CPT (exp. 1 &amp; 2)</td>
<td></td>
</tr>
</tbody>
</table>

Study design: RCT – Randomised controlled trial; CT – Controlled trial; CC – Case control
Pain manipulation: CPT – Cold pressor task; LS – Laser stimulation
Main findings: EEG - Electroencephalography
### Table 1. An overview of priming studies

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<th>Design</th>
<th>Memory manipulation</th>
<th>Source of pain</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meerman et al. [51]</td>
<td>Healthy adults</td>
<td>80</td>
<td>RCT, between</td>
<td>Subliminal priming with either health complaint words or bodily sensation, neutral or negative words</td>
<td>CPT</td>
<td>Significantly lower pain tolerance in participants primed with health complaint words compared to those primed with neutral words. No effects for bodily sensation or negative words.</td>
</tr>
<tr>
<td>Meerman et al. [50]</td>
<td>Healthy adults</td>
<td>97</td>
<td>RCT, between</td>
<td>Subliminal priming of either health complaint words or bodily sensation, neutral or negative words</td>
<td>CPT</td>
<td>No significant findings.</td>
</tr>
<tr>
<td>Meerman et al. [49]</td>
<td>Healthy adults</td>
<td>76</td>
<td>RCT, between</td>
<td>Subliminal priming of either self-referent ('I') or non self-referent ('X') along with either health complaint or neutral words</td>
<td>CPT</td>
<td>No interaction between self-referent priming and word type. No main effect of word type. A measure of self-focussed attention (SFA) moderated the effect of self-referent priming such that when primed with 'I' as opposed to 'X', participants with low SFA demonstrated a higher pain tolerance.</td>
</tr>
<tr>
<td>Meng et al., exp. 1 [52]</td>
<td>Healthy adults</td>
<td>20</td>
<td>RCT, within</td>
<td>Colour pictures of others' limbs in painful and non-painful situations</td>
<td>Painful or non-painful heat from a circular thermode</td>
<td>Participants' pain intensity ratings were higher after viewing painful pictures than non-painful pictures. Using EEG, smaller P2 amplitudes were observed on painful than on non-painful picture conditions where participant received painful stimulus but not when they received non-painful heat.</td>
</tr>
<tr>
<td>Moseley et al. [55]</td>
<td>Patients with complex regional pain syndrome (CRPS) of one hand</td>
<td>37 (20 CRPS)</td>
<td>CC, mixed</td>
<td>Motor imagery task of the affected hand</td>
<td>Naturally occurring clinically significant pain in the hand</td>
<td>Significant increase in pain of the hand after motor imagery in CRPS patients but not non-CRPS patients, relative to baseline.</td>
</tr>
</tbody>
</table>

**Study design:** RCT – Randomised controlled trial; CT – Controlled trial; CC – Case control  
**Pain manipulation:** CPT – Cold pressor task; LS – Laser stimulation  
**Main findings:** EEG - Electroencephalography
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Total number of participants</th>
<th>Design</th>
<th>Memory manipulation</th>
<th>Source of pain</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowe et al. [66]</td>
<td>Patients with non-CRPS of one hand Healthy adults</td>
<td>95</td>
<td>RCT, between</td>
<td>Priming with secure or anxious attachment or neutral information</td>
<td>CPT</td>
<td>Significantly higher pain tolerance in participants primed with secure and anxious attachment information than those with neutral information. No differences in reported pain intensity between conditions.</td>
</tr>
<tr>
<td>Weiss et al. [76]</td>
<td>Adults with migraine (tested during migraine free period)</td>
<td>17</td>
<td>CT, within</td>
<td>Priming with either pain-related affective words, pain-related somatosensory words or neutral words</td>
<td>LS</td>
<td>Higher pain ratings after presentation of both types of pain-related words than neutral words but effect was not significant. Larger positive amplitude (recorded on EEG) after presentation of pain-related words relative to neutral words.</td>
</tr>
<tr>
<td>Worthington [78]</td>
<td>Healthy adults</td>
<td>90</td>
<td>RCT, between</td>
<td>Imagining of pleasant or neutral images that the participant either chose themselves or another participant chose under conditions of self-verbalisation or no self-verbalisation</td>
<td>CPT</td>
<td>Significantly higher pain tolerance and lower pain reporting when participants chose the imagery themselves but no effect of imagery type.</td>
</tr>
</tbody>
</table>

Study design: RCT = Randomised controlled trial; CT = Controlled trial; CC = Case control
Pain manipulation: CPT = Cold pressor task; LS = Laser stimulation
Main findings: EEG - Electroencephalography
Table 2. Ratings of methodological quality for priming studies according to the new CASP checklist

<table>
<thead>
<tr>
<th>Study</th>
<th>Screening</th>
<th>Methodological quality</th>
<th>Presentation of results</th>
<th>External validity</th>
<th>Total</th>
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</thead>
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<td>3 4 5 6 7</td>
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<tr>
<td>deWied &amp; Verbaten [16]</td>
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<tr>
<td>Grimm &amp; Kanfer [27]</td>
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<tr>
<td>Kenntner-Mabiala &amp; Pauli [34]</td>
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</tr>
<tr>
<td>Kirwilliam &amp; Derbyshire [36]</td>
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<tr>
<td>Meagher et al. [48]</td>
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<td>Meerman et al. [51]</td>
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<td>0.5 0.5</td>
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<tr>
<td>Meerman et al. [49]</td>
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<tr>
<td>Weiss et al. [76]</td>
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<td>1 0.5</td>
<td>1</td>
</tr>
<tr>
<td>Worthington [78]</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5 0.5 0.5 0.5 0.5</td>
<td>1 0.5</td>
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</tr>
</tbody>
</table>

found that pain tolerance on a CPT was lower after unpleasant pain-related pictures than it was after unpleasant pictures alone. They concluded that the content of priming materials, as well as affective quality, is an important determinant of pain tolerance, possibly because pain-related content is likely to further increase levels of arousal. Similarly, Meagher et al., exp. 1 [48] found that fear and disgust slides decreased pain intensity thresholds relative to neutral slides but only fear slides decreased pain tolerance thresholds.

It is notable that Greenstein [26] presents contradictory picture priming data. However, this study obtained the lowest quality rating in this section due to its failure to implement sufficient methodological controls and so its conclusions should be taken with caution.

Pictures were also found to alter pain-related physiological states. Moseley et al. [55] found a significant increase in clinical pain as well as an 8% increase in swelling in participants’ hands that were used to imagine painful movements depicted in an image. Pain catastrophizing contributed significantly to the increase in swelling (but not pain reporting) when baseline pain was included in their regression analyses. Using EEG, Meng et al. [52] found smaller positive amplitudes on painful trials after viewing pain-related pictures. EEG data presented by Kenntner-Mabiala and Pauli [34] did not reveal any significant effects.

Four studies primed participants with words. Weiss et al. [76] failed to find an effect of word type (somatosensory, affective, neutral) on pain ratings in a study using laser stimulation. However, they did find significantly larger laser evoked potentials (LEPs) after the presentation of affective words. Meerman et al. [51] found a decrease in pain tolerance on a CPT in participants who had been subliminally presented with health complaint words (such as allergy, headache) relative to those subliminally presented with neutral, negative or bodily sensation (such as tight, tickling) words. Meerman et al. argued that these unconsciously and involuntarily perceived words activated illness-related memory and decreased pain tolerance via increasing attention towards physical sensations. This was a high quality study overall. However, the authors did not match words on dimensions such as arousal or valence. They also used a one-tailed test to evaluate their hypothesis. These factors may explain why they failed to replicate their data in 2012 [50]. Meerman et al. [49] also looked at whether self-focussed attention moderated the effect of health...
complaint words on pain tolerance. They failed to find an effect of word type but they did find that presenting words with the self-referent I increased pain tolerance in participants with low self-focused attention. Meerman and colleagues suggest that an effect of word type on pain may be small and that future studies implement tight controls.

A small number of priming studies used more novel methods. Aminabadi et al. [1] found that children reported significantly lower levels of pain during a dental injection after they had been primed with a story about a successful trip to the dentist than after they had been primed with a similar story about the hairdressers. This effect is probably anxiety-related, as this was also reduced in the test group. Fowler et al. [23] and Rowe et al. [66] used participants’ autobiographical memories to prime them for gender roles and attachment orientations respectively. Fowler et al. found that men primed with female gender roles reported significantly less pain on a CPT than women. However, the authors did not measure pain tolerance and so were not able to ascertain whether this was a genuine decrease in pain experience or a difference in reporting. Rowe et al. [66] found an increase in pain tolerance but not pain intensity reporting after priming of both secure and anxious attachments relative to neutral primes. They argued that both styles of attachment would activate pleasant relational information. It is nevertheless surprising that they did not also find a difference in pain tolerance between secure and anxious primes, as secure attachment primes might be expected to elicit more pleasant memories than anxious ones.

3.1.4. Primary conclusions

Overall, data show that priming by negative and pain-related materials decreases pain tolerance and increases subjective pain ratings relative to neutral or pleasant materials. As discussed, some studies have shown no effect, perhaps because they have failed to account for various confounds such as state mood and anxiety and so this conclusion should be taken with caution. Pictures appear to be a more robust medium for priming in this area, possibly due to their richer detail. It is important that studies in this area implement tight methodological controls, particularly with respect to memory manipulations.
3.2. Expectancy studies

3.2.1. Study characteristics

Thirteen studies looked at the effect of warnings on pain (see Table 3). In many studies, participants were presented with meaningful and specific information about a forthcoming painful experience in order to create expectation about it. Expectancy was then manipulated by providing inaccurate cues about upcoming pain stimuli. Two studies [11,37] gave participants a conditioning, or training phase during which a warning cue was paired with a particular stimulus. Expectancy studies differed from priming studies because they presented participants with specific information about what would happen next rather than general information about pain or emotion and they differed from placebo/nocebo studies because no substance or intervention was given.

3.2.2. Methodological quality

Quality ratings for expectancy studies are presented in Table 4. The mean quality rating was 8.31 and the standard deviation was 1.09 (range 6 – 10). Although there was some variance in the degree to which studies controlled for factors known to affect pain perception overall, they were of high quality overall and many studies [e.g. 29,38] did control for factors, including the use of analgesics. Many expectancy studies presented participants with clear cues about upcoming painful stimuli, even if they did not match the actual stimuli. For example, Brown et al. [8] presented one of four anticipatory words (low, medium, high, unknown). As such, manipulation checks to determine that cues had been understood, were generally not necessary. However, other studies where ambiguous cues had been paired with painful stimuli at baseline, during a conditioning phase, did require manipulation checks. One study in this section by Chan et al. [11] conducted checks.

3.2.3. Results

Data across 12 of the 13 studies that issued warnings to participants about upcoming pain stimuli demonstrated clear effects on pain ratings, such that high
Table 3. An overview of expectancy studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Number of participants</th>
<th>Design</th>
<th>Memory manipulation</th>
<th>Source of pain</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlas et al. [3]</td>
<td>Healthy adults</td>
<td>19</td>
<td>CT, within</td>
<td>Accurate or ambiguous auditory cue about the temperature of upcoming heat stimulus</td>
<td>TS</td>
<td>Thermal stimuli were rated as significantly more painful after a warning cue that signified a high temperature than after one that signified a low temperature. Using fMRI, high temperature warning cues created greater activity in the insular, anterior cingulate cortex and thalamus.</td>
</tr>
<tr>
<td>Brown et al. [8]</td>
<td>Healthy adults</td>
<td>15</td>
<td>RCT, within</td>
<td>Accurate visual cues about the intensity of to-be-presented LS vs. ambiguous cue</td>
<td>LS</td>
<td>Accurate warnings increased pain ratings for moderate LS and decreased pain ratings for low LS relative to ambiguous cues. Anticipatory EEG activity varied according to warning/cue type.</td>
</tr>
<tr>
<td>Chan et al. [11]</td>
<td>Healthy adults</td>
<td>18</td>
<td>RCT, within</td>
<td>After pain stimulus at time 1, participants either maintained the painful stimulus in memory for 3000ms (perception condition) or mentally generated and maintained a corresponding non-painful stimulus that had been conditioned at baseline (imagery condition)</td>
<td>ES to the ankle</td>
<td>Significantly lower level of reported pain in the imagery condition relative to the perception condition on mild to moderate pain trials only. No significant difference on high pain trials</td>
</tr>
<tr>
<td>Henchoz et al. [29]</td>
<td>Patients with chronic low back pain (N = 22), Healthy adults (N = 22)</td>
<td>44</td>
<td>CC, mixed</td>
<td>Accurate valid vs invalid warning about the temperature of to-be-presented TS</td>
<td>TS</td>
<td>High heat warning significantly increased pain intensity ratings relative to low heat warning in healthy adults and patients. Significantly higher levels of myoelectric activity in the spine during a concurrent back-flexion task after the high heat warning relative to the low heat warning in healthy adults only.</td>
</tr>
</tbody>
</table>

Study design: RCT – Randomised controlled trial; CT – Controlled trial; CC – Case control
Pain manipulation: CPT – Cold pressor task; LS – Laser stimulation; ES – Electrical stimulation; TS – Thermal stimulation
Main findings: EEG - Electroencephalography
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</tr>
</thead>
<tbody>
<tr>
<td>Höfle et al. [30]</td>
<td>Healthy adults</td>
<td>28</td>
<td>CT, within</td>
<td>Participants were informed of the probability of receiving a painful or non-painful stimulus that was delivered whilst viewing a hand either being pricked by a needle or touched by a Q-tip (cotton-bud)</td>
<td>ES</td>
<td>Participants rated pain after viewing the needle prick as more unpleasant than pain after viewing the Q-tip. However, this was dependent on the level of expectation a participant had for pain. In conditions where they had a low expectation of receiving pain, there was no priming effect. In conditions where they had a low expectation of receiving pain, there was no priming effect.</td>
</tr>
<tr>
<td>Keltner et al. [33]</td>
<td>Healthy adults</td>
<td>27</td>
<td>RCT, within</td>
<td>Accurate vs. inaccurate visual cues about the temperature of to-be-presented pain stimulus</td>
<td>TS</td>
<td>Significantly higher reported pain when it was preceded by a high intensity visual cue relative to a low intensity cue regardless of stimulus intensity.</td>
</tr>
<tr>
<td>Koyama et al. [37]</td>
<td>Healthy adults</td>
<td>10</td>
<td>CT, within</td>
<td>Expectation of pain intensity conditioned at baseline then manipulated during experimental trials.</td>
<td>TS</td>
<td>Expectations of low pain led to both significantly lower ratings of pain and reduced activity in pain-related regions of the brain.</td>
</tr>
<tr>
<td>Lang et al. [38]</td>
<td>Patients referred for renal procedures</td>
<td>159</td>
<td>CT, between</td>
<td>Retrospective classification of patients into two groups depending on comments made to them prior to painful procedure; negatively loaded comments (n = 33) vs. any other comment type (n = 126)</td>
<td>Vascular or percutaneous renal procedures</td>
<td>Patients who heard negatively loaded comments reported significantly more pain than those who did not hear such comments</td>
</tr>
<tr>
<td>Leventhal et al., exp. 1 [42]</td>
<td>Healthy adults</td>
<td>50</td>
<td>RCT, between</td>
<td>Provided with information about the quality and magnitude of the to-be-experienced painful stimulus (sensory, arousal and control crossed with high, low pain warnings)</td>
<td>CPT</td>
<td>Significantly less distress reported by participants in the sensory group relative to those in the arousal and control groups. Reduction in distress for the sensory group in the low warning condition relative to the high warning condition (p &lt; .06)</td>
</tr>
</tbody>
</table>

Study design: RCT – Randomised controlled trial; CT – Controlled trial; CC – Case control
Pain manipulation: CPT – Cold pressor task; LS – Laser stimulation; ES – Electrical stimulation; TS – Thermal stimulation
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<tbody>
<tr>
<td>Lorenz et al. [46]</td>
<td>Healthy adults</td>
<td>6</td>
<td>CT, within</td>
<td>Valid or invalid auditory cue about the intensity of to-be-presented LS or uninformative cue</td>
<td>LS</td>
<td>Participants perceived high intensity LS as less painful and low intensity stimulus as more painful after an invalid cue relative to a valid cue.</td>
</tr>
<tr>
<td>Moseley &amp; Arntz [54]</td>
<td>Healthy adults</td>
<td>33</td>
<td>CT, within</td>
<td>Accurate visual cue about the intensity of upcoming pain stimuli that was presented under conditions of looking either towards or away from the pain stimulus</td>
<td>Cold probe</td>
<td>Significantly higher intensity and unpleasantness ratings after the high intensity cue relative to the low intensity cue. Significantly higher pain ratings after the high intensity cue only when looking at the pain stimulus compared to when looking away.</td>
</tr>
<tr>
<td>Ott et al. [58]</td>
<td>Healthy adults</td>
<td>98</td>
<td>CT, between</td>
<td>Warned with either 'sting' or 'beware' prior to pain stimulus</td>
<td>Venous blood sampling</td>
<td>Significantly higher pain rating after warning issued with 'sting' relative to 'beware'.</td>
</tr>
<tr>
<td>Robinson et al. [64]</td>
<td>Healthy adults (50% male)</td>
<td>120</td>
<td>CT, between</td>
<td>Given a gender-specific expectation of how long they could tolerate a CPT (either 30s or 90s)</td>
<td>CPT</td>
<td>Without the tolerance expectation, females had significantly lower pain tolerance. There was no difference in CPT tolerance between males and females in either expectation condition.</td>
</tr>
</tbody>
</table>

Study design: RCT – Randomised controlled trial; CT – Controlled trial; CC – Case control
Pain manipulation: CPT – Cold pressor task; LS – Laser stimulation; ES – Electrical stimulation; TS – Thermal stimulation
Main findings: EEG - Electroencephalography

32
Table 4. Ratings of methodological quality for expectancy studies according to the new CASP checklist

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<tr>
<th>Study</th>
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<th>Methodological quality</th>
<th>Presentation of results</th>
<th>External validity</th>
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<td>3 4 5 6 7</td>
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<td>Keltner et al. [33]</td>
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<td>Lorenz et al. [46]</td>
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<tr>
<td>Moseley &amp; Arntz [54]</td>
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<td>1 0.5 0.5 0.5 0.5</td>
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<td>1</td>
<td>7.5</td>
</tr>
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<td>Ott et al. [58]</td>
<td>1 1</td>
<td>1 1 1 1 0.5 0.5</td>
<td>1 1</td>
<td>1</td>
<td>9</td>
</tr>
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<td>Robinson et al. [64]</td>
<td>1 1</td>
<td>1 1 0.5 0.5 0.5</td>
<td>0.5 0.5</td>
<td>1</td>
<td>7.5</td>
</tr>
</tbody>
</table>

expectancy cues increased pain perception relative to low expectancy cues, regardless of the actual intensity of pain stimuli.

Two studies were included in this section, although they arguably also incorporated priming tasks, because the priming tasks were co-dependant with the level of expectation for pain. Hofle et al. [30] looked at pain ratings after participants had viewed a video clip of either a painful or non-painful scene. They found that the effect of priming was only present when participants had a high expectation of pain. Robinson et al. [64] gave participants information based on their gender about how long they might be expected to tolerate a CPT. They found that males tolerated the water for longer than females in the no warning condition but when either gender received the same gender-specific expectation of tolerance (i.e. “the typical man/woman lasts 30s in this task”), there was no difference. However, they did not also give participants performance expectation without mention of gender, making it difficult to tease apart potential mechanisms for this effect (i.e. is it due to warning or activation of gender stereotype?).

It is notable that Leventhal et al., exp. 1 [42] did not find an effect of warning on pain ratings but they did find that providing accurate information about the sensory quality of the upcoming CPT led to lower levels of participant distress.

In studies by Lang et al. [38] and Ott et al. [58], participants were given certain words and phrases prior to routine clinical pain exposure from a medical procedure. Lang et al. found that patients who heard negatively loaded comments about an upcoming medical procedure (such as you’ll feel a little sting here), reported significantly more pain than patients who had not. Similarly, Ott et al. [58] found that the word sting spoken as part of a warning to participants significantly increased pain ratings relative to the word beware. These studies demonstrate that providing simple preparatory information about common painful procedures can have a significant impact on experienced pain.

Four studies [3,8,33,54] found that accurate warnings augmented pain ratings; that is, low pain warnings decreased pain intensity and/or unpleasantness ratings for low intensity stimuli and high pain warnings increased pain intensity and/or unpleasantness ratings for high intensity stimuli. Conversely, where invalid cues were given, participants gave lower pain intensity ratings on high stimulus intensity trials [29,46] and higher pain intensity ratings on low stimuli trials [46]. Similarly, studies
that conditioned expectancy [11,37] found that pain intensity ratings were significantly attenuated when participants engaged in activities that had been paired with a low stimulus intensity relative to when they engaged in activities that had been paired with a high stimulus intensity, regardless of the actual intensity of the stimulus. Some studies also looked at physiological markers of pain anticipation and perception. For example, Henchoz et al. [29] found increased myoelectric activity in the spine during a back-flexion task with concurrent painful heat stimulation to the lumbar region after a high pain stimulation warning cue relative to a low stimulation warning cue. Looking at anticipation, Brown et al. [8] found that Stimulus Preceding Negativity (SPN) in response to warning cues predicted P2 peak amplitudes for LEPs in response to pain stimuli. Using fMRI, Atlas et al. [3], Keltner et al. [33] and Koyama et al. [37] all found greater activity, after high pain expectancy cues, in brain areas consistent with the Pain Processing Network (PPN) such as the insular, Anterior Cingulate Cortex (ACC) and the thalamus and greater activity in these areas was associated with higher pain reporting. These studies suggest that warnings can ‘activate’ pain centres in the brain, which then bias pain ratings.

3.2.4. Primary conclusions

Overall, data from studies in this group were consistent and there were few contradictions. It is clear that information about an upcoming painful stimulus can have an effect on both behavioural and physiological responses to pain. There is also evidence that expectancy modulates anticipatory activity, particularly at the physiological level. Subsequently, this may create activation of brain systems that influence both physiological and behavioural responses to pain.

4. Discussion

The aim of this systematic review was to identify and critically appraise studies investigating the effect of memory on pain. A narrative synthesis of 29 studies indicates several ways in which memory can affect pain, both at the behavioural level, with respect to pain ratings, and at the physiological level.
4.1. How does memory affect pain?

The largest group of studies, on priming, showed that negative and/or pain-related materials decreased pain tolerance relative to neutral or pleasant materials. Studies using pictures demonstrated the most robust findings in this group and there were inconsistent data for studies that used words to prime participants. An outstanding question is whether the effect of negatively-valenced materials on pain is due to memory or state mood. Data suggest that although mood is implicated, priming materials that additionally comprise specific information about pain elicit a greater pain response [16]. However, this remains uncertain. The second group of expectancy studies demonstrated consistent data showing that presenting meaningful information, even if inaccurate, about to-be-experienced pain stimuli affected pain ratings and physiological responses. The role of expectation is clearly important and studies including physiological data in this group showed effects of anticipation i.e. the body readying itself, both physically and psychologically, for pain.

Human memory, by nature, not only encodes information 'verbatim' at the time of exposure but continually updates that information in line with data from a number of other systems and functions e.g. physiological, social, cognitive. These updated memories may then provide a basis for future pain responding. This is particularly evident in studies that took physiological measures between the memory manipulation and pain stimulus [3,8,33,46,52,76]. Some studies that did not meet criteria for inclusion in this review provide additional evidence. They found that memories of prior pain experiences are correlated with subsequent painful experiences and that these memories are often better predictors of future pain reporting than other variables such as actual pain reporting or anxiety [15,24,57,73].

There is evidence that memories directly relating to personal experience of upcoming pain may have a greater impact on pain perception than those that do not. Studies in the expectancy group that encouraged participants to consider to-be-experienced pain stimuli via conditioning tasks or warnings generally found clear effects of memory on pain. By contrast, it could be said that most priming studies presented pain-related or unpleasant information that was removed from participants’ direct experience of pain within the experimental setting. This, as well as methodological issues (discussed below), may explain why data from priming studies
were more varied. It is noteworthy that Meerman et al. [49] found that increasing self-focussed attention overall increased pain tolerance, although this was true for priming with both neutral and health complaint words.

4.2. Possible mechanisms for the effect of memory on pain

A number of studies reviewed here have looked to activation-based accounts of their findings [e.g. 3,33,37,51,55,76]. According to these theories, materials presented at study (i.e. before pain stimuli), create ‘activation’ at both physiological and cognitive levels. Activation then ‘primes’ the body for responding. At the physiological level, materials relevant to the pain stimulus (e.g. warnings), increase neurological activation in the PPN. This then makes it more likely that pain is experienced because these activated areas are known to mediate pain responding in the brain [see 62,67]. Evidence of increased activation in the PPN during expectancy from placebo studies provides weight to this argument [see 4,62,72,74]. At the cognitive level, semantic priming using negative and/or pain-related materials increases activation of pain-related schemata which then lowers the threshold for responding so that pain is more likely to be experienced. Semantic activation is thought to be automatic [5,56], i.e. fast and without conscious awareness, and it is particularly effective when materials presented at study are highly relevant to subsequent behavioural responses. In support of this, larger priming effects have been found for pain-related negative materials than for negative materials [16]. These activation-based accounts fit well with wider cognitive models of memory [e.g. 2,12] as well as specific models of memory and health that aim to explain chronic pain conditions and unexplained symptoms [9,57]. However, although the studies in this review provide support for activation-based accounts, they do not fully allow such theories to be tested because they have not been designed with them in mind.

Others have used a motivational priming model [39] to account for their data [e.g. 16,34,48]. This model states that emotions mediate psychological and physiological responses via two opponent motivational systems, appetitive and aversive. Pleasant materials are thought to prime the appetitive system and unpleasant materials prime the aversive system. Moreover, as the arousal of the
materials increases so too does the magnitude of the memory effect. This model predicts that varying arousal for materials of the same valence would increase the effect of priming on pain and some studies under review have provided data in support of this [16,48].

4.3. Crucial factors in determining the effect of memory on pain

As quality ratings demonstrate, methodological quality was variable. Priming studies were most variable and this may account for at least some of the contradictory data within that group. Given the multidisciplinary nature of researchers working in this area, it should be expected that there will be heterogeneity in the theoretical underpinnings, methodological strategies and conclusions of studies. However, it is clear that in order to find effects of memory on pain, whilst also being clear about probable mechanisms for such effects, studies must be informed by theories in the field of memory and pain. Furthermore, they must utilise appropriate methodologies that maximise data collection and then use these data fully during statistical analyses. More recent studies have tended to be more tightly controlled and it is these studies that have contributed the most consistent data overall.

Studies in this review, particularly those in the priming group suggest a publication bias. Many priming studies demonstrated small effects that were close to the 5% significance level making it possible that similar studies were not disseminated. It is probable that some effects (particularly those of priming with words) are particularly sensitive to study design. Unfortunately, publication biases are widespread within the scientific literature [17], and it is likely that researchers will continue to be ignorant of others’ null data. Inevitably, this slows progression within the field because it hampers meaningful discussion amongst researchers, particularly those from disparate disciplines, about crucial factors that affect memory and pain.
4.4. Future directions

As we have seen, the multidisciplinary nature of articles included in this review brings different perspectives on memory and pain that are valuable. However, as we have shown it also brings significant challenges. The area of research has moved forward haphazardly, with papers emerging from a wide variety of researchers and with varying aims and methodologies. Despite this, a narrative synthesis has allowed similarities between studies to be explored in the current review. Researchers now need to move increasingly towards using theories of memory and pain to drive experimental design. Top-down design of studies (i.e. using theory to inform study design and predictions, particularly counterintuitive ones), in addition to tight methodologies and carefully planned statistical analyses, make it more likely that the mechanisms for the effects researchers find are clear as well as relevant to established theories in the field. For example, activation-based accounts predict that varying the level of activation, by varying associative strength between priming materials and pain schemata will increase the effect on pain perception. They also predict that varying the level of processing of priming materials, for example, by varying presentation speed or conditions of study will also influence the priming effect on pain. To our knowledge, these issues have not been investigated.

Another task facing future researchers is to increase the ecological validity of their studies. The effect of memory on pain perception clearly has clinical utility, yet a minority of studies included in this review actually recruited patients with naturally occurring pain. Increasing the ecological validity of memory manipulations may prove to be more difficult. As humans, we are constantly ‘online’; processing information and integrating it within existing memory structures and knowledge bases as suggested by cognitive models that may be applied to memory and pain [9,57]. However, researchers may need to be more creative in devising memory manipulations if they are to ensure that their work is generalizable. Increasing ecological validity without sacrificing experimental control will be a significant challenge for future studies.
4.5. Strengths and limitations of this review

The multidisciplinary nature of researchers working in the field of memory and pain meant that the literature search had to encompass a wide range of research. As such, even with just five search terms employed, almost eight thousand articles were identified for further inspection. Given the size of this task, it is possible that some articles were incorrectly excluded. Even given the breadth of the search, it is possible that it was not wide enough as demonstrated by the identification of a further nine articles from reference sections.

The topic covered by this review has not progressed in a particularly focussed way for four decades. It is hoped that as well as identifying relevant literature on which to consider future studies, this review has provided a methodological and theoretical focus for future research.

5. Conclusions

Through identifying and critically appraising relevant literature, this review has shown that memory and processes of memory can affect pain perception, both at behavioural and physiological levels. The most robust data come from studies on expectancy, whilst studies on priming have produced mixed findings. A number of factors such as methodological design and quality, and theoretical underpinning of studies have been suggested as important in determining the effect of memory on pain. This review demonstrates that this is an area worthy of further investigation and has identified ways in which researchers might move forward.
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References


Some words hurt more than others: Semantic activation of pain concepts in memory and subsequent experiences of pain.

The following paper has been prepared for submission to Pain. The author information pack is provided in Appendix I. Specific guidelines for basic science reports can be found in Appendix III. Tables and figures are given in-text to aid understanding in this thesis.

Word count
Total: 6351
Total (excluding figures and tables): 5943
Abstract: 233
Some words hurt more than others: Semantic activation of pain concepts in memory and subsequent experiences of pain.

Abstract
Memory is a psychological factor that has been shown to play a significant role in pain perception. Theory suggests that as activation of pain concepts in memory increases, so too does subsequent pain perception. Activation of pain concepts is thought to be automatic, unconscious and common to everyone. In line with this, researchers have found that activating pain concepts in memory increases pain perception relative to neutral information. However, they have not attempted to quantify the nature of the association between information presented at study and ensuing pain perception. We subliminally presented words that had either a low or high degree of association to the word ‘pain’ prior to the delivery of randomized laser heat stimuli, at one of three intensity levels (low, moderate, high), and measured the effect of this on subjective and objective (electrophysiological) pain measures. Participants (N = 27) rated moderate and high intensity laser stimuli as more painful after viewing high relative to low associates of pain; these effects remained present when measures of mood, anxiety and physical symptom reporting were controlled for. Similar effects were observed physiologically, with higher stimulus preceding negativity after high relative to low associates and greater amplitudes for the N2 component of the laser-evoked potential (LEP) after presentation of high associates in the moderate and high laser stimuli conditions. These data provide support for activation-based models of the effects of memory on pain perception.

1. Introduction
Memory has been cited as playing an important role in the perception of pain and the development and maintenance of chronic pain conditions [4,11,15,52]. Theory suggests that memorial processes may be particularly relevant to understanding pain that occurs in the absence of noxious stimulation or peripheral pain pathology. According to Brown [9], for example, such “unexplained” pain can result from the chronic activation of pain-related information in memory. A number
of sources for this chronic activation have been hypothesized, including pain-related illness behaviour, worrying and ruminating about one's own and others' painful experiences, and repeated exposure to pain messages in the family, media and elsewhere. Activation of pain-related information in memory may also bias the individual to look for, notice and respond to pain-related information within the wider environment, setting up a vicious cycle. Activation of pain-related information in memory is thought to be common to everyone and largely unconscious.

In support of this model, there is evidence that noxious stimuli are rated as more painful after participants have been exposed to (or 'primed' by) supraliminal pain-related pictures rather than neutral pictures [16,41,36]. Physiological effects have also been shown using electroencephalography (EEG) with larger N2 – P2 peak-to-peak amplitudes for laser evoked potentials (LEPs) after supraliminal presentation of pain-related words relative to neutral words [62]. Consistent with the assertion that activation of pain-related information can also occur unconsciously, Meerman and colleagues [39] found lower pain tolerance after exposure to subliminally presented health-complaint words relative to neutral words. Subsequent attempts to replicate this effect have been unsuccessful, however [37,38].

Although they provide some support for the impact of memory activation on pain perception, there are a number of problems with studies in this area. For example, researchers have not attempted to quantify the association between materials presented at study and the subsequent activation of pain-related concepts in memory. This is crucial because Brown's model predicts that increased semantic activation of pain-related information has a direct relationship with ensuing pain. Moreover, stimuli are not always matched on important dimensions such as arousal or valence, which could have a significant impact on pain ratings.

To this end, the current study examined both behavioural and physiological responses to painful laser stimuli following the subliminal presentation of words that shared either a low or high degree of association to the word pain. We expected higher subjective pain ratings, as well as increased electrophysiological activity consistent with the processing of painful stimuli, in the high associate conditions. Brown’s model [9] proposes that the activation of pain-related concepts in memory is
a normal cognitive process. It was therefore hypothesized that these effects would be present even when various measures of mood and anxiety were controlled for. However, it was also expected that there would be a positive correlation between physical symptom reporting and the priming effect, on the grounds that high symptom reporters are likely to have a lower threshold of activation for pain-related concepts in memory.

2. Methods

2.1. Participants

Twenty-seven healthy participants (19 female, 8 male; $M = 24.91$ years, $SD = 4.01$) were included in the study. All participants were right-handed and reported being free of neurological or other conditions that affect pain perception. None of the participants were taking pain medication at the time of the study. The study was approved by the Manchester University Research Ethics Committee and participants gave written and informed consent. Participants were told what would happen to them during the study but they were not told about the use of subliminal priming so as to keep the processing of pain associates unconscious. All participants were fully debriefed at the end of the study.

2.2. Experimental design and procedure

This was a 2 x 3 repeated measures design. Associate of pain (low or high cue-to-target strength) was crossed with laser intensity level (low, moderate, high) to yield six conditions. A total of 96 trials were split into four blocks of 24 trials, two containing low associates and two containing high associates. Blocks were ordered according to a Latin square design with half the participants beginning with a block of low associates. Associates were presented three times within each block, once each for low, moderate and high laser intensity levels. Trials were pseudo-randomised so that the same associate or intensity level was not presented more than twice in a row.
Three minute breaks, during which participants were asked to complete a non-verbal task, punctuated blocks. This allowed participants’ skin to rest and any pain-related activation in memory to subside before the next block.

A CO₂ laser was used to administer heat stimuli of 150ms duration and with a beam diameter of 15mm to the dorsal surface of each participant’s right forearm. During the inter-trial interval, the laser was moved randomly over an area covering approximately 3 x 8cm in order to prevent habituation, sensitization or skin damage. Protective laser safety goggles were worn throughout the experiment.

Prior to experimental trials, a psychophysics procedure determined individual pain thresholds for levels 3, 5 and 7 on a 10-point scale where 3 corresponded to low pain (‘just feeling a sharp sensation’), 5 corresponded to moderate pain (‘sharp pin prick or spit of fat’) and 7 corresponded to high pain (‘very sharp pin prick or spit of fat. Do not want it to go higher’). A ramping procedure, increasing laser intensity by 0.6v each time, was repeated until consensus was reached. Participants completed questionnaires whilst the EEG cap was fitted. Custom built software programmed using VC++ was used to run experimental trials. On each trial (see Fig. 1), a fixation cross, shown for 1s, was immediately proceeded by a single associate of the word pain for 33ms, a latency that has been used extensively in previous subliminal priming studies [e.g. 10,20,27,39]. In order to remove the word from the retina (and thus prevent conscious recognition of it), each word was immediately followed by a backward mask of nonsense Chinese characters, presented for 1s. Participants were told that their memory for the Chinese characters would be tested later, both ensuring attention to the word stimuli and helping to conceal the true purpose of the experiment. After an inter-stimulus interval (ISI) of 2s, the pain stimulus was delivered and after a second ISI of 2s, instructions appeared asking participants to provide a verbal rating of pain on the scale used during the psychophysics procedure. An interval of 2s then preceded the beginning of the next trial. After the final block, participants were told that some words had been briefly presented immediately before the Chinese characters and they were asked to complete a recognition test for these.
2.3. Materials and measures

2.3.1. Associates of pain

Sixteen semantic associates of the word pain were chosen from the University of Florida Free Association Norms (Florida word norms) [45]. The Florida word norms are the largest database of word norms in the world, providing data from over 6,000 participants. The database provides cue-to-target probabilities that index the likelihood that one word will bring another (in this case pain) to mind in the absence of any other information or constraints. Cue to target probabilities provide a measure of the accessibility, and therefore the activation of, semantically related words in memory [23,47]. The database has been shown to be reliable overall ($r = .89$) [44].
Eight high associates and eight low associates were selected (see Appendix A). Cue to
target probabilities ranged from .64 to .25 for the high associates and .05 to .01 for
low associates. High and low associates significantly varied in the probability with
which they brought the target word pain to mind ($t (14) = -8.99, p < .001$). High and
low associates were matched for length ($t (14) = -.13, p = .90$), frequency ($t (14) =
1.19, p = .26$), emotional valence ($t (14) = 1.53, p = .15$) and emotional arousal ($t (14)
= .12, p = .91$).

2.3.2. Recognition test

A recognition test comprising all 16 associates, 8 related lures (i.e. words
related to pain that were not presented during experimental trials), the critical
lure (i.e. pain) and 8 unrelated lures acted as an awareness check to determine whether
associates had been processed subliminally. It also provided information on the types
of memories participants had for low and high associates as well as their ability to
discriminate targets from false alarms (i.e. sensitivity) and their response criterion
(i.e. general tendency to say that they recognised the words, regardless of whether
they had been presented). Participants responded ‘yes’ or ‘no’ to indicate whether
they thought each item had been presented during the experimental trials. Where
they had answered ‘yes’ they were asked to rate the item according to the type of
memory they had for it, following the widely-used ‘Remember-Know’ procedure
[18,58]. ‘R’ (remember) responses indicated a conscious recollection of the word, ‘K’
(know) responses indicated familiarity without conscious recollection and ‘G’ (guess)
responses indicated that the word felt vaguely familiar but they could not be sure
whether they saw it or not. Remember and know responses are thought to reflect
quantitatively distinct judgements based on a continuum of certainty and confidence
[65,66]. It was assumed that R responses represented consciously formed memories,
probably reflecting supraliminal processing of associates and K and G responses
represented unconsciously formed memories, probably reflecting subliminal
processing of associates. Response types for lures (but not necessarily targets) are
thought to be a measure of activation in memory [48], and so we were interested in
differences in these responses between related and unrelated lures.
2.3.3. Patient Health Questionnaire (PHQ-9)

Since low mood can have a significant impact on pain perception [33], participants’ mood during the preceding two weeks was measured using the PHQ-9 [30]. This comprises nine items corresponding to criteria for major depression in the Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM-IV) [2]. Items are scored from '0' (not at all) to '3' (nearly every day). The PHQ-9 is reliable (test-retest = .84; Cronbach’s α = .86 [30]) and has good sensitivity (estimates ranging from .77 to .88) and specificity (estimates ranging from .88 to .94) [19,30,64]. It is widely used for both clinical and research purposes. In the current study, Cronbach’s α = .76.

2.3.4. Patient Health Questionnaire (PHQ-15)

Physical symptom reporting was hypothesized to correlate with the priming effect in the current study. The PHQ-15 [31] asks participants to rate how much of the commonest symptoms seen in primary care have bothered them over the preceding month, from ‘0’ (not at all) to ‘2’ (bothered a lot). The PHQ-15 is reported to have good internal consistency (Cronbach’s α = .80), test-retest reliability (.83), and sensitivity (0.71) and specificity (0.78) for identifying DSM-IV somatoform disorders [59]. In the current study, Cronbach’s α = .72.

2.3.5. The Generalized Anxiety Disorder questionnaire (GAD-7)

Both state and trait anxiety are associated with increased reporting of pain intensity [57]. The GAD-7 [55] asks how often participants were bothered by various anxiety related symptoms in the two weeks preceding the study. Responses range from ‘0’ (not at all) to ‘3’ (nearly every day). The GAD-7 has good sensitivity (.89) and specificity (.82) for DSM-IV Generalized Anxiety Disorder (GAD) [56], as well as good internal reliability (Cronbach’s α = .92) and test-retest reliability (.83) [32,55]. In the current study, Cronbach’s α = .81.

2.3.6. The Fear of Pain questionnaire – short form (FPQ-SF)

There is evidence that fear increases hypervigilance to pain and subjective pain reporting [14]. To account for this, the FPQ-SF [3], a 20-item short form of the Fear of Pain Questionnaire III (FPQ-III) [35], was used. Questions are answered on a
5-point scale from ‘1’ (not at all) to ‘5’ (extreme). It features four, factorially separate, subscales of severe, minor, injection and dental pain and has been shown to have good construct validity and internal consistency (Cronbach’s $\alpha = .91$) [3]. In the current study, Cronbach’s $\alpha = .90$.

2.3.7. The Short Health Anxiety Inventory (SHAI)

Health anxiety is common [1] and often correlates with pain reporting [46]. The SHAI [49] is an 18-item inventory that measures health anxiety independent of physical health status. Each item provides 4 statements around health-related issues such as worries and thoughts about illness and noticing bodily sensations. Individuals are asked to choose the statement that best reflects their feelings over the preceding 6 months. It has good internal consistency (Cronbach’s $\alpha = $ ranging from .81 to .91), test-retest reliability (.87) and is regarded as a psychometrically sound tool for use with both clinical and non-clinical samples [1]. In the current study, Cronbach’s $\alpha = .93$.

2.3.8. The Positive and Negative Affect Schedule (PANAS)

In order to control for individual differences in current mood state, the PANAS was used to measure participants’ affect during the study. The PANAS [61] comprises 10 words that reflect positive affect and 10 words that reflect negative affect. Individuals rate the extent to which they are feeling each item on a 5 point scale from ‘1’ (very slightly or not at all) to ‘5’ (extremely). The PANAS has good internal consistency (Cronbach’s $\alpha = .89$ for positive and .85 negative items respectively) and is reported to be a valid and reliable measure of positive and negative affect in non-clinical samples [13].

2.4. EEG data acquisition

EEG data were recorded using an ActiCap 64-channel active electrode system with a BrainAmp amplifier (Brain Products GmbH, Munich, Germany). Data were recorded against the reference at the right mastoid and the ground was embedded within the cap at AFz. Muscle movements were recorded via an electrode placed at
the left mastoid and ocular artifacts were measured via electrodes placed above and below the right eye. The remaining 59 electrodes were placed equidistantly across the scalp according to the extended standard 10-20 system. The data were recorded at a sampling rate of 500Hz; online filters were not used. The impedance of all electrodes was maintained below 5 kΩ.

EEG data were processed and analyzed using Brain Vision Analyzer, version 2 (Brain Products GmbH, Munich, Germany). Prior to analyses, data were down-sampled to 125Hz. A notch filter of 50Hz and a low-pass filter of 25Hz were applied. Data were epoched into single trials -3600ms to 1500ms around the onset of the laser stimulus and then baseline corrected to the first 500ms of the epoch. Linear trends were removed using DC detrend and then ocular artifacts were removed using Independent Components Analysis (ICA). Remaining artifactual components were manually removed. Epochs for each condition were subject to a second DC detrend to remove remaining linear trends and then two baseline corrections. The first, for Stimulus Preceding Negativity (SPN) was performed at -3600ms to -3100ms, the second, for Laser Evoked Potentials (LEPs) was performed at -500ms to 0ms. Epochs for both SPN and LEP data were then averaged before being referenced to the common average.

SPN was examined during the 500ms leading up to the pain stimulus. Average data for this time period was extracted. The electrode at which negative activity was maximal (Cz) was identified and data were averaged across the 9 electrodes around this (CP1, CPz, CP2, C1, Cz, C2, FC1, FCz, FC2). As participants did not know at what level the laser would fire on each trial, data were collapsed across laser intensity and SPN for the two associate conditions (low vs high) was compared.

By examining averaged epochs for painful conditions (i.e. intensity level 7) and corresponding topographical maps, 20 participants were identified as having P2 peaks and 15 participants as having N2 peaks. Latencies were identified for the electrode at which activity was maximal for P2 (Cz) and N2 (FCz) peaks and data were then extracted +/- 2 data points (i.e. 16ms) either side of this point. Finally, data were averaged across the 9 electrodes around the peak maximum. For P2, included
electrodes were CP1, CPz, CP2, C1, Cz, C2, FC1, FCz, FC2 and for N2, they were C1, Cz, C2, FC1, FCz, FC2, F1, Fz, F2.

2.5. Data analyses

Proportions of ‘no’, ‘yes R’, ‘yes K’ and ‘yes G’ responses for each type of recognition item were calculated and paired-samples t-tests were used to identify any differences in response types given for associates, related lures and unrelated lures. Signal Detection Theory (SDT) measures of d’ (sensitivity) and c (criterion) were calculated. Calculations were corrected using the Snodgrass and Corwin [54] correction whereby 0.5 was added to the number of hits and false alarms and the corrected score was divided by N+1. This was used in order to prevent values of 1.0 and 0. For sensitivity, 0 indicates performance at chance and larger values indicate better memory performance; for criterion, values above 0 represent a conservative response bias (a tendency to say ‘no’) and values below 0 represent a liberal response bias (a tendency to say ‘yes’).

To test the hypothesis that high associates would create greater anticipatory activity across the 500ms before the laser fired, a paired-samples t-test compared SPN between low and high associate conditions. To test the hypothesis that the priming effect would be greater for high associates, separate 2 x 3 repeated measures ANOVAs with associate and laser intensity as factors were conducted for averaged subjective pain ratings, P2 and N2 data. Separate 2 x 3 repeated measures ANCOVAs with mean-centred questionnaire responses for PHQ-9, PHQ-15, GAD-7, SHAI, FPQ-SF, PANAS positive scale and PANAS negative scale were then conducted to see if effects remained after controlling for mood, anxiety and symptom reporting. Simple main effects were assessed using a series of one-way ANOVAs/ANCOVAs and paired-samples t-tests. The alpha level was adjusted so that the family-wise error rate did not exceed .05. Where the assumption of sphericity was not met, a Greenhouse-Geisser correction was used.
3. Results

3.1. Behavioural data

3.1.1. Manipulation checks

Signal detection Theory (SDT) measures indicated that participants had a conservative response bias ($c = .50$), that is, they were more likely to say ‘no’ than ‘yes’ across all recognition items. Overall, participants were good at discriminating targets and lures ($d' = .93$).

3.1.1.1 Was the processing of associates subliminal?

Overall proportions of hits and false alarms for items on the recognition test are presented in Table 1. ‘Yes’ responses to targets conformed to a bi-modal distribution, such that most participants either had very low or very high hit rates. None of the 41% of participants with low (i.e. < 25%) hit rates provided any R (i.e. conscious memory) responses, indicating that presentation was entirely subliminal for these individuals. In contrast, all of the 41% of participants with high (i.e. < 75%) hit rates gave ‘R’ responses to more than half of their ‘yes’ responses, indicating that perception was likely to have been supraliminal for at least some of their associates. These data suggest individual variation in the extent to which the processing of associates was subliminal.

3.1.1.2. Did pain associates activate memory networks for pain?

The false alarm rate (i.e. ‘yes’ responses) for related lures was significantly higher than the false alarm rate for unrelated lures ($t (26) = 3.08, d = .79$) and the false alarm rate for the critical lure pain was significantly higher than the false alarm rate for unrelated lures ($t (26) = 2.01, d = .55$). Significantly more R, K and G responses were given for related lures than for unrelated lures ($t (26) = 2.28, d = .46$; $t (26) = 2.48, d = .58$; $t (26) = 2.18, d = .54$ respectively). These data are suggestive of activation of pain concepts in memory.
Table 1.

Total proportion of hits for targets (low and high associates presented on experimental trials) and false alarms for related lures (words semantically related to pain but not presented), the word ‘pain’ and unrelated lures (words semantically unrelated to pain and not presented).

<table>
<thead>
<tr>
<th>Response type</th>
<th>Targets</th>
<th>Lures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low associate</td>
<td>High associate</td>
</tr>
<tr>
<td>Yes (total)</td>
<td>.49</td>
<td>.52</td>
</tr>
<tr>
<td>R</td>
<td>.25</td>
<td>.28</td>
</tr>
<tr>
<td>K</td>
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</tbody>
</table>

3.1.1.3. Were low and high associates processed differently?

There was a higher proportion of hits overall for high associate targets as well as a higher proportion of ‘R’ responses, although these differences were not significant ($p = .33; p = .16$ respectively). Furthermore, there were no differences in either response bias or sensitivity between recognition responses to low and high targets ($p = .30$ for both differences). Any differences in pain perception after viewing low versus high associates are therefore not due to differences in the way that they were processed during experimental trials.

3.1.2. The effect of priming on pain ratings

Pain ratings (Mean, SD) for low associates in low, moderate and high intensity conditions respectively were: 1.77 (.73), 3.03 (.79) and 4.83 (.84), and for high associates they were: 1.92 (.83), 3.52 (.74) and 5.20 (.91). ANOVA revealed main effects of intensity ($F (1.52, 39.41) = 232.74, \eta^2_p = .90$, low < moderate < high) and associate ($F (1, 26) = 22.63, \eta^2_p = .47$, low < high). These were qualified by an
intensity x associate interaction \((F(1.56, 40.57) = 3.53, \eta^2_p = .12)\), see Fig. 2. The source of the interaction was a significant effect of associate for moderate \((t(26) = -4.43, d = .64)\) and high \((t(26) = -3.60, d = .42)\) intensity levels but not for the low intensity level \((t(26) = -1.63, d = .19)\). This interaction remained when each of the covariates was added separately to the model (PHQ-9: \(F(2, 50) = 4.67, \eta^2_p = .16\); PHQ-15: \(F(1.57, 39.17) = 3.43, \eta^2_p = .12\); GAD-7: \(F(1.58, 39.57) = 3.61, \eta^2_p = .13\); FPQ-SF: \(F(1.58, 38.86) = 3.55, \eta^2_p = .12\); SHAI: \(F(1.53, 38.34) = 3.46, \eta^2_p = .12\); PANAS positive: \(F(1.53, 38.33) = 3.59, \eta^2_p = .13\); PANAS negative: \(F(2, 50) = 3.93, \eta^2_p = .14\)). 95% confidence intervals for parameter estimates crossed 0 for each of the covariates in each condition, except for the PHQ-9 in the high associate, moderate intensity

![Graph](image-url)

**Fig. 2.** Mean pain ratings in low, moderate and high laser intensity conditions after subliminal presentation of low and high pain associates at -3033ms. 95% confidence intervals are displayed for each condition.
condition ($B = .84$, $95\% \text{ CI} = .009 - .158$, $\eta_p^2 = .18$), indicating that pain ratings significantly increased by .84 for every unit of PHQ-9 score.

Contrary to prediction, the priming effect in the moderate and high intensity conditions was not correlated with symptom reporting on the PHQ-15 (moderate intensity: $r = .08$, $p = .68$; high intensity: $r = .08$, $p = .69$). When PHQ-15 scores were restricted to those items specifically asking about pain symptoms, the correlations were higher but remained non-significant (moderate: $r = .12$, $p = .54$; high: $r = .18$, $p = .37$).

Because there is evidence that processing of associates was not subliminal for everyone, we repeated the above analyses and included processing as a between factor, with two levels: subliminal (i.e. number of hits to targets in the lower quartile range; $N = 11$) and supraliminal (i.e. number of hits to targets in the upper quartile range; $N = 11$). The pattern of results were similar to those of the whole group, with effects of associate ($F(1, 20) = 33.11$, $\eta_p^2 = .62$), intensity ($F(1.55, 30.89) = 210.22$, $\eta_p^2 = .91$) and an intensity x associate interaction ($F(1.46, 29.17) = 4.19$, $\eta_p^2 = .17$). The effect of processing was not significant ($p = .46$). For both groups, t-tests showed significant differences between low and high associates in the moderate (subliminal: $t(10) = 4.58$, $d = 1.13$; supraliminal: $t(10) = 2.46$, $d = .59$) and high (subliminal: $t(10) = 3.54$, $d = .71$; supraliminal: $t(10) = 2.66$, $d = .47$) intensity conditions only. The pattern of results was the same or approaching significance when each covariate was added to the model.

### 3.2. EEG data

#### 3.2.1. Stimulus preceding negativity (SPN)

There was an effect of associate ($t(22) = 2.13$, $d = .17$) such that SPN was more positive in the low associate condition ($M = 1.24$, $SD = 2.01$) than it was in the high associate condition ($M = 0.88$, $SD = 2.14$). This effect remained significant when the PHQ-9 ($\eta_p^2 = .18$), GAD-7 ($\eta_p^2 = .17$), FPQ-SF ($\eta_p^2 = .17$), HAI ($\eta_p^2 = .17$) and PANAS positive ($\eta_p^2 = .18$) were added separately to a one-way ANCOVA. The effect was close
to significance when the PHQ-15 \((p = .055, \eta^2_p = .16)\) and PANAS negative \((p = .057, \eta^2_p = .16)\) were added.

The difference in SPN between high and low associate conditions was not correlated with the same difference for post-stimulus activity, either in P2 \((r = -.13, p = .59)\) or in N2 \((r = .34, p = .21)\).

### 3.2.2. N2 component of the LEP

ANOVA revealed a main effect of associate \((F (1, 14) = 4.93, \eta^2_p = .26)\) such that averaged N2 amplitude for the LEP was higher in the high \((M = -3.02, SD = 1.31)\) than the low associate condition \((M = -2.47, SD = 1.07)\). There was also a main effect of intensity \((F (1.35, 18.85) = 23.51, \eta^2_p = .63)\). N2 amplitude was significantly higher in the high intensity condition \((M = 7.74, SD = 3.11)\) than it was in the moderate \((M = 4.85, SD = 2.98)\) and low intensity \((M = 2.08, SD = 1.94)\) conditions and higher in the moderate intensity condition than the low intensity condition. Although there was no associate x intensity interaction, there was a significant difference in average N2 amplitude between low and high associate conditions when the laser fired at moderate intensity \((t (14) = 2.85, d = .61)\), but not when it fired at low \((p = .32)\) and high \((p = .49)\) intensities (see Fig. 3). The N2 component of the LEP for low and high associate conditions is displayed in Figure 4., along with corresponding topographic maps.

The effect of associate remained when the SHAI, FPQ-SF and PANAS positive were added separately to the model and it approached 0.05 significance when the PHQ-9 \((p = .07)\), PHQ-15 \((p = .09)\) and GAD-7 \((p = .06)\) were added. The effect of associate was not significant when the PANAS negative was added to the model \((p = .19)\). The effect of intensity remained when each covariate was added to the model.

### 3.2.3. P2 component of the LEP

There was a main effect of intensity for the P2 LEP \((F (2, 38) = 60.85, \eta^2_p = .73)\).
Fig. 3. N2 amplitude averaged across electrodes C1, Cz, C2, FC1, FCz, FC2, F1, Fz, F2. Average amplitude is defined as the mean area ± 16ms either side of the latency at which N2 amplitude was maximal. Data are presented for low, moderate and high laser intensity conditions after subliminal presentation of low and high pain associates at -3033ms. 95% confidence intervals are displayed for each condition.

$\eta_p^2 = .76)$. Averaged P2 amplitude was significant higher in the high intensity condition ($M = 7.74, SD = 3.11$) than in the moderate ($M = 4.85, SD = 2.98$) and low intensity ($M = 2.08, SD = 1.94$) conditions and higher in the moderate intensity condition than the low intensity condition. There was no main effect of associate or associate x intensity interaction. Averaged P2 amplitudes for low, moderate and high laser intensities in low and high associate conditions are shown in Figure 5. The P2
Fig. 4. Average waveforms and topographic maps for the N2 component of the LEP in low and high associate conditions. The temporal range displayed is -500ms to 1000ms. SPN was averaged over -500ms to 0ms (highlighted by the shaded area) and the N2 LEP peak was identified at 288ms. An earlier N1 peak is also evident. However, this was not analyzed as it was not present in all participants with N2 peaks.

The component of the LEP for low and high associate conditions is displayed in Figure 6 along with corresponding topographic maps.

The effect of intensity remained when each covariate was added to the model.
**Fig. 5.** P2 amplitude averaged across electrodes CP1, CPz, CP2, C1, Cz, C2, FC1, FCz and FC2. Average amplitude is defined as the mean area ± 16ms either side of the latency at which P2 amplitude was maximal. Data are presented for low, moderate and high laser intensity conditions after subliminal presentation of low and high pain associates at -3033ms. 95% confidence intervals are displayed for each condition.
Fig. 6. Average waveforms and topographic maps for the P2 component of the LEP in low and high associate conditions. The temporal range displayed is -500ms to 1000ms. SPN was averaged over -500ms to 0ms (highlighted by the shaded area) and the P2 LEP peak was identified at 424ms.
4. Discussion

Three key findings emerged from this study. First, we found higher subjective pain ratings after priming with high associates of pain relative to priming with low associates, but only when stimuli were ambiguous or painful (i.e. levels 5 and 7). Second, there was greater SPN around central electrodes, indicative of anticipatory activity, after priming with high associates than after priming with low associates. Third, for the N2 component of the LEP, there was greater averaged amplitude in the high associate condition than in the low associate condition, but only when the stimulus was ambiguous (i.e. level 5). All these effects either remained significant or were approaching significance ($p < .06$) when measures of mood, anxiety and symptom reporting were controlled for. However, the effect of associate for N2 was not significant when state negative mood was controlled for.

4.1. Psychological responses to priming

The predicted finding that increasing semantic activation of pain concepts in memory also increases subjective ratings of pain supports theories of memory and pain such as Brown's model of unexplained symptoms [9]. This describes pain, particularly in the absence of peripheral pain pathology, as the result of unconscious chronic activation of pain concepts in memory. Consistent with this model, the effect of priming remained when various measures of mood, anxiety and symptom reporting were controlled for, suggesting that the effect is not specific to particular psychological conditions such as anxiety. We found the effect regardless of whether participants had processed the associates subliminally or supraliminally. Many participants were unaware of the majority of associates in the study, yet still gave higher pain ratings after the presentation of a high associate than after a low associate. This supports the model's assertion that activation of pain concepts can occur without conscious awareness of exposure to pain-related information in everyday life. It also suggests that conscious awareness of that information does not eliminate its effect.
The Brown model implies that high symptom reporting, particularly reporting of pain symptoms, could be linked to a lower threshold of activation for pain concepts in memory, and therefore increased susceptibility to the priming effect. Contrary to expectation however, there was no correlation between the priming effect and symptom reporting measured by the PHQ-15. The low PHQ-15 score of our sample (mean = 4.22, sd = 3.11; [31]) suggests that this might be attributable to restricted variance in symptom reporting. Replicating the study with a larger sample with more varied PHQ-15 scores may provide a better test of this hypothesis.

Pain ratings increased with low mood measured by the PHQ-9 in the high associate, moderate pain condition and this is consistent with previous findings. Not only can activation levels for mood-relevant materials be higher in those who are clinically depressed [22,24,43], depression also makes it more difficult to monitor the source of semantic activation [21,42,63]. In the face of highly relevant material, and when pain stimulus is ambiguous, pain may therefore be more likely to be falsely attributed to an external stimulus (i.e. laser) than an internal one (i.e. rogue semantic activation of pain and related concepts in memory).

4.2. Physiological responses to priming

High associates created greater SPN than low associates and this is consistent with other studies showing that warnings reflecting a high intensity pain stimulus create higher levels of anticipatory activity in the brain than those reflecting a low intensity stimulus [5,8,26]. However, our study showed an effect on SPN for subliminally presented, pain-related words, rather than words warning of the upcoming pain stimulus intensity that were consciously perceived, and this is a novel finding.

Anticipation of pain is thought to increase neurological activity in the ‘pain matrix’ [8,26,29,50,60]. The pain matrix [40] includes lateral areas such as primary and secondary somatosensory cortices and medial areas such as anterior insular and anterior cingulate cortices (ACC). This activity is then thought to influence neurophysiological responses to pain stimuli as well as behavioural pain ratings [6,7].
In the current study, the difference between low and high words in the N2 component of the LEP is consistent with this. The correlation between SPN and the N2 LEP was .34, a moderate relationship, but not statistically significant \((p = .21)\), possibly due to the small number of participants in the N2 group \((N = 15)\).

It is unclear why we did not also find an effect of associate for the P2 component of the LEP. After pain stimuli, early electrical activity in somatosensory areas, reflected in early LEP components such as N1 and N2, are followed by activation of areas such as the ACC, usually reflected in the P2 component but also in late N2 components too [17,34]. ACC activity is thought to represent psychological processes such as emotional and cognitive responses to pain, and might therefore be expected to be modulated by the activation of pain-related concepts in memory. Given the nature of the pain associates used in the current study, there is no theoretical basis for the discrepancy between data for N2 and P2, and it may therefore be an artefact of experimental conditions.

The effect of associate for the N2 component remained significant or was approaching statistical significance when measures of mood, anxiety and symptom reporting were controlled for. However, it was not significant \((p = .19)\) when state negative mood was controlled for. How can we reconcile different effects of state mood (measured by the PANAS) and longer term mood (measured by the PHQ-9) on N2 peaks? A possible explanation lies in studies from false memory research showing that state negative mood creates lower levels of semantic activation for mood-related material in memory [28] and that longer standing low mood (for example measured by the PHQ-9) is associated with higher levels of semantic activation for mood-related material [24]. Thus, state negative mood may have mediated priming at the physiological level, for example by dampening activity in the pain matrix.

4.3. Clinical implications and future directions

In the time-limited confines of this study we obtained an effect of priming on pain ratings. By extension, one may surmise that chronic pain conditions are also influenced by this, given potentially limitless sources of activation in the
environment. The results of this study support commonly used therapies for chronic pain such as Cognitive Behavioural Therapy and mindfulness (i.e. paying attention to the present moment, on purpose and without judgement [25]). Both these approaches advocate an awareness of thinking styles and reduction in unhelpful strategies such as rumination. Rumination about pain is likely to increase activation of pain concepts in memory which, according to the results of this study, will increase physiological and psychological responses to pain.

Future studies should extend findings from the current study to chronic pain patients. Brown’s model [9] predicts that pain patients will have a lower threshold of activation for pain concepts in memory, resulting in a greater priming effect. In the current study, we varied activation levels of pain concepts in memory by manipulating the degree of backward association to pain. However, other techniques may be equally effective in differentiating low and high activation of pain concepts in memory, for example, manipulating the level at which associates are processed. Deep processing (e.g. embedding words within a story) should create higher levels of activation than shallow processing (e.g. list learning under divided attention conditions).

4.4. Methodological issues

Data from the memory recognition test indicate that priming of associates was not subliminal for everyone. Associates were presented at 33ms each i.e. two refresh rates of the computer monitor. This presentation speed has been used in other subliminal priming studies [e.g. 10,20,27,39] and similar presentation speeds have been used to activate concepts in memory [e.g. 12,51]. It is likely that even if participants in the current study did perceive associates, they were unlikely to have done so on every trial. Each associate was repeated six times in total and this would have increased the overall probability of hits to targets. Individual differences in the speed with which materials are processed is not uncommon in subliminal priming research [e.g. 53,67]. In the current study we decided not to remove data from
participants who may have perceived associates supraliminally because they are unlikely to have differentially processed low and high associates.

Despite individually calibrated laser voltages, ratings were not as high as anticipated during experimental trials. Overall, mean pain ratings were 1.85, 3.28 and 5.01 for levels 3, 5 and 7 respectively. The majority of participants began with pain ratings that were consistent with those elicited during the psychophysics procedure but many quickly habituated to the pain stimulus. Although it may have been useful to have a re-calibration phase after block 2, this would have increased the risk of skin damage and was therefore avoided.

5. Conclusion

To our knowledge, this is the first study specifically investigating how differing levels of semantic activation for pain concepts in memory affect pain responding. We found that relative to low levels, high levels of activation of pain concepts in memory led to significantly higher subjective ratings of pain as well as increased electrical activity in the brain that was consistent with both anticipation of, and responding to, pain. The results support activation-based accounts of the inter-play between memory and pain processing.
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APPENDIX A

Low and high associates of pain selected from the Florida word norms for inclusion in the study.

<table>
<thead>
<tr>
<th>Low associates</th>
<th>High associates</th>
</tr>
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<tbody>
<tr>
<td>Surgery (.05)</td>
<td>Agony (.64)</td>
</tr>
<tr>
<td>Abuse (.02)</td>
<td>Hurt (.52)</td>
</tr>
<tr>
<td>Infection (.02)</td>
<td>Ache (.50)</td>
</tr>
<tr>
<td>Accident (.02)</td>
<td>Discomfort (.42)</td>
</tr>
<tr>
<td>Prick (.02)</td>
<td>Torture (.38)</td>
</tr>
<tr>
<td>Rash (.01)</td>
<td>Headache (.36)</td>
</tr>
<tr>
<td>Limp (.01)</td>
<td>Ulcer (.31)</td>
</tr>
<tr>
<td>Hungry (.01)</td>
<td>Injury (.25)</td>
</tr>
</tbody>
</table>

Cue (associate) to target (pain) probabilities are in parentheses
References


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PAPER 3

Critical reflection and evaluation

Word count: 5994
1. Introduction

The systematic review (Paper 1) is a comprehensive overview of studies looking at the effect of memory on pain. Selected studies were evaluated with respect to methodological quality and a narrative synthesis was used to make sense of the studies in light of their aims, findings and theoretical underpinnings. The review identified two types of study: priming and expectancy. Across both study types, effects of memory were demonstrated. Data from priming studies indicated that priming with negative and/or health-related materials increased pain ratings relative to priming with pleasant or neutral materials but this effect was more consistent for pictures than for words. Data from expectancy studies showed that high expectancy cues increased pain ratings relative to low expectancy cues. These effects were also present in physiological measures of pain perception, using EEG and fMRI. Quality was found to be variable, particularly for priming studies. Furthermore, many studies did not link their methodologies and hypotheses with theories of memory and pain, thus limiting the conclusions that could be drawn.

Following on from conclusions of Paper 1, the study described in Paper 2 was designed with a cognitive model of medically unexplained symptoms in mind and tight methodological controls were implemented. Paper 2 investigated the effect of varying levels of activation of pain concepts in memory on ensuing pain perception. Subjective pain ratings as well as physiological responses to pain, measured using EEG, were greater after subliminal presentation of high semantic associates of the word pain than after subliminal presentation of low semantic associates. Data from this study make a novel contribution to the research literature on memory and pain.

A number of issues pertaining to both papers warrant further discussion here. Paper 3 will focus on reflections around the systematic review process, as it was applied in this thesis, as well as methodological and theoretical concerns of the empirical paper. Finally, clinical implications of research on the effect of memory on pain in this thesis are discussed. Limitations of the work described, as well as ideas for future research, are discussed throughout.
2. The systematic literature review (Paper 1)

The literature search

Given the number of studies referring to memory and pain, the identification of relevant papers was challenging. There was no way of discriminating, at the keyword level, between studies looking at the effect of pain on memory and those looking at the effect of memory on pain. The former were not relevant to the purpose of the systematic review and yet they are numerous within the literature. Another challenge was the multidisciplinary nature of studies in the area of interest, incorporating psychology, medicine and various physiological disciplines. Studies were heterogeneous in the keyword terms they used to describe memorial processes and this made it difficult to ensure that the search was specific enough to be meaningful, yet sensitive enough to capture all studies of interest. Keywords were chosen by reading a selection of papers that were highly relevant to the topic. Initially, the search employed four search terms (‘pain, memory, schema, priming’) but later, this was expanded to include ‘expectation’ after it became clear that some relevant articles had not been captured. Due to the size of the selection (almost 8000 articles), duplicates could not be removed and it was only possible to skim article titles as a basis for further inspection. It is therefore possible that some relevant articles were incorrectly excluded at this stage.

Selection of the evaluative tool

The assessment of quality and susceptibility to bias is a central part of any systematic review (Sanderson, Tatt & Higgins, 2007). A number of quality assessment tools were considered, including the Scottish Collegiate Guidance Network (SIGN; 2007) the Effective Public Health Practice Project (EPHPP; 2009), Grading of Recommendations Assessment, Development and Evaluation (GRADE; 2011) and the Critical Appraisal Skills Programme (CASP; 2013). Many of these tools have been devised for use with clinical populations or particular types of study such as Randomised Controlled Trials (RCTs). Given heterogeneity in the methods employed
by studies looking at memory and pain, none of them were deemed appropriate. Authors of other systematic reviews have encountered similar difficulties and they have resorted to devising their own tool (e.g. Kelly et al., 2011). The CASP includes various rating tools that map on to the types of study under review, including RCTs and non RCTs. Therefore, a new assessment tool, taking relevant items from various CASP checklists was devised (see Appendix IV). This bespoke checklist included questions about recruitment (e.g. ethical issues, bias), methodological design (e.g. control of independent and dependent variables), statistical methodologies (e.g. risk of error, effect sizes) and how the findings sit with similar research and relevant theory. CASP rates items on 3 levels: ‘no, can’t tell, yes’. Items on the new checklist were evaluated in the same way but they were also given corresponding numbers 0 (no), 0.5 (can’t tell), 1 (yes). GRADE advocates the use of numbers to rate quality (see Bals hem et al., 2011) so that studies can be compared quickly. They were used in Paper 1 for this reason. Whilst it is important to note that these numbers are not an objective measure of quality, they did make it easy to compare studies, both within the groups in which they were placed (i.e. priming, expectancy) and across groups.

The systematic review process

The systematic review process was new to the Trainee and there were pros and cons to this approach. The process was informed by principles from Centre for Reviews and Dissemination (CRD; 2009). Briefly, this advises on the types of research questions that are best answered via systematic review, identifying relevant literature, key areas to cover in a review, advice for critically appraising review articles and constructing a narrative synthesis. Although the guidelines are targeted at reviews of clinical and/or public health questions, the principles can be applied to any type of systematic review and proved very useful when planning and writing Paper 1.

The formulaic and well-defined steps of systematic review meant that the process was transparent and replicable. This compares favourably with the traditional style of review where multiple searches are conducted over a wide time-
frame and articles are sourced using non-replicable means, such as conference attendance and peer discussions. However, the process was also a source of frustration. Initially, four groups of study type were identified for the narrative synthesis. These were priming, warning, conditioning and episodic. However, after lengthy discussion about the best way to make sense of research on memory and pain, as well as the appropriateness of some of the studies, this was reduced to two larger groups (priming and expectancy). Episodic studies (Danneker, Price & Robinson, 2003; Gedney & Logan, 2006; Noel et al., 2012; Versloot, Veerkamp & Hoogstraten, 2008) administered pain at two intervals and investigated how memory for pain at Time 1 was associated with pain perception at Time 2. Overall, they found that remembered pain from Time 1 was more closely associated with pain perception at Time 2 than various other factors, including pain intensity at Time 2. Although these studies are interesting and they add weight to arguments made in this thesis (i.e. that memory for pain-related material is associated with subsequent pain perception), they did not directly manipulate memory. The audience of the target journal for the review (Pain) are likely to place particular value on tightly controlled experimental studies and, in light of this, it was decided that episodic memory studies should be excluded. The conditioning group only comprised two studies. In some ways these were different to the expectancy studies in that a stimulus-response relationship had been established prior to experimental trials. In warning studies, this was not necessary because information given on each trial (e.g. ‘high’) would have been clearly understood without any prior training. However, since both types of study gave participants information about upcoming pain intensity levels and all reported similar findings (i.e. that meaningful information affects pain ratings), it was decided that they were better placed in a superordinate group of expectancy studies. Incorporating larger groups in the narrative synthesis allowed for more detailed discussion of themes across the studies, particularly in relation to physiological data and theories used to account for findings.

As discussed in the literature review, it is likely that a publication bias exists, particularly for priming studies. Publication bias is the tendency to submit or accept manuscripts for publication based on the direction or strength of empirical findings (Dickersin, 1990). Bias potentially compromises the replicability of findings reported
in the review because studies are unlikely to be representative of all work in the area. This is a well-known problem, perpetuated by publishers choosing work that reports statistically significant data (usually $p < .05$) but also by researchers, since many studies reporting null data are never even prepared for dissemination (Song et al., 2009). To address this, a search including ‘grey literature’ (Auger, 1989), such as conference abstracts and unpublished theses might have been included in Paper 1. However, given that grey literature can be difficult to source and the size of the initial search was particularly large, this was decided against. More generally, Song et al. (2000) recommend that peer-reviewed electronic journals with no space limitations are required in order to reduce the risk of publication bias. They argue that editorial policy should be changed to encourage article selection based on methodological quality only and not outcome data or the impact of their findings. Furthermore, they recommend the prospective registration of all studies, particularly those that are likely to show data that is clinically relevant as publication bias for these studies can be particularly damaging to resources and patient care.

3. The empirical paper (Paper 2)

Ethical issues

There were clearly ethical issues around administering pain to others, albeit healthy volunteers who had been fully informed of what would happen to them. The study was assessed and passed by the University Research Ethics Committee and the NHS Foundation Trust where it was taking place (see Appendices V & VI). It was anticipated that there might be issues with gaining ethical clearance for the study. However, given that colleagues had conducted many similar studies and had assisted in providing full explanations of all stages of the experiment, the committee granted approval with only minor amendments.

It was important to help participants feel relaxed during the experiment as it is known that anxiety can exacerbate pain perception (Tang & Gibson, 2005). In order to achieve this, testing did not commence until the Trainee was completely confident
in administering all elements of the study, including questionnaires (see Appendix XI), EEG equipment and laser equipment. Protocols were also in place in the eventuality that a participant became distressed, either when completing the questionnaires (see Appendix XII) or during the experimental trials (see Appendix XIII). Fortunately these were not required at any point during data collection. An experienced pain lab technician was also present at all times during the experiment. In line with University regulations on the use of lasers in research settings, the Trainee attended a course on laser safety training and passed an accompanying examination (see Appendix VII).

Methodological issues

Given the mixed findings of previous priming and pain studies, attention to methodological design and control was critical to finding any publishable effects. Although close attention was paid to ensuring the design of the study was as tight as possible, potential weaknesses are discussed here.

Varying activation levels of pain concepts in memory

The choice of words used to differentially activate pain concepts in memory was crucial to the success of the study. However, this has never been attempted before according to the literature on memory and pain. The Trainee looked to her previous doctoral work on false memories using the Deese-Roediger-McDermott (DRM) paradigm (Roediger & McDermott, 1995) to devise an effective and measureable technique for activating pain concepts in memory. In the DRM paradigm, participants are typically presented at study with a list of 12 semantic associates of a critical lure (CL) that is not itself presented, for example, for the CL sleep, presented associates might include bed, rest, awake, tired, dream etc. At test, the CL is normally present on around 40% of recall protocols and false alarms for the CL and related words are made on around 70% of recognition tests (Roediger & McDermott, 1995). Using an Activation-Monitoring (AM) account, researchers have argued that the CL is falsely remembered because semantic activation in memory spreads from presented associates to related words that are not themselves presented. When levels of
activation reach a critical point and individuals also commit a source monitoring error (i.e. attribute a word as being externally generated during list learning, as opposed to internally generated via semantic activation), false remembering is likely to occur (see McDermott & Watson, 2001; Roediger, Balota & Watson, 2001; Roediger et al., 2001). The DRM paradigm consistently produces a false memory of the CL because word lists are constructed so that activation summates on it. Moreover, it is difficult to monitor the source of memories in the DRM paradigm because of the uniform (i.e. list learning) presentation of words. Backward associative strength (BAS; the probability that an associate elicits the CL on free association tasks) is understood to be a measure of false remembering and therefore an indirect measure of activation of the CL (Howe, Wimmer & Blease, 2009; Knott, Dewhurst & Howe, 2012). Assuming an AM account of memory, in the current study it was proposed that increasing BAS should allow more activation to spread from presented pain associates to the CL (i.e. pain) and related non-presented words and concepts. Activation was assumed to remain relatively unchecked by source monitoring because participants were not asked to remember presented associates during experimental trials and associates were presented subliminally.

The Florida word association norms (Nelson, McEvoy & Schreiber, 1998) are the largest database of free association norms in the USA. Over six thousand individuals participated in a free association task in which they were asked to write down the first word that came to mind when presented with a cue word. For example, if presented with agony, they might write pain. Importantly, this is a measure of BAS and therefore an indication of activation levels for pain and related concepts in memory. The Florida norms were used in the current study because they included pain as a target word and they have also been used widely in studies that have sought to activate particular target words in memory, both in the USA (e.g. Brainerd & Wright, 2005; Hicks & Starns, 2006; Roediger et al., 2001) and in the UK (e.g. Howe, Wimmer & Blease, 2009; Knott, Dewhurst & Howe, 2012). However, the use of this database can also be criticised, for example, associates were not normed on a UK population. Gathering participant ratings of the strength of association between associates and pain was considered. However, asking participants to rate words before the experimental trials would have activated pain concepts in memory,
negating the priming manipulation and asking them to do it at the end of the study would have invalidated the ratings as pain concepts would have already been activated by the priming task. Word association norms are available in the UK, for example, the Edinburgh Associative Thesaurus (EAT; Kiss et al., 1973). However, they do not give as much information about the target word pain as the Florida norms. A quick comparison between associates selected for the current study and those provided by the EAT showed that they are comparable: 6 of the 8 high associates chosen appeared in the top 10 associates given by the EAT and all of the low associates appeared in the bottom half.

Unconscious activation of pain concepts

In the current study, associates of pain were presented for 33ms, followed by a backward mask for 1s. As discussed in Paper 2, this presentation duration has been used in previous subliminal priming studies (e.g. Carlson & Reinke, 2010; Hattori, Sloman & Orita, 2013; Kiefer, 2002; Meerman, Verkuil & Brosschot, 2011). Research using the DRM paradigm has also demonstrated that false remembering can occur when associates are presented as quickly as 20ms (Seamon, Luo & Gallo, 1998), suggesting that activation of concepts in memory can occur unconsciously. In the current study, the speed with which associates were perceived differed between participants; some participants saw all/most of the associates and some saw none. This meant that additional analyses had to be completed in order to confirm that the priming effect was indeed present for participants who had perceived associates subliminally. Future studies might present associates for less time, perhaps 20ms as in the Seamon et al. (1998) study in order to ensure presentation is subliminal for more participants. In the current study, due to technical constraints it was only possible to present associates for multiples of monitor refresh rates (i.e. 16.5ms, 33ms etc) and one refresh rate was deemed too fast based on previous literature (see Draine & Greenwald, 1998 for discussion).

EEG in the research setting

Electroencephalography or EEG is the recording of electrical activity across the scalp. Briefly, neurons generate two types of electrical activity, action potentials
and postsynaptic potentials. Action potentials, reflecting voltages running the length of axons, can only be measured using invasive techniques because they are very fast and the organisation of neurons means they fire at slightly different intervals, cancelling electrical activity out at the surface of the scalp. Postsynaptic potentials reflect voltages that are created when neurotransmitters bind to receptors on postsynaptic cells, usually cortical pyramidal cells as these are normally aligned and fire together, creating summation of electrical activity. Importantly, this activity can be measured by EEG on the surface of the scalp (see Luck, 2005). In research settings, postsynaptic potentials are measured in relation to an event of interest. These Event Related Potentials (ERPs) are time-locked sequences that are averaged over multiple trials. In the current study, the ERPs were referred to as Laser Evoked Potentials (LEPs) because the firing of the laser was the primary event of interest.

EEG has been used extensively in research settings. It compares favourably with other physiological measures as it is non-invasive, has excellent temporal resolution and it is relatively inexpensive (Luck, 2005). Its temporal resolution means it is matched well with laser stimuli and both techniques allow precise methodological control. However, given that ERPs are small and normally contaminated by other electrical activity, it is necessary to incorporate enough trials in order to find meaningful patterns from averaged data. This creates a trade-off for LEP studies between collecting enough data for analyses whilst adhering to ethical principles regarding the amount of pain participants are reasonably expected to endure.

There were several issues with the use of EEG in the current study. For example, the Trainee was unfamiliar with EEG at the start of the project and had to learn about the theory of EEG as it was relevant to the current study, learn how to fit the EEG cap confidently during the experiment and gain good rates of impedance in order to obtain the best quality recordings possible. Once data had been collected a lengthy period of EEG pre-processing ensued, taking approximately 3 hours per participant to extract averaged amplitudes for SPN, N2 and P2 from raw EEG data files (see Appendix XIV for pre-processing steps). Some stages of pre-processing such as applying a notch filter to remove the influence of electrical noise in the building
were objectively defined and relatively straightforward. However, many steps were subjective and at times this created anxiety, particularly given that this was a new area of learning. An example was deciding which components to remove during the Independent Components Analysis (ICA). ICA is applied during pre-processing to remove physiological artefacts, particularly ocular ones, from the data set. Removal of ocular components is a significant challenge, even for experienced EEG researchers because of similarities between ocular and cerebral activity (see Jung et al., 2000). In the current study, a trial and error approach was taken whereby grand averages for each condition were always calculated prior to ICA and inspected for the presence of LEPs. Comparisons were then made between pre and post ICA data sets and if it was clear that the ICA had been too aggressive, it was repeated. In addition, topographical maps were always consulted before removal of a component as the focus of electrical activity is different for LEPs (activity focussed around electrodes Cz and FCz) and ocular artefacts (activity focussed above one/both eyes) (e.g. see Iriate et al., 2003). Peer support was sought throughout from fellow doctoral students and post-doctoral researchers and this was very helpful.

In conclusion, EEG was a valuable and interesting addition to the study, not only in terms of its contribution to the quality of the data collected and the conclusions that could be made, but also in relation to the skill-set of the Trainee.

The Co2 laser

CO2 lasers activate Aδ and C nociceptors by stimulating free nerve endings in the superficial skin layers (Leandri et al., 2006). At pain threshold, the sensation is akin to a pinprick or spit of fat that fades very quickly, becoming stronger and with a longer aftermath with increasing laser energy.

There were several advantages of using the CO2 laser over other methods of pain stimulation such as the cold pressor task (CPT) or thermal stimulation. The CO2 laser allowed for precise control of stimulation, with respect to individual pain thresholds. It also allowed for a fast, multi-trial experiment that matched the temporal resolution of EEG. Laser stimulation is focussed and fast and the skin recovers quickly. Other methods such as the CPT are associated with strong
cardiovascular responses which in and of themselves can influence pain perception (Rau et al., 1994).

Although they were outweighed by the advantages, there were some disadvantages. Bespoke software had to be engineered by a programmer to subliminally present associates whilst also controlling the laser. The programme was designed to send one of 6 codes pertaining to each experimental condition via parallel port to the EEG recording software at the point the laser fired. The development of this software was time consuming and delayed commencement of the experiment significantly. Moreover, some individuals did not demonstrate LEPs, even though they experienced significant levels of pain meaning that the sample sizes for analyses of behavioural and LEP data are different and not directly comparable. This is not uncommon in LEP research (see Bromm & Lorenz, 1998 for a review).

Analyses

Analyses in the current study were generally straightforward. However, some issues warrant further discussion here.

At the planning stage, power calculations stipulated that with 40 participants, the study would have 80% power to detect effect sizes of at least .45 at the .05 alpha level. However, technical difficulties, slow participant recruitment due to the nature of the study and the length of time it took to test each participant, meant that the final sample only reached 27 participants. Reduced power may account for the lack of associate x intensity interaction in the P2 component of the LEP; it may also be responsible for the effects of interest in the study (e.g. the associate x intensity interaction in the behavioural data) being close to the alpha level used in the study.

There were also implications for the way in which ANCOVAs were conducted. Initially the seven covariates were to be entered into the model together. However, a medical statistician recommended they were entered separately because each covariate takes a degree of freedom and the interaction terms between factors and covariates cannot be removed in SPSS. This leaves a statistical model with all covariates underpowered to detect differences between groups. In order to enter
them together, the statistician advised that at least 70 participants, using a within-subjects design, would have been required. Given that it took approximately 5 hours to test each participant and pre-process their EEG files, this was not possible within the confines of this project.

Additional theoretical issues and implications

The past decade has seen an explosion in research and theory on pain; its physiological origins, its neurophysiological mechanisms and more recently, social and psychological components. Likewise, the topic of ‘memory’ within the larger field of cognition encompasses a wide range of theoretical stances and empirical findings. Bringing the two areas together and making links between relevant theories was a significant challenge.

Paper 2 was devised in order to test Brown’s model of medically unexplained symptoms (MUS; Brown, 2004, 2006). Brown argues that consciousness (i.e. thoughts, feelings, behaviours) is governed by incoming information from the environment as well as internally held information (i.e. memories; autobiographical, semantic, episodic). Incoming information activates internally held information and together they activate hypotheses about the meaning of the input. Hypotheses are then selected by a Primary Attentional System (PAS), depending on their relative strength of activation. Importantly, the selection of hypotheses by the PAS is automatic and it is not amenable to conscious control. In a normally working system, these processes aid cognition in that they allow for fast and efficient decision making. Once hypotheses are selected, they then act to drive behavioural responses at a conscious level.

Applied to unexplained pain, it follows from the model that some individuals will have a higher baseline level of activation for pain concepts in memory, probably due to their particular experiences such as illness and messages they have been exposed to in the media and families. Incoming information about physiological stimuli generates multiple hypotheses about the origin of sensation and what it means for general functioning. However, higher levels of activation about pain-
related hypotheses mean they are more likely to be selected by the PAS, and therefore reach consciousness, triggering behavioural responses such as avoiding actions perceived as causing pain or worrying. These behaviours serve to strengthen activation of pain concepts in memory, creating a vicious cycle.

A recommendation of Paper 1 was that future studies looking at the effect of memory on pain should seek to design studies in a top-down manner (i.e. using theory to inform methodological design) so that findings could be used to drive theory forward in an organised and meaningful way. Paper 2 was designed with this in mind and decisions about methodologies were informed by components of Brown’s model of MUS in the following way: The model states that the PAS acts unconsciously. Therefore, it was important that pain associates were presented subliminally in order to provide a test of this. As discussed in Paper 2, although analyses suggested that perception was not subliminal for everyone, additional analyses demonstrated that the effect was present or approaching significance for all of those for whom perception was likely to have been subliminal, as well as for those for whom processing was likely to have been supraliminal. A control condition comprising neutral words, unrelated to pain was also considered for inclusion into the study. However, since a difference between neutral and pain-related materials has already been established in the literature (deWied & Verbaten, 2001; Kenntner-Mabiala & Pauli, 2005; Meerman, Verkuil & brosschot, 2011) and Brown’s model makes specific predictions about varying activation levels and subsequent pain perception, this was deemed unnecessary, particularly given the tight timescale of a ClinPsyD project. Lastly, a healthy sample was recruited into the study. This was because the model suggests that the processes that underpin behavioural responses to pain and other symptoms, such as activation of internally held information on receipt of incoming stimuli, are common to everyone. However, as discussed in Paper 2, the model predicts a lower threshold of activation for pain concepts in memory for individuals with medically unexplained pain, therefore it is expected that such a population would be more amenable to the effect shown.

The notion that activation of concepts in memory can influence subsequent behaviour fits well with AM accounts of memory within the wider memory literature.
As discussed, these theories are well-established and make specific claims about how activation spreads as well as factors that impact on the spread of activation and determine monitoring processes. Both Brown’s model of MUS and AM accounts of memory assume that activation is largely unconscious and automatic, meaning that, in most cases, its impact on behaviour is outside of conscious volition. Future studies might look to clarify the nature of activation for MUS in particular. One anomaly in Paper 2 was the absence of the predicted correlation between symptom reporting and the priming effect. This is puzzling because activation accounts predict that increased experience of symptoms should increase baseline activation levels for symptom-related concepts in memory, particularly those related to pain. The increased correlation between pain-related symptom reporting specifically and the priming effect described in Paper 2 provides limited support for the hypothesis, although this was still non-significant. As discussed in Paper 2, this may have been due to the healthy sample of participants and the restricted range on the PHQ-15, which indicates that few high symptom reporters were included in the study. Alternatively, it may mean that the theory is incorrect and that more research is needed in order to fully understand the nature of activation for pain-related concepts in memory. Future studies might seek to differentially activate pain concepts in low versus high pain symptom reporters, perhaps utilising clinical samples of individuals with medically unexplained pain.

4. Clinical implications of Papers 1 and 2

Chronic pain is persistent pain that lasts for more than three months. It can affect any part of the body and individuals of any age. Often, the cause of pain is known, for example, trauma or disease but sometimes the cause is not known, for example in fibromyalgia (Turk & Melzack, 2011). Chronic pain is associated with significant levels of disability, unemployment and mental health problems such as low mood and anxiety (e.g. Crombez et al., 1999; Glombiewski, Hartwish-Tersek, & Rief, 2010; Raferty et al., 2012). The results of this thesis fits well with medically unexplained chronic pain because it is not best understood using a physiological
model of pain; psychological processes play a significant role (see Turk & Okifuji, 2002; Turk, Swanson & Tunks, 2008 for reviews).

In 2008, the Chief Medical Officer concluded that approximately 5 million individuals in the UK will develop a chronic pain condition each year, of whom only two thirds recover (D of H, 2008). The remainder require significant input from services, particularly the NHS and this poses a significant burden to society. For example, it was estimated in 2008 that chronic back pain alone costs the UK economy £12.3 billion a year (D of H, 2008).

In recent years, the emphasis within pain research, particularly chronic pain, has shifted somewhat from a biological and physiological view of its aetiology and maintenance to a full bio-psycho-social model. Findings described in this thesis support the view that a holistic approach to the diagnosis and treatment of pain conditions is crucial to understanding, both for the individual and the clinician. However, the bio-psycho-social approach poses significant challenges to health-care providers. The National Pain Audit (2012) stated that, although psychological factors are now known to have a significant impact on chronic pain conditions, health care providers are still failing to meet the needs of their patients. They argue that the lack of psychological provision overall, as well as the lack of post-qualifying formal training for clinical psychologists working in pain management is ‘concerning’. Moreover, although many medics are increasingly aware of the value of psychological perspectives in treating medically unexplained pain, the medical model is still very dominant within health care settings (Linton & Shaw, 2011). Patients too can be reluctant to view their condition as comprising a psychological component as it potentially invalidates their experiences. More research that is clinically relevant is needed to develop the bio-psycho-social model of pain experience, particularly with regard to applying theory to the development of therapeutic techniques that can help alleviate painful conditions.

How can pain-related information in memory be de-activated? This is a key clinical question, particularly in the context of findings presented in Paper 2 i.e. that activation can occur unconsciously. Although activation is thought to occur unconsciously, the processes that maintain activation of pain-related information in
memory such as rumination about pain or bodily focussed attention are amenable to conscious control. Many evidence-based techniques within Cognitive Behavioural Therapy (CBT) are consistent with bringing these sources of activation under conscious control, as well as reducing or altering the emphasis placed on them. For example, actively challenging pain-related beliefs, forming new (i.e. non pathological) hypotheses about the meaning of physical discomfort and bringing awareness to the ways in which symptoms are appraised. Techniques such as these have been found to be effective ways of managing chronic pain conditions (see McCracken & Turk, 2002; Palermo et al., 2010 for reviews). An influential model that has been used to inform therapeutic techniques within CBT is the fear-avoidance model (Vlaeyen & Linton, 2000). This describes how fear of further pain leads to avoidance of activities perceived as exacerbating pain. With time, this causes deconditioning, low mood and further physical pain. The focus of treatment here is the promotion of physical and social activity, using a graded approach for example.

More recently, mindfulness techniques have increasingly been adopted in the treatment of chronic pain, often alongside CBT approaches (see Veehof et al., 2011). The aim here is to pay attention to the present moment, on purpose and without judgement (Kabat-Zinn, 1994). Mindfulness may be seen as the opposite to rumination and worry about illness, where judgements about the origin and meaning of discomfort are made, for example. Reducing attention to symptoms using techniques such as mindfulness should also reduce activation of pain-concepts in memory.

In relation to Brown’s (2004) model of unexplained symptoms, therapeutic approaches such as the ones described here could impact on activation of pain concepts in two ways: First, activation for pain-related hypotheses would be weakened. Second, new hypotheses about the benefits of activity and potential non-threatening causes of discomfort would be strengthened. Both mechanisms could act to supress pain-related hypotheses, making them less likely to be selected by the PAS and, therefore, less likely to drive behavioural responses.

Overall, the contents of this thesis suggest that the intensity of a noxious stimulus is not a lone contributor to pain experience and this fits well with the
experiences of many patients for whom there is no definable pain pathology. There is
good evidence to suggest that a single clinical approach is ineffective in isolation (see
Eccleston, Morley & Williams, 2013). Often the most effective treatments are those
that incorporate all aspects of the bio-psycho-social approach. Medical input where
appropriate as well as effective evidence-based techniques that are derived from
relevant theories such as those described here, give patients the best chance of
recovery from this complex condition.

5. Personal reflection

The complexity of setting up the study, given the Trainee’s lack of previous
experience in EEG research and familiarity with the software and hardware required
to run the study was a source of frustration. A number of start dates for testing
participants were put in place, only to be pushed back due to technical issues and
then a period of maternity leave. Coming back to the study after maternity leave at a
point where equipment was not working in synch took a lot of determination.
However, the steep learning curve, particularly in relation to operating EEG
equipment and pre-processing EEG files, made this a fulfilling process.

6. Conclusion

This critical reflection and evaluation has enabled further discussion of the
systematic review process as well as ethical, methodological and theoretical
considerations of the empirical paper. It is hoped that the work in this thesis has
made a valuable contribution to the literature on how memory affects pain. The
process of devising, conducting and evaluating the work in this thesis has provided a
learning experience that has both challenged and advanced the personal and
professional development of the Trainee.
References


APPENDIX I

Author information pack for the journal *Pain*
PAIN®
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INFORMATION PACK

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PREPARATION

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APPENDIX II

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For more information about what constitutes a good systematic review, see the PRISMA statement (www.prisma-statement.org/index.htm). The review should include a descriptive and succinct title; a structured abstract; an introduction that specifies the purpose of the review; a methods section that identifies the databases that were searched, search terms used, and inclusion/exclusion criteria for identified articles; an assessment of the validity of reviewed studies; and a summary that includes future directions for studies in this area. Each study mentioned in the review should include the study design, a description of the study population (age range, disease/severity), the dose and duration of each treatment administered, and the data and P values to accompany any valid comparisons). For further information on reviews, see CD Mulrow. The medical review article: State of the science. Ann Intern Med 1987;106:485-8 and AD Oxman et al. User's guide to the medical literature. VI. How to use an overview. Evidence-based medicine working group. JAMA 1994;272:1367-71.

The manuscript must contain an Abstract (unstructured, 250 words) Introduction, Methods, Results, Discussion, Acknowledgments, and References.

File format should be Microsoft Word, and manuscript pages should be numbered.

Title page. The title page should include the following: (i) complete title (preferably no chemical formulas or arbitrary abbreviations); (ii) full names of all authors; (iii) complete affiliations of all authors; (iv) the number of text pages of the entire manuscript (including pages containing figures and tables) and the actual number of figures and tables; (v) the author to whom correspondence should be sent and this author’s complete mailing address, telephone number, fax number, and e-mail address, and, if available, institutional URL.

Acknowledgments. Place acknowledgments at the end of the text before the reference list and specify the following: (1) contributions that need acknowledging but do not justify authorship; (2) acknowledgments of technical help; (3) acknowledgments of financial and material support, specifying the nature of the support; (4) financial arrangements that may represent a possible conflict of interest.

This would also include any of the following arrangements, such as if any of the authors have a financial relationship to the work;

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are stockholders of the company;

are members of a speakers bureau; or

have received any other form of financial support.
Conflict of Interest. A Conflict of Interest statement must be included for all manuscripts within the Acknowledgments section. Even if there are no conflicts of interest, please explicitly state this.

References. Cite literature references in the text using bracketed numbers that correspond to the alphabetized and numbered reference list as follows: "Pain is made worse if you hit the already injured site [15]." For multiple references in the text, please use the format [number,number] (with a comma and no spaces). For example: [2,4,28,33].

- All references cited in the text must be listed at the end of the paper. They should be numbered, double spaced, and arranged alphabetically by first author last name.

- All authors must be listed in the references; the use of et al. is not acceptable.

- References must be complete, including initial(s) of author(s) cited, title of paper, journal, year of publication, and volume and page numbers.

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Tables. Tables, with their captions and legends, should be intelligible with minimal reference to the text. Tables of numerical data should each be typed (double spaced) on a separate page, numbered in sequence with Arabic numerals (i.e., Table 1, Table 2, etc.), provided with a title/heading, and referred to in the text as Table 1, Table 2, etc. Provide a detailed description of its contents and any footnotes below the body of the table.

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APPENDIX III

Author guidelines for an empirical paper for the journal *Pain*
Clinical/Basic Science Research Reports

The manuscript must contain an Abstract (unstructured, 250 words), Introduction (500 words), Methods (no word limit), Results (no word limit), Discussion (1,500 words), Acknowledgments, and References.

File format should be Microsoft Word, and manuscript pages should be numbered.

Title page. The title page should include the following: (i) complete title (preferably no chemical formulas or arbitrary abbreviations); (ii) full names of all authors; (iii) complete affiliations of all authors; (iv) the number of text pages of the entire manuscript (including pages containing figures and tables) and the actual number of figures and tables; (v) the author to whom correspondence should be sent and this author’s complete mailing address, telephone number, fax number, and e-mail address, and, if available, institutional URL.

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This would also include any of the following arrangements, such as if any of the authors have a financial relationship to the work;

have received any government or company grants or research support;

are employees of a company;

are consultants for a company;

are stockholders of the company;

are members of a speakers bureau; or

have received any other form of financial support.

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APPENDIX IV

The bespoke quality assessment tool
1. Did the study address a clearly focussed issue? In terms of:
   a. Population studied
   b. Interventions given
   c. Outcomes considered
2. Did the authors use an appropriate method to answer their question?
   a. Did it address the study question?
   b. Did the method introduce unnecessary levels of pain?
3. Were participants recruited in an acceptable way?
   a. Is appropriate ethical approval in place?
   b. Is there evidence of selection bias?
   c. Is there something special about participants and is that acknowledged?
   d. Are groups of participants comparable where indicated?
4. Did the authors take appropriate measures of their independent variable(s)?
   a. Is the IV and its levels adequately defined?
5. Did the authors take appropriate measures of their dependent variable(s)?
   a. Is the DV and its levels adequately defined?
   b. Is the DV measured appropriately?
6. Have the authors identified all important confounding factors?
   a. Including genetic, environmental, social, socio-economic (particularly relevant is the use of analgesic medication)
7. Have the authors taken account of potential confounding factors in the design and/or analyses? Particularly in relation to:
   a. Participant recruitment
   b. Number of participants (e.g. large sample size)
   c. Statistical analyses (e.g. the use of covariates)
8. What are the results of this study?
   a. Was an appropriate statistical method used?

All sub-section prompts taken from CASP checklists. * have been added by the author.

CASP score each section according to yes/can't tell/don't know. In the current checklist, these criteria have been altered to 1/0.5/0 so that an overall numerical value can be awarded to each study.
9. Do you believe the results?
   a. Could the effect be due to bias, chance or confound (big effects are more convincing)?
   b. Are design and methods sufficiently flawed to render results unreliable?

10. How valuable is the research?
    a. Does it link with theory?
    b. Does the authors prompt/suggest further work?
APPENDIX V

Ethical approval letter from University of Manchester
Secretory to Research Ethics Committees  
Room 2.004 John Owens Building  
Tel: 0161 275 2206/2046  
Fax: 0161 275 5697  
Email: timothy.stibbs@manchester.ac.uk  
ref: ethics/12015  

Dr Ellen Swannell,  
Division of Clinical Psychology,  
2nd floor Zochonis Building  
6th June 2012

Dear Ellen,

Research Ethics Committee 2  
Swannell, Brown, Brown, Jones: Unconscious activation of pain concepts in memory: influences on pain anticipation and perception (ref 12015)

I write to thank you for attending the meeting on 30th April and to confirm that the amended documents set out in your email of 29th May satisfy the concerns of the Committee and that the project has been given a favourable ethical opinion.

This approval is effective for a period of five years and if the project continues beyond that period it must be submitted for review. It is the Committee’s practice to warn investigators that they should not depart from the agreed protocol without seeking the approval of the Committee, as any significant deviation could invalidate the insurance arrangements and constitute research misconduct. We also ask that any information sheet should carry a University logo or other indication of where it came from, and that, in accordance with University policy, any data carrying personal identifiers must be encrypted when not held on a university computer or kept as a hard copy in a location which is accessible only to those involved with the research.

Finally, I would be grateful if you could complete and return the attached form at the end of the project or by May 2013.

Yours sincerely,

Timothy Stibbs
Secretary to the University Research Ethics Committee

Enclosed: Report form
APPENDIX VI

Ethical approval letter from Salford Royal Hospital
18th October 2012

Dr Ellen Swannell
Trainee Clinical Psychologist
Division of Clinical Psychology
2nd Floor, Zochonis Building
University of Manchester
Oxford Road
Manchester M13 9PL

Dear Dr Swannell

Study Title: Unconscious Activation of Pain Concepts in Memory: Influences on Pain Anticipation and Perception

UoM EC Reference: 12015
EuDrACT Reference: N/A
R&D Reference: 2012/081DERM

Thank you for forwarding all the required documentation for your study as above. I am pleased to inform you that your study has been registered with NHS Salford+D and has gained NHS R&D approval from the following NHS Trust:

- Salford Royal NHS Foundation Trust


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All researchers who do not hold a substantive contract with the Trust must hold an honorary research contract before commencing any study activities related to this approval. The ‘Research Passport Application Form’. This can be obtained from web addresses: http://www.gmregroup.nhs.uk/researchers/passports.html and http://www.hope-academic.org.uk/academic/salfordr/Research%20Passports.html This form should be completed and returned, with a summary CV and recent (within 6 months) CRB to the address shown above.

It is a condition of both NRES and NHS R&D approval that participant recruitment data should be forwarded on a regular basis. Therefore, progress reports must be submitted annually to the main REC and copied to the R&D office until the end of the study. http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/
Where clinical trials of investigational medicinal products are sponsored by Salford Royal NHS Foundation Trust or Salford Primary Care Trust, it is a condition of Trust approval that Chief Investigators submit quarterly progress reports (to include Annual Safety Reports at the appropriate time) to R&D. For clinical trials of investigational medicinal products hosted within Salford Royal NHS Foundation Trust and Salford Primary Care Trust, the local PI will be expected to submit bi-annual progress reports to R&D. It is also a condition of approval that delegated duties (as agreed within clinical trial agreements and trial delegation loge) are fulfilled by oly those delegated to undertake a specific duty. This will be monitored by the Sponsor’s Representative during routine monitoring of the trial. Persistent non-compliance with these requirements may result in removal of Sponsorship or Trust R&D Approval.

Any amendments to the study should also be notified and approval sought by Ethics Committee and R&D Department. Where Salford Royal NHS Foundation Trust or Salford Primary Care Trust is acting as Sponsor then amendments or changes MUST be discussed with the Sponsor prior to REC submission.

On completion of the study you are required to submit a ‘Declaration of End of Study’ form to the main REC, which should also be copied and forwarded to the R&D office at the address shown above.

Any serious adverse events or governance issues related to the research must be notified to the R&D office.

Yours sincerely,

Sue Gowland
R&D Manager

C.C. Research Sponsor
APPENDIX VII

Laser safety certificate
Staff Training & Development Unit

This is to certify that

Ellen Swannell

Has attended and successfully completed any assessment requirements for the following course(s)

Laser Safety Training

Valid until 5 years after dated

27/09/12

Paul Dixon
Manager

Date
APPENDIX VIII

Participant information sheet
Participant Information Sheet

Study title: Cognitive processing and pain perception

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Don’t hesitate to contact me using the details provided at the end of this information sheet if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?

The study will investigate how you process visual stimuli presented on a computer screen and how this changes when you are exposed to painful stimuli. We are also interested in how your brain anticipates and perceives pain signals and whether brain activity is different during periods of increased concentration.

Am I suitable for the study?

In order to take part in the study you must be aged 18 – 35 years and generally in good health. English must also be a first language i.e. the one you learnt first as a child. You must read this participant information sheet carefully and sign a consent form in order to participate.

You are not eligible to take part if any of the following are applicable:
- You have participated in a pain study within the last two weeks.
- You have a history of brain tumours or any other neurological condition.
- You have a medical condition that means you experience pain.
- You have a medical condition that affects your pain perception.
- You are taking pain medication.
- You are left handed.
Where will the study take place?

The study will be conducted in the Human Pain Research Group laboratories at Salford Royal NHS Foundation Trust in Salford. You will be required to attend for one session lasting about an hour and forty minutes.

Do I have to take part?

Your participation in the study is voluntary and you are free not to take part or to withdraw from it at any time. If you decide to withdraw from the study once it has started then any data gathered from your participation as well as any personal data you have provided will be destroyed.

What compensation will I receive for taking part?

You will receive £20 to compensate you for your time and travel expenses.

What will happen to me if I take part in the study?

You will need to attend one session that will last approximately 100 minutes. During this time, the following will take place:

- When you arrive at the laboratory, you will have an opportunity to ask any questions you may have about the study. If you would like to proceed with the study, you will be asked to sign a consent form to say you have read this information sheet and you agree to participate.

- We are interested in electrical activity in the brain that occurs when anticipating and experiencing painful stimuli. We will record this brain activity using a procedure called electroencephalography (EEG). This will involve wearing a stretchy elastic cap containing a number of electrodes that make contact with your scalp. This is a totally safe and non-invasive procedure. In order to make good contact with your scalp, each electrode will be filled with a type of gel. The gel will be in your hair throughout the task but there will be facilities for you to wash and dry your hair before you leave. To help obtain good recordings we ask you to have clean hair that day and not to use hair conditioning or styling products such as wax, gel or spray.

- Whilst the electrodes are being attached you will be asked to complete some short questionnaires. These will include personal questions about your physical and mental health. You are advised not to participate in this study if you think that answering such questions could be unduly distressing for you.

- We are also interested in how you rate painful stimuli. A laser stimulator will be used to administer very brief heat sensations to your forearm. Tolerance to painful stimuli varies between individuals and we will conduct an assessment to determine your individual tolerance thresholds. We will do this by slowly turning up the heat of the laser stimulator until you report low, moderate and high levels of pain. We will then make keep a record of these levels to use later in the study. Low levels of pain should feel very uncomfortable but not especially painful and moderate levels of pain should feel uncomfortable and more painful. A high level of pain will feel unpleasant; however, it should not make you feel unduly distressed and you will not be asked to endure levels of pain that you find intolerable. You will determine how much pain is tolerable for you. However, you are advised not to take part in the study if you think that experiencing any pain could be unduly distressing for you. The Chief Investigator has been trained in the use of a laser to administer safe levels of pain to participants.
- You will be asked to sit at a computer screen for the experimental part of the study, which will comprise 96 trials. During each trial you will be asked to attend to visual stimuli presented on the screen. Then a very brief heat sensation from the laser will be applied to your forearm. This will be at either a low, moderate or high level (levels determined during the assessment of your pain tolerance). Upon perceiving the heat sensation, you will be asked to rate how painful it was. After every 24 trials (approximately every 4 minutes), you will have a break of 3 minutes during which you will be asked to complete a simple task that is separate to the pain ratings. During the experimental trials EEG readings of electrical activity in your brain will be recorded.
- After the experimental trials, you will be asked to complete a short task about what you remember about the study.
- Information will be provided at the end of the study about what we hope to find. You will also have an opportunity to ask questions.

**What are the risks associated with taking part in the study?**

You will be asked to answer some personal questions about your mental and physical health on the questionnaires and some people may find this distressing. All questionnaire responses will be anonymous. However, you should note that although the chief investigator will not provide general feedback on your questionnaire responses, you may be asked further questions if your responses indicate risk to your life. In such a case you will be asked to volunteer the details of your GP.

You will be asked to tolerate pain but this should not be unduly distressing for you and we have protocols to follow to ensure that no one is exposed to inappropriate levels of distress. After your participation, you may experience some reddening of the skin on your arms due to the laser heat pulses, but this should disappear within a few hours to days. There is a risk that you may have some mild soreness of the skin, in which case advice will be given to you about this before you leave. Also, it is possible that this area of skin may have a change in pigmentation, which should return to normal within 4-6 weeks. However, in the 10 years that the Human Pain Research Group at Salford Royal Hospital has been using this technique, two cases have been brought to our attention where this pigmentation has persisted.

An ethics committee has examined and approved all the details of this study before it was advertised.

**Will my data be anonymous?**

Any personal details you provide as well as questionnaire responses will be stored in a locked cabinet at Manchester University. Data generated by your participation will be stored on separate secure databases that are password protected. You can be assured that only the researchers directly involved in this study will have access to any of this information. Any publications of data from the study will not make reference to individual participants.

You will have the option of receiving a summary of the study aims and findings once the whole study has ended. If you would like this then you will be asked to provide contact details (e.g. your email or house address). These contact details will also be stored on a secure database and they will not be made available to third parties.
How do I volunteer for this study?

If you would like to take part in this study, please contact Dr Ellen Swannell at ellen.swannell@postgrad.manchester.ac.uk to assess whether you are suitable for the study and to arrange a time for you to attend our research laboratory.

If you would like to learn more about some of the research that is currently taking place in the Human Pain Research Group then please visit the website at www.hop.man.ac.uk/painresearch.

Complaints

If you have concerns about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 583 or 0161 275 8093 or by email to research.complaints@manchester.ac.uk.

In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against the University of Manchester and Salford Royal NHS Foundation Trust but you may have to pay your legal costs.
APPENDIX IX

Consent form
Participant Consent Form

Study title: Cognitive processing and pain perception

Please read each item below and put your initials in the corresponding box if you agree.

☐ I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.

☐ I have read the Participant Information Sheet and I understand everything written in it, including information about any risks to me.

☐ I understand that I have the right to withdraw from the study at any time, without giving a reason and without my legal rights being affected. In such a case any data generated by my participation will be destroyed.

☐ I understand that sections of data collected during the study may be looked at by responsible individuals from Manchester University, regulatory authorities or Salford Royal NHS Foundation Trust where it is relevant to my taking part in the research. I give permission for these individuals to have access to my data.

☐ I agree that the following is true:
  • I have not participated in a pain study within the last two weeks.
  • I do not have a history of brain tumours or any other neurological condition.
  • I do not have a medical condition that means I experience pain.
  • I do not have a medical condition that affects my pain perception.
  • I am not taking pain medication.
  • I am not left-handed.

☐ I agree to participate in this study voluntarily and without coercion.

_________________________________________  __________________________________________
Participant’s name (printed)               Chief investigator’s name

_________________________________________  __________________________________________
Participant’s signature                     Chief investigator’s signature

Date
APPENDIX X

Debrief sheet
Participant Debrief Sheet

Study title: Cognitive processing and pain perception

Now that you have participated in this study I would like to provide you with some additional information about it. You may or may not have noticed during the experimental trials that some words were presented to you on the computer screen. Individual words were presented very quickly (for 33 milliseconds) immediately before the ‘XXX’ appeared on the screen. They were presented very quickly so that you would not consciously perceive them, that is, they were subliminally presented. These words were related to the word ‘pain’. Some of the words were highly related to ‘pain’ and some were not highly related.

What was the study about?

It is thought that the way we experience bodily sensations is influenced by information in our memory, particularly memories that are related to pain. Sometimes, these memories can influence the way we think, feel and behave, even if we are unaware of it at the time. Researchers have found that presenting different types of words to people without them being aware of it (i.e. subliminally) influences their subsequent experience of pain, so that it feels better or worse, depending on the type of word that was presented. This is because certain words can trigger memories of pain, which then influence how they feel.

In this study, words that were related to the word ‘pain’ were presented to you very quickly so that you were probably not consciously aware of them. Half of the words were highly related to the word ‘pain’ and half were not. We are interested in whether you rated the heat sensation from the laser as being more painful after you had been presented with a word that was highly related to ‘pain’ than you did after you had been presented with a word that was not highly related. There is some evidence that people’s brains can anticipate pain before they feel it. Therefore, electrical activity in your brains was recorded during the study. We predict that you displayed more brain activity in anticipation of pain when you had been subliminally presented with a word that was highly related to ‘pain’ than after you had been presented with a word that was not highly related. Additionally, we expect your questionnaire responses to provide...
information about how you think of pain and about your physical and mental health more generally.

**Why was it necessary to deceive me at the start?**

In order to test our hypothesis that *unconscious* perception of pain related words can influence anticipation and perception of potentially painful sensations, it was necessary to deceive you at the start. If you had been told about the presentation of the words then you may have looked out for them, making it more likely that you would see them. You may also have had more conscious thoughts about pain which may have altered your responses to the heat stimuli from the laser.

**Can I find out any more information about the study?**

Please feel free to ask me (Ellen Swannell) any additional questions about the study. If you have any questions once you have left then you can contact me via the email given at the end of this debrief sheet. If you would like a summary of findings once the study has ended and you have not yet supplied contact details for this then please do let me know before you leave.

**Should I expect any side effects from taking part in this study?**

You may experience some reddening of the skin on your arms due to the laser heat pulses, but this should disappear within a few hours to days. In this case, you are advised to keep your skin cool after the experiment and apply non-perfumed moisturising lotion. There is a risk that you may have some mild soreness of the skin, in which case advice will be given to you about this before you leave. Also, it is possible that this area of skin may have a change in pigmentation, which should return to normal within 4-6 weeks. However, in the 10 years that the Human Pain Research Group at Salford Royal Hospital has been using this technique, two cases have been brought to our attention where this pigmentation has persisted.

If you do experience persistent soreness of changes in skin pigmentation then we recommend that you inform us of it using the email address given at the end of this debrief sheet.

**Are my data confidential?**

Personal details you have provided and your questionnaire responses will be stored in a locked cabinet at Manchester University. Data generated by your participation will be stored on separate secure databases that are password protected. If you have not opted to receive a summary of findings sheet once the study has ended then your contact details will be destroyed after you leave today. You can be assured that only the researchers directly involved in this study will have access to any information about you. Publications of data from this study will not make reference to individual participants.

**For further information:**

Contact Ellen Swannell: ellen.swannell@postgrad.manchester.ac.uk
APPENDIX XI

Questionnaires
Patient Health Questionnaire—PHQ-9

Name: ______________________________         Date of Birth:_____________

Date:____________

Fill in the boxes with pen or pencil to mark your answers.

A. Over the last 2 weeks, how often have you been bothered by any of the following problems?

<table>
<thead>
<tr>
<th>Problem</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td></td>
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<tr>
<td>3. Trouble falling/staying asleep, sleeping too much</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>4. Feeling tired or having little energy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5. Poor appetite or overeating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Feeling bad about yourself – or that you are a failure or have</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>let yourself or your family down.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>or watching television.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8. Moving or speaking so slowly that other people could have noticed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>or the opposite – being so fidgety or restless that you have been</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>moving around a lot more than usual.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in some way.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Score _____ = _____+ _____+ _____+_____
If you have been bothered by any of the 9 problems listed above, please answer the following:

How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? Not difficult at all

Somewhat Difficult   Very Difficult   Extremely Difficult

[ ]   [ ]   [ ]

This health survey was adapted from the PRIME-MD® Patient Health Questionnaire © 1999, Pfizer Inc. Reproduced with permission. For research information, contact Dr. Robert L. Spitzer at rls8@columbia.edu.

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### Patient Health Questionnaire 15-Item Somatic Symptom Severity Scale (PHQ-15)

During the *past 4 weeks*, how much have you been bothered by any of the following problems?  

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not bothered at all</th>
<th>Bothered a little</th>
<th>Bothered a lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Stomach pain</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>b. Back pain</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Pain in your arms, legs, or joints (knees, hips, etc.)</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>d. Menstrual cramps or other problems with your periods [Women only]</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>e. Headaches</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>f. Chest pain</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>g. Dizziness</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>h. Fainting spells</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>i. Feeling your heart pound or race</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>j. Shortness of breath</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>k. Pain or problems during sexual intercourse</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>l. Constipation, loose bowels, or diarrhea</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>m. Nausea, gas, or indigestion</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>n. Feeling tired or having low energy</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>o. Trouble sleeping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

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# Generalised Anxiety Questionnaire 7

<table>
<thead>
<tr>
<th>GAD-7</th>
<th>Over the last 2 weeks (or other agreed time period) how often have you been bothered by any of the following</th>
<th>not at all</th>
<th>several days</th>
<th>more than half</th>
<th>nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

GAD-7 total score =
Fear of Pain Questionnaire – Short Form

**AMOUNT OF FEAR**

INSTRUCTIONS: The items listed below describe experiences. Please look at each item and think about how FEARFUL you are of experiencing the PAIN associated with each item. If you have never experienced the PAIN of a particular item, please answer on the basis of how FEARFUL you expect you would be if you had such an experience. Circle one rating per item to rate your FEAR OF PAIN in relation to each event.

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>A fair amount</th>
<th>Very much</th>
<th>Extreme</th>
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<tr>
<td>1</td>
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<td>4</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1. Being in an automobile accident
2. Biting your tongue while eating
3. Breaking your arm
4. Cutting your tongue licking an envelope
5. Having a heavy object hit you in the head
6. Breaking your leg
7. Hitting a sensitive bone in your elbow – your funny bone
8. Having a blood sample drawn with a hypodermic needle
9. Having someone slam a heavy car door on your hand
10. Falling down a flight of concrete stairs
11. Receiving an injection in your arm
12. Receiving an injection in your hip/buttocks
13. Receiving an injection in your mouth
14. Getting a paper-cut on your finger
15. Cutting yourself while shaving with a sharp razor
16. Gulping a hot drink before it has cooled
17. Getting strong soap in both your eyes while bathing or showering
18. Having a tooth pulled
19. Having sand or dust blow into your eyes
20. Having one of your teeth drilled
HAI (short version)

Each question is this section consists of a group of four statements. Please read each group of statements carefully and then select the one which best describes your feelings, over the past six months. Identify the statement by ringing the letter next to it, i.e. if you think that statement (a) is correct, ring statement (a); it may be that more than one statement applies, in which case, please ring any that are applicable.

1. (a) I do not worry about my health.
   (b) I occasionally worry about my health.
   (c) I spend much of my time worrying about my health.
   (d) I spend most of my time worrying about my health.

2. (a) I notice aches/pains less than most other people (of my age).
   (b) I notice aches/pains as much as most other people (of my age).
   (c) I notice aches/pains more than most other people (of my age).
   (d) I am aware of aches/pains in my body all the time.

3. (a) As a rule I am not aware of bodily sensations or changes.
   (b) Sometimes I am aware of bodily sensations or changes.
   (c) I am often aware of bodily sensations or changes.
   (d) I am constantly aware of bodily sensations or changes.

4. (a) Resisting thoughts of illness is never a problem.
   (b) Most of the time I can resist thoughts of illness.
   (c) I try to resist thoughts of illness but am often unable to do so.
   (d) Thoughts of illness are so strong that I no longer even try to resist them.

5. (a) As a rule I am not afraid that I have a serious illness.
   (b) I am sometimes afraid that I have a serious illness.
   (c) I am often afraid that I have a serious illness.
(d) I am always afraid that I have a serious illness.

6.  
(a) I do not have images (mental pictures) of myself being ill.  
(b) I occasionally have images of myself being ill.  
(c) I frequently have images of myself being ill.  
(d) I constantly have images of myself being ill.

7.  
(a) I do not have any difficulty taking my mind off thoughts about my health.  
(b) I sometimes have difficulty taking my mind off thoughts about my health.  
(c) I often have difficulty in taking my mind off thoughts about my health.  
(d) Nothing can take my mind off thoughts about my health.

8.  
(a) I am lastingly relieved if my doctor tells me there is nothing wrong.  
(b) I am initially relieved but the worries sometimes return later.  
(c) I am initially relieved but the worries always return later.  
(d) I am not relieved if my doctor tells me there is nothing wrong.

9.  
(a) If I hear about an illness I never think I have it myself.  
(b) If I hear about an illness I sometimes think I have it myself.  
(c) If I hear about an illness I often think I have it myself.  
(d) If I hear about an illness I always think I have it myself.

10.  
(a) If I have a bodily sensation or change I rarely wonder what it means.  
(b) If I have a bodily sensation or change I often wonder what it means.  
(c) If I have a bodily sensation or change I always wonder what it means.  
(d) If I have a bodily sensation or change I must know what it means.

11.  
(a) I usually feel at very low risk for developing a serious illness.  
(b) I usually feel at fairly low risk for developing a serious illness.
(c) I usually feel at moderate risk for developing a serious illness.
(d) I usually feel at high risk for developing a serious illness.

12.  
(a) I never think I have a serious illness.
(b) I sometimes think I have a serious illness.
(c) I often think I have a serious illness.
(d) I usually think that I am seriously ill.

13.  
(a) If I notice an unexplained bodily sensation I don't and find difficult
to think about other things.
(b) If I notice an unexplained bodily sensation I sometimes find it
difficult to think about other things.
(c) If I notice an unexplained bodily sensation I often find it difficult to
think about other things.
(d) If I notice an unexplained bodily sensation I always find it difficult to
think about other things.

14.  
(a) My family/friends would say I do not worry enough about my health.
(b) My family/friends would say I have a normal attitude to my health.
(c) My family/friends would say I worry too much about my health.
(d) My family/friends would say I am a hypochondriac.

For the following questions, please think about what it might be like if
you had a serious illness of a type which particularly concerns you (such
as heart disease, cancer, multiple sclerosis and so on). Obviously you
cannot
know for definite what it would be like; please give your best estimate
of what you think might happen, basing your estimate on what you
know about yourself and serious illness in general.

15.  
(a) If I had a serious illness I would still be able to enjoy things in my
life quite a lot.
(b) If I had a serious illness I would still be able to enjoy things in my
life a little.
(c) If I had a serious illness I would be almost completely unable to enjoy things in my life.
(d) If I had a serious illness I would be completely unable to enjoy life at all.

16.
(a) If I developed a serious illness there is a good chance that modern medicine would be able to cure me.
(b) If I developed a serious illness there is a moderate chance that modern medicine would be able to cure me.
(c) If I developed a serious illness there is a very small chance that modern medicine would be able to cure me.
(d) If I developed a serious illness there is no chance that modern medicine would be able to cure me.

17.
(a) A serious illness would ruin some aspects of my life.
(b) A serious illness would ruin many aspects of my life.
(c) A serious illness would ruin almost every aspect of my life.
(d) A serious illness would ruin every aspect of my life.

18.
(a) If I had a serious illness I would not feel that I had lost my dignity.
(b) If I had a serious illness I would feel that I had lost a little of my dignity.
(c) If I had a serious illness I would feel that I had lost quite a lot of my dignity.
(d) If I had a serious illness I would feel that I had totally lost my dignity.
The Positive and Negative Affect Schedule

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you have felt this way today. Use the following scale to record your answers.

1  2  3  4  5
Very slightly or not at all  A little  Moderately  Quite a bit  Extremely

.................... Interested  .................... Irritable

.................... Distressed  .................... Alert

.................... Excited  .................... Ashamed

.................... Upset  .................... Inspired

.................... Strong  .................... Nervous

.................... Guilty  .................... Determined

.................... Scared  .................... Attentive

.................... Hostile  .................... Jittery

.................... Enthusiastic  .................... Active

.................... Proud  .................... Afraid
APPENDIX XII

Distress protocol for use during questionnaire completion
Participant verbalizes distress and/or shows visible signs of distress (e.g. crying, shaking)

- Ask if they are ok
  - NO
    - Suspend questionnaire completion
    - With permission, discuss source of distress with participant and refer to sources of support leaflet
    - Ask if they want to continue
      - NO
        - End of participation
      - YES
        - Continue, plus monitor participant for further signs of distress
          - LOW RISK
          - HIGH RISK

Participant does NOT answer 'not-at-all' to question 9 on PHQ-9

- Ask questions about suicidal ideation, intent, support at home AND refer to sources of support leaflet and suggest participant visits G.P.
  - CI to review the risk to participant
    - LOW RISK
    - HIGH RISK
      - End of participation
      - Ask for GP details
        - YES
          - Call GP
        - NO
          - Advise they visit GP and direct to sources of support again
            - Distressed
              - Call someone to collect
            - Not distressed
              - Go home
APPENDIX XIII

Distress protocol for use during experimental trials
APPENDIX XIV

EEG pre-processing protocols
**Protocol for pre-processing EEG data**

1. Change sampling rate from 500hz to 125hz  
2. Apply notch (50hz) and low pass/high cut-off (25hz) filters  
3. Check that all channels are sound. If not, topographically interpolate channel.  
4. Raw data inspection – inspect full data set and mark any parts that have artefacts that should be removed e.g. muscle activity, DC detrend.  
5. Segment data – all segments.  
6. Apply baseline correction (-3600 to -3100ms) i.e. cleanest part of segment, 500 ms before anything is presented.  
7. DC detrend (100 to 500ms)  
8. Segment each painful (level 7) condition and average. Check presence of LEP and topography.  
10. Select potential components for removal by examining patterns and comparing with eye and muscle channels and topography (aim to remove eye movement and muscle movements)  
11. Segment each painful (level 7) condition again and average to compare pre-ICA. If the LEP and/or accompanying topography has been compromised by the ICA then re-run ICA (and possibly be less aggressive). Also consider overlaying ICAs.  
12. Artefact rejection – to remove segments that are still contaminated by muscle movement, DC detrend.  
13. Segment for each condition and perform the following:  
   a. DC detrend  
   b. Baseline correction for LEP (-500 to 0ms)  
   c. Average  
   d. Re-reference (for all channels)  
   e. From after step a; baseline correction for SPN (-3600 to -3100ms)  
   f. Average  
   g. Re-reference  

**Protocol for peak (LEP) detection**

1. Visually inspect latency window for painful conditions (i.e. level 7) for P2 and N2. Also use topography to confirm latency of LEP.  
2. Semi-automatic search using window of time around identified potential latency.  
3. Visually inspect and adjust if necessary.  
4. If LEPs are prominent enough for less painful conditions (i.e. levels 3 & 5), then also visually inspect latency window to search for these conditions too. If not, use latencies for
level 7 conditions as a reference search window. If noise only then use confirmed latency of level 7 LEPs.

Protocol for deciding on inclusion of EEG data for analyses

1. Check presence of LEPs for conditions 12 and 22 (i.e. level 7 pain data)
2. If present for both N2 and P2 then include
3. If present for N2 or P2 then just include for that peak
4. If unsure then check topography to see if it confirms LEP activity
5. If unsure but a participant has good topography for one of the painful conditions then include.

Participants 1, 5 and 17 were not included in analyses of LEPs at all. Participants 2, 3, 6, 9, 12, 14, 18, 19, 22, 23, 26, 27 were included for N2 and P2, participants 4, 13 and 20 for N2 peaks only and participants 7, 8, 10, 11, 15, 16, 21 and 24 for P2 peaks only.
APPENDIX XV

Recognition test
Memory recognition test

During the experimental trials you may or may not have noticed that some words were presented very quickly, immediately before the Chinese characters. We would like to know whether you saw any of these words and if so, how sure you are of your memory for them.

Below is a list of words. Some of them were presented during the experimental trials and some were not. For each word, please write ‘Y’ for yes if you saw it and ‘N’ for no if you did not.

If you mark ‘Y’ for any word then please say whether you remember it (R response), you know you saw it (K response) or you are just guessing (G response).

An R (Remember) response indicates that you remember seeing the word and can recollect something specific about when you saw it. For example, you may remember a particular thought that the word triggered.

A K (Know) response indicates that you know you saw the word. It feels familiar but you can’t remember anything specific about seeing it.

A G (Guess) response is just a guess. It feels vaguely familiar but you can’t be sure whether you saw it or not.
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<th>If ‘yes’</th>
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