

The context of a noxious stimulus affects the pain it evokes

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Received 1 August 2006; received in revised form 14 February 2007; accepted 5 March 2007

Abstract

The influence of contextual factors on the pain evoked by a noxious stimulus is not well defined. In this study, a -20°C rod was placed on one hand for 500 ms while we manipulated the evaluative context (or ‘meaning’) of, warning about, and visual attention to, the stimulus. For meaning, a red (hot, more tissue damaging) or blue (cold, less tissue damaging) visual cue was used. For warning, the stimulus occurred after the cue or they occurred together. For visual attention, subjects looked towards the stimulus or away from it. Repeated measures ANCOVA was significant ($\alpha = 0.0125$). Stimuli associated with a red cue were rated as hot, with the blue cue as cold (difference on an 11 point scale ~ 5.5). The red cue also meant the pain was rated as more unpleasant (difference ~ 3.5) and more intense (difference ~ 3). For stimuli associated with the red cue only, the pain was more unpleasant when the stimulus occurred after the cue than when it didn’t (difference ~ 1.1). Pain was rated as more intense, and the stimulus as hotter, when subjects looked at the red-cued stimulus than when they didn’t (difference ~ 0.9 for pain intensity and ~ 2 for temperature). We conclude that meaning affects the experience a noxious stimulus evokes, and that warning and visual attention moderate the effects of meaning when the meaning is associated with tissue-damage. Different dimensions of the stimulus’ context can have differential effects on sensory-discriminative and affective-emotional components of pain.

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Keywords: Meaning; Cross-modal interaction; Attention; Expectation

1. Introduction

That the context of a noxious stimulus affects the pain it evokes is intuitively sensible and almost universally accepted (Merskey and Bogduk, 1994). There are different dimensions of a noxious stimulus’ context that may influence how it is experienced. For example, its perceived tissue damaging properties (its evaluative context or ‘meaning’), whether it is preceded by a warning signal or not (its temporal context), and whether the subject focuses visual attention to it or not. There are correlational studies reporting an association between

the evaluative context of noxious stimuli and pain reports, but only a few experimental demonstrations (Arntz and Claassens, 2004).

That warning of noxious stimuli affects the intensity of perceived pain is well established – if the stimulus occurs after a cue then the effect of the expectation seems to match that implied by the cue – the so-called expectation effect (Ploghaus et al., 1999; Price et al., 1999; Petrovic and Ingvar, 2002; Wager et al., 2004; Wager, 2005; Keltner et al., 2006). For example, a noxious stimulus hurts more, and attentional processes are more interrupted, if the stimulus is preceded by a cue that denotes a high intensity stimulus than if it is preceded by a cue that denotes a low intensity stimulus (Crombez et al., 1998a,b; Keltner et al., 2006). Expectation can also reduce pain: if one expects pain relief,

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one is more likely to get it (see Benedetti et al. for review).

The visual attentional context of a noxious stimulus includes gaze direction and the nature of visual input, both of which are known to affect the perception of non-noxious tactile stimuli. If one looks at, or in the direction of, a non-noxious stimulus, tactile acuity is increased and sensory detection threshold is decreased. (Zhou and Fuster, 2000; Spence, 2002; Taylor-Clarke et al., 2002; Fiorio and Haggard, 2005; Forster and Eimer, 2005; Schaefer et al., 2005). The mechanisms by which looking at a tactile stimulus changes tactile function probably involve modulation of spatial attention and interaction between vision and touch – cross-modal interaction. The potential influence of looking at a noxious stimulus is utilised almost universally in clinical practice, for example asking patients to look away during an injection, but the effect is yet to be determined.

The aim of the current study was to determine the effect of the tissue-damaging meaning of a noxious stimulus, warning about the stimulus and visual attention to the stimulus on the experience it evokes.

2. Methods

2.1. Subjects

Thirty-three right-handed healthy volunteers (24 females, mean \pm SD age = 28 ± 7 years) were recruited via notice boards advertising the project. Written consent was obtained and approval was granted by the Institutional Human Research Ethics Committee.

2.2. Materials

An aluminium probe (200 mm length, 18 mm diameter) was cooled in a freezer to -20°C . For stimulation, the probe was inserted into an in-house device that connected, via a 9 V battery, to a red light and a blue light. The lights were fixed to a panel (30 mm \times 10 mm), which in turn could be attached at the base of the device, adjacent to where the probe would make contact with the skin. Three switches could operate the device. One switch controlled whether the red light or blue light was

connected to the circuit. Another switch controlled whether the light would be illuminated manually (the light could be turned on before the probe touched the skin) or via a pressure-sensitive pad that was placed inside the device (the light would turn on in time with the probe touching the skin). A monitor was placed in front of the subject.

2.3. Procedure

Sitting subjects placed their hands comfortably on a desk. All subjects were right handed. One hand was randomly chosen to be the experimental hand. Subjects were told that the experiment was investigating the effect of vision and timing of a visual cue on pain and temperature perception and that probes of different temperatures would be placed on the back of the experimental hand for 500 ms at a time. With the probe held perpendicular to the skin, the end of the probe (surface area = 254 mm^2) was placed on the dorsal surface of the experimental hand for 500 ms. This stimulus is non-damaging when used at this location and for this duration.

Stimuli were delivered by an experienced operator, previously verified as reliable for pressure and duration of contact (intra-operator ICC for 15 trials >0.92 for both). After each stimulus, the exact location was moved slightly ($\sim 10\text{ mm}$) to allow the skin to return to pre-stimulus temperature. The operator was blinded to which light turned on, and to the timing of the light, but not to the location of the panel, on which the lights were fixed. Each subject received 32 stimuli. Interstimulus interval was randomly between 25 and 35 s. This paradigm meant that there were four stimuli delivered in each of eight conditions (Table 1).

2.4. Measures

After each stimulus, several visual analogue scales (VAS) were presented on a computer screen in random order. The VAS regarded four aspects of the experience evoked by the stimulus: temperature (anchored at left with “extremely cold” and at right with “extremely hot”), pain unpleasantness, pain intensity (both anchored at left with “not at all” and at right with “most”) and pressure (anchored at left with “none” and at right with “extreme”). Subjects moved the marker using a computer mouse, held in their non-experimental hand. The average VAS score from four stimuli in each condition were the primary outcome measures that were used for analysis. No feedback was given about the subject’s VAS or volunteered responses.

Table 1

There were eight conditions, representing two levels each of three factors: CUE, WARNING and VISUAL

Condition	CUE colour of visual cue Randomised	WARNING stimulus and cue simultaneous or stimulus delayed Randomised	VISUAL subject looking towards or away from the stimulus Block randomised
1	Blue	Simultaneous	Towards
2	Blue	Simultaneous	Away
3	Blue	Delayed	Towards
4	Blue	Delayed	Away
5	Red	Simultaneous	Towards
6	Red	Simultaneous	Away
7	Red	Delayed	Towards
8	Red	Delayed	Away

2.5. Design

The first factor related to the evaluative context of the stimulus and concerned the colour of a visual cue. This factor was called CUE, with two levels – blue or red. Subjects were told that the blue light denoted ‘cold’ and the red light denoted ‘hot’ (Arntz and Claassens, 2004). We chose these colours to maximise the evaluative potency of the visual cues – red is widely linked to hot and blue to cold, which makes the cues implicitly meaningful. The second factor related to the temporal context of the stimulus. The stimulus occurred either simultaneous with the visual cue, or after the cue by a period between 1 and 2 s. The delay between cue and stimulus was varied to avoid the subject predicting the exact moment of contact. This factor was called WARNING (Fig. 1a). The third factor related to visual input of the stimulus and was manipulated by changing the location of the panel that held the lights. For one set of stimuli, the panel was attached at the base of device that held the probe, which meant that the lights were ~5 mm above the skin when the probe made contact (Fig. 1b). This was done so that subjects could look at the stimulus regardless of the timing of the visual cue. During these trials, subjects were told to look at the stimulus. For the other set of stimuli, the panel was placed at head-height on the opposite side of the subject. During these trials, subjects were told to look at the lights. In neither case were the lights visible to the operator of the device. This factor was called VISUAL (Fig. 1b). For convenience, the location of the lights was not randomised for individual stimuli, but rather block-randomised so that the location was changed once for each subject. Because a block

design probably makes it easier to ignore the visual cues, subjects were reminded between stimuli to look at the lights. Pilot trials demonstrated that by reminding subjects to look at the lights, there was no increase in reaction time in a choice reaction time task, which implies that subjects remain oriented toward the lights.

At the conclusion of data collection, subjects were debriefed as to the true purpose of the study and the true nature of the stimuli that were delivered.

2.6. Analysis

There were three hypotheses: (i) When the noxious stimulus is associated with a red visual cue, it hurts more and is perceived as hotter, than when the same stimulus is associated with a blue visual cue; (ii) When the visual cue precedes the stimulus, the stimulus hurts more than when the visual cue and the stimulus occur together; (iii) When the subject looks at the stimulus, it hurts more than when the subject looks away from the stimulus. To test these hypotheses, we undertook repeated measures analyses of covariance (ANCOVA) on each VAS, with factors CUE (red or blue), WARNING (cue before or together with stimulus) and VISUAL (looking toward or away from stimulus). Because gender may influence pain ratings (Fillingim, 2003), gender was included as a covariate. We adjusted for multiple measures such that significance was set at $\alpha = 0.025$.

Secondary analyses were undertaken for exploratory reasons. To investigate the association between the different ratings a series of Multi Level Analyses were done. First, the correlations between all measures were computed, ignoring the conditions. These correlations indicate to what degree

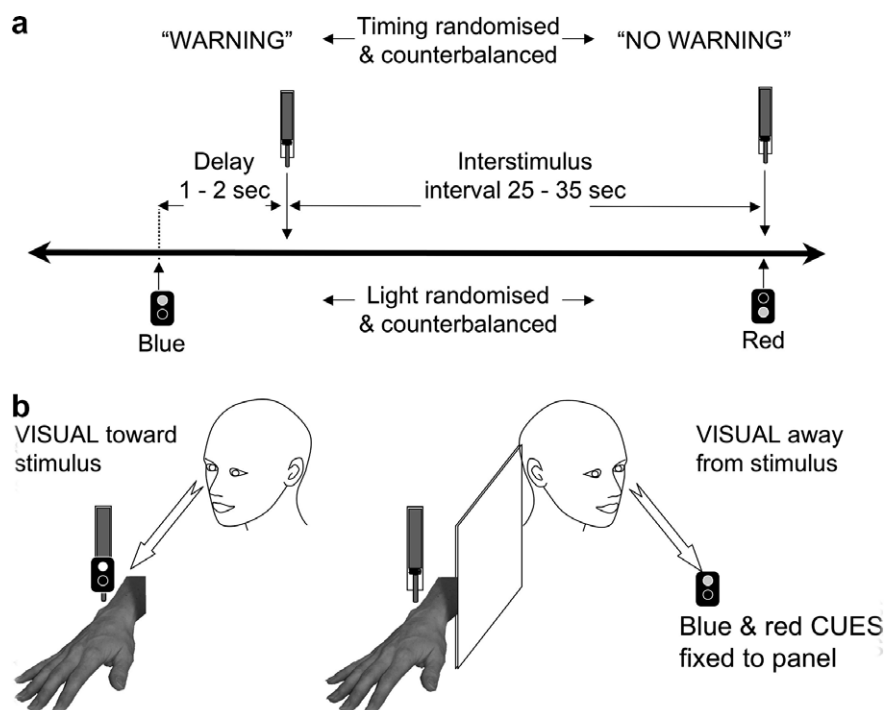


Fig. 1. Experimental set-up. The -20°C probe was applied to the back of the hand. (a) The colour of the visual CUE (red or blue) and the relative timing of the cold probe and the light (light before probe, ‘WARNING’ or light and probe simultaneously, ‘NO WARNING’). (b) The direction in which the subject looked (either VISUAL toward the stimulus or VISUAL away from the stimulus) during testing was block-randomised. The experimenter was blinded to which light and which timing was used for each stimulus, but not to the location of the panel.

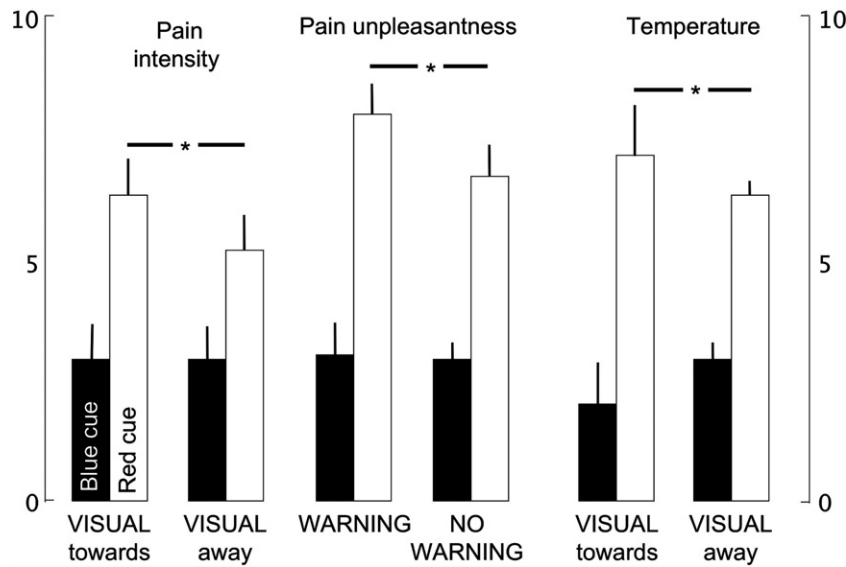


Fig. 2. Significant effects of visual attention and warning on visual analogue scale for pain unpleasantness and intensity (left Y bar; question = “how intense (unpleasant) was your pain?”; 0 = ‘not at all’, 10 = ‘most intense’ (‘unpleasant’)) and perceived temperature (right Y bar; question = “how would you rate the temperature of that stimulus; 0 = ‘extremely cold’, 10 = ‘extremely hot’), of a -20°C stimulus applied to the back of the hand. Group mean (columns) and standard error of the mean (error bars), for trials associated with the blue visual CUE (filled columns) or red visual CUE (open columns). Note effect of subject looking at the stimulus (VISUAL towards) or away from the stimulus on pain intensity and temperature, but only in association with the red visual cue. Note also effect of WARNING, again only in association with the red visual cue. Asterisk denotes significant ($p < 0.025$).

the ratings correlate over the eight experimental conditions. Next, the experimental conditions and their interactions were entered in the analysis. With this analysis the average correlations within conditions, and influences of experimental factors and their interactions were assessed.

3. Results

There was no effect of gender. The control measure, VAS for perceived pressure of the stimulus, was not affected by any of the experimental manipulations.

3.1. Effects of visual cue, warning and visual attention on pain and temperature ratings (Fig. 2)

There was a main effect of CUE on each VAS ($F(1,31) > 13$, $p < 0.002$ for all). When the red light

was on, the stimulus was rated as hotter (mean, 95% CI = 7.3, 6.2–8.4), and the evoked pain was rated as more unpleasant (mean, 95% CI = 6.3, 5.7–6.8) and more intense (mean, 95% CI = 5.6, 5.1–6.1), than when the blue light was on (mean, 95% CI = 1.8, 1.0–2.6 for temperature; 2.8, 2.0–3.6 for pain unpleasantness; 2.6, 2.0–3.2 for pain intensity). There was no main effect of WARNING or VISUAL.

3.2. Interactive effects between the cue, warning and visual attention on pain and temperature ratings

There was an interaction between CUE and WARNING on pain unpleasantness and an interaction between CUE and VISUAL on temperature and pain intensity (Table 2).

Table 2

Mean (95% CI) for each VAS for significant interactions between CUE and TIMING, and between CUE and SPATIAL

	Temperature	Pain unpleasantness	Pain intensity
RED CUE × TIMING			
Stimulus delayed	5.2 (4.6–5.9) $F = 2.71$, $p = 0.112$	6.9 (6.4–7.3) $F = 5.56$, $p = 0.025$	4.9 (4.2–5.6) $F = 2.49$, $p = 0.125$
Stimulus and cue simultaneous	4.8 (4.1–5.6)	5.8 (5.3–6.4)	5.2 (4.7–5.7)
RED CUE × SPATIAL			
Looking at stimulus	8.3 (7.5–8.9) $F = 5.69$, $p = 0.023$	6.3 (5.8–6.8) $F = 0.001$, $p = 0.971$	5.5 (5.1–5.9) $F = 5.62$, $p = 0.025$
Looking away from stimulus	6.3 (5.6–7.0)	6.3 (5.7–6.8)	4.6 (4.2–5.0)

F -values (1,31) and p -values for repeated measures ANCOVAs, with three two-level factors: CUE (blue/red), TIMING (before/together) and SPATIAL (at stimulus/away) undertaken on mean visual analogue scale (VAS) score from four stimuli in each condition are also shown. Bold shows significant interactions at $\alpha = 0.025$.

Table 3

Correlations between self-report measures without correction for condition effects

	Unpleasantness	Pain intensity	Pressure
Temperature	.59***	.43***	-.08
Unpleasantness		.46***	-.01
Pain Intensity			.03

* $p < .05$; ** $p < .01$; *** $p < .001$ (2-tailed).

- (i) CUE \times WARNING: When the red light was on subjects rated the evoked pain as more unpleasant if the light preceded the stimulus than if it occurred at the same time as the stimulus. They did not rate the stimulus as hotter, nor the pain as more intense.
- (ii) CUE \times VISUAL: When the red light was on, subjects rated the pain as more intense and hotter, if they were watching the stimulus than if they were not. However, subjects did not rate the pain as more unpleasant.

3.3. Relationship between pain and temperature ratings

Table 3 presents the correlations between the self-report measures without correction for experimental conditions. As is clear from the table, all subjective ratings covary strongly over conditions. Only pressure is not related to the other variables. When the $2 \times 2 \times 2$ experimental factors are added in the analyses, the correlations become non-significant. This indicates that the experimental manipulations were responsible for most of their covariance (Table 4). The association between temperature and unpleasantness was however modified by a significant interaction with CUE condition, $F(1,248) = 12.16$, $p < .001$. In the red cue conditions, temperature and unpleasantness correlated positively ($r = .32$), in the blue condition slightly negatively ($r = -.11$). Thus, when the stimulus was cued as hot, higher temperature ratings were associated with higher unpleasantness ratings. Moreover, the association between unpleasantness and intensity ratings was modified by a significant CUE \times WARNING interaction, $F(1,248) = 7.91$, $p < .01$. In the red and no delay trials, unpleasantness and intensity ratings correlated positively, $r = .43$; whereas in the blue and delay conditions

Table 4

Correlations between self-report measures with correction for condition effects

	Unpleasantness	Pain intensity	Pressure
Temperature	.10*	.00	-.06
Unpleasantness		.07	.07
Pain intensity			.10

* $p < .10$ (2-tailed).

the correlations were small and N.S. All other condition effects on correlations were N.S.

4. Discussion

These results uphold the first hypothesis that when the noxious stimulus is associated with a red visual cue, signalling that the stimulus is hot, it hurts more and is perceived as hotter, than when the same stimulus is associated with a blue visual cue, signalling that the stimulus is cold. The results also uphold the hypotheses that the stimulus hurts more when the visual cue precedes the stimulus than when it doesn't and that the stimulus hurts more when the subjects look at it than when they don't, but only for trials in which the stimulus was associated with the red visual cue. That there were differential effects on pain unpleasantness and pain intensity suggest the effect is mode-specific and unlikely to reflect a reporting bias.

That evaluative context of the noxious stimulus affects the pain it evokes corroborates a previous study (Arntz and Claassens, 2004) and that warning increased pain ratings is broadly consistent with investigations of expectation of pain. For example, expecting a painful stimulus enhances the cortical response to a non-noxious stimulus (Arntz and Hopmans, 1998; Chua et al., 1999; Ploghaus et al., 1999; Sawamoto et al., 2000) and increases pain ratings in response to a noxious stimulus (Fields, 2000; Lorenz et al., 2005; Keltner et al., 2006). It is notable that in the current study warning affected pain unpleasantness but not pain intensity. Also, warning about the stimulus only had an effect on ratings when the stimulus was associated with the red visual cue and, when the stimulus was cued with a red light but there was no delay, unpleasantness and intensity ratings correlated positively, while in the other conditions they didn't. This effect is consistent with the literature, which suggests that the effect of expectation occurs at higher pain ratings, in the order of those evoked here in association with the red light but not the blue light (Chua et al., 1999; Ploghaus et al., 1999; Fields, 2000; Sawamoto et al., 2000; Keltner et al., 2006). This intensity-dependent effect may also apply to the effect of looking at the stimulus, which only increased pain in association with the red cue. What seems to be important then is that top-down processes can guide information processing such that the evaluative cue, or the meaning of the stimulus, is important for other modulating processes to take place. Furthermore, it seems that top-down processes can have differential effects on the information processing within the sensory-discriminative and affective-motivational domains.

Sensory-discriminative performance in response to a non-noxious stimulus is affected by looking at it – tactile acuity increases and tactile threshold decreases. Those

effects have been attributed to modulation of attention and cross-modal interaction (see Maravita et al., 2003; Spence et al., 2004 for reviews). Although many studies have investigated the interrelationship between attention and pain (Matthews et al., 1980; Eccleston, 1994; Crombez et al., 1996, 1997; Asmundson et al., 1997; Duckworth et al., 1997; Eccleston et al., 1997; McCracken, 1997; Crombez et al., 1998a, 1999; Eccleston and Crombez, 1999; Peters et al., 2000), consensus is lacking: some data suggest that attending to pain amplifies it and attending away from pain nullifies it, and others suggest the opposite.

Most studies that have investigated *spatial* attention and pain have been interested in the impact on information processing performance and only recently has the effect of looking at a noxious stimulus been investigated (Naveteur et al., 2005). That study used a dual task paradigm: First, subjects indicated when an electrocutaneous stimulus delivered to one hand became painful (pain threshold). Second, subjects had to concentrate on a LED light and press a button when the intensity of the LED light changed, which occurred approximately once every 5 s. This maintained their visual orientation either towards or away from the stimulus. Pain threshold was higher when the LED light was placed ipsilateral to the stimulated hand and the authors suggest that the result may be evidence that orienting to pain *inhibits* defensive responses and negative affect associated with noxious stimuli (Donaldson et al., 2003). The current data contrast with that – here, looking in the direction of the stimulus *increased* pain intensity and perceived temperature. The contrast may relate to their use of different modalities, or of a demanding cognitive task (Naveteur et al., 2005). In such a task, the effect on pain may relate to the load that pain imparts on central nervous system resources rather than the effect of looking towards or away from the stimulus. Thus, the current data add to the debate, rather than settle it.

Relevant to the spatial data obtained in the current work is the fact that this condition was block randomised, which has three possible implications. First, repeated trials make visual cues easier to ignore. Although pilot work established that reminding subjects to look at the lights eliminated any effect on reaction time to the cues, it remains possible that attention to the cues wavered. Second, subjects may not have actually looked at the stimuli. Although this doesn't undermine the main findings, it raises the possibility that other effects went undetected. Third, because the device operator was not blind to the location of the lights, there may have been a bias in the way they applied the probe. This is important because greater pressure would change skin temperature more rapidly and thus increase cutaneous receptor discharge (Meyer et al., 2006). Although any change in pressure was not detected by the pressure

ratings, and pressure ratings did not relate to other ratings, this possibility can't be ruled out. Further work should clarify these issues.

Contrasting with the effect of warning on pain unpleasantness and not on pain intensity was the effect of visual direction on pain intensity but not unpleasantness. That is, looking at the stimulus up-modulated the sensory-discriminative, but not the affective-emotional, domain of pain. This seems consistent with what happens when we look at a non-noxious tactile input – increase in tactile acuity and decrease in tactile detection threshold, but no reported changes in perceived magnitude or unpleasantness (Spence, 2002). The nature of the effects of vision underpins proposals that it depends on local changes in the response profile of bimodal (visuo-tactile) cells within S1 (Zhou and Fuster, 2000), or within the dendritic arbour of S1 (Buonomano and Merzenich, 1998), or within other brain areas that deal with bimodal information, for example superior colliculus (Meredith and Stein, 1986). However, it seems we don't really know where it happens. We don't know how it happens either – the early “energy summation mechanism” proposal, which states that subthreshold inputs from each modality sum to evoke a response in the target neuron (Todd, 1912), might apply, but so might other theories (see Diederich and Colonius, 2004 for review of such theories).

The current study did not measure anxiety, catastrophic thinking or fear of pain, which is a limitation. The likely effect of the protocol on anxiety is not obvious. For example, anxiety might have been greater when subjects were warned that the stimulus would be very hot, because very hot is perceived to be more dangerous (in the sense of tissue damaging) than very cold (Arntz and Claassens, 2004). On the other hand, anxiety might have been greater when there was no warning because the type of stimulus would then be unpredictable. Then again, some individuals find unpredictable noxious stimuli to be less anxiety-provoking than predictable noxious stimuli (Moseley et al., 2003). The effect of anxiety on pain is not obvious either. Some reports link increased anxiety to increased pain during clinical procedures (Gore et al., 2005; Pud and Amit, 2005; Schupp et al., 2005; Klages et al., 2006) and during experimentally induced pain (Tang and Gibson, 2005), but other reports suggest no effect (Arntz et al., 1990, 1994). Relevant reviews conclude that the influence of anxiety on pain is probably largely dependent on attention (Arntz et al., 1994; Ploghaus et al., 2003).

Catastrophic thinking about pain, fear and neuroticism has been linked to biases in attention to pain-relevant cues (Goubert et al., 2004; Van Damme et al., 2004a,b). This study did not aim to elucidate the impact of these variables, but one might expect that they would influence the effects observed in the current work. Future studies could verify this.

In summary, the current work suggests that the tissue-damaging meaning of a noxious stimulus, warning about the stimulus and visual attention to the stimulus all affect the evoked experience. Importantly, warning and visual attention only affected ratings in association with the red visual cue (i.e., with information suggesting potential tissue damage), which suggests that those contextual factors depend on the evaluative context of the stimulus, or its perceived intensity, or both. These findings provide evidence of a differential effect of different aspect of the stimulus' context on the sensory-discriminative and affective-emotional dimensions of pain.

Acknowledgement

G.L.M. is supported by a Nuffield Medical Research Fellowship.

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