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Pain relief as an opponent process: a psychophysical investigation

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Abstract

Relief from pain in humans is frequently measured by computing the reduction on an 11-point pain intensity scale. However, this definition of relief may be insufficient to capture the utility of pain relief for the individual. Based on pain literature and evidence from studies examining relief and reward, it is clear that pain relief is a broad concept comprising several factors, only one of which is pain intensity reduction. According to opponent process theory, all sensations consist of a primary process and a slow 'opponent process' of opposite valence, the purpose of which is to reduce the deviation from homeostatic balance. Here, opponent process theory provided a framework to explore the interaction between pain, relief and reward. We devised three psychophysical studies examining the temporal (Experiment I) and magnitude (Experiments I and II) relationships between pain severity and its subsequent relief. In Experiment III, we further manipulated the magnitude and pleasantness of relief experienced by applying innocuous cooling following noxious heat stimulation of capsaicin-sensitized skin. Results confirmed predictions from opponent process theory and showed that pain intensity reduction was significantly stronger than relief intensity ratings. Furthermore, continuous relief ratings appeared to reflect the speed of pain intensity reduction. Varying pain intensity parametrically confirmed that relief increases with pain intensity. That innocuous cooling following primary hyperalgesia intervention significantly increased the intensity, pleasantness and duration of relief provides further evidence that pain relief encapsulates more than a reduction in pain intensity. Importantly, the high relief pleasantness ratings confirmed the hypothesized link between relief and reward.

Introduction

Relief from pain is most often measured by computing the reduction on an 11-point pain intensity scale (Farrar *et al.*, 2001). However, clinicians have long noted that patients often describe their pain experiences in terms of relief (Huskisson, 1974; Bird & Dixon, 1987) and there is growing evidence that global ratings of pain relief represent something more than merely pre-treatment to post-treatment changes in pain intensity (Jensen *et al.*, 2005). Relief scales have been used to determine the clinical importance of analgesic drug treatments (Farrar *et al.*, 2000, 2001). Interestingly, many analgesic drugs that cause pain relief are also considered highly pleasurable and rewarding. It has been suggested that pleasure (reward) and analgesia might share a common neural substrate (Franklin, 1998).

The rewarding effect of relief from unpleasant states other than pain is well documented. For instance, food tastes better when it relieves hunger (Small *et al.*, 2001; Kringelbach *et al.*, 2003). In general, the reward value (pleasantness) of a stimulus increases the more effective that stimulus is in restoring bodily equilibrium (homeostasis) (Cabanac, 1979; Craig, 2003). The opponent process theory (Solomon & Corbit, 1974) proposes that all deviations from homeostasis are accompanied by an opponent process and that, if the primary sensation is abruptly terminated, a sensation of the opposite valence will be felt (Fig. 1). Thus, a painful sensation, if removed quickly enough, would be replaced briefly by a pleasant feeling that may be conceptualized as a sensation of pain relief. The opponent process framework has proven useful in the understanding of drug addiction (Koob & Le Moal, 2001).

Here, we devised three psychophysical studies where relief was induced by the cessation of noxious thermal stimulation to test certain predictions of the opponent process model with respect to pain and relief. Importantly, because relief is thought to be caused by an opponent process that is weaker and slower than the original unpleasant feeling, the model predicts that relief from an unpleasant sensation is always less intense than the unpleasant sensation itself (Solomon, 1980). This hypothesis was tested in Experiment I, which also employed continuous ratings of pain and relief intensity to investigate the temporal relationship between these two measures. The opponent process theory predicts that the degree of relief experienced depends on the speed with which the unpleasant sensation or state is terminated. The prediction that relief is stronger with more unpleasant sensations was tested in Experiment II, where we used a parametric design to investigate the correlation between pain and its relief. We also investigated the relationship between relief and pain-related arousal, as measured by galvanic skin response. Experiment III was designed to test the prediction that the opponent process of pain is rewarding, and measured the intensity and pleasantness of relief from hyperalgesic skin using the heat/capsaicin model of hyperalgesia (Petersen & Rowbotham, 1999). This experiment employed an

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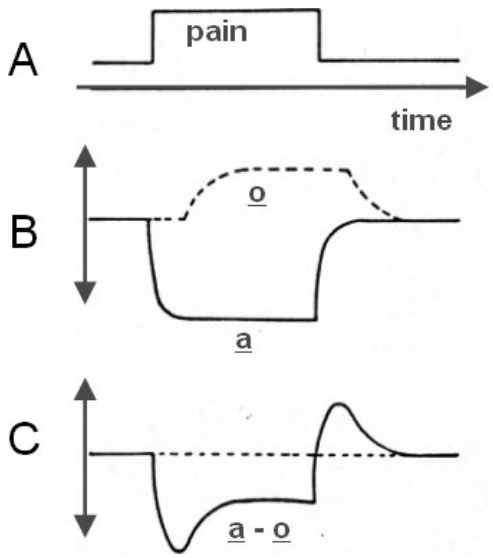

FIG. 1. The opponent process theory. (A) Outline of the event (painful thermal stimulation). The arrows in B and C signal hedonic valence. a, primary process, reflecting negative valence; o, opponent process. (C) Net result of the two opposing processes. The late peak reflects pleasant relief. Adapted from Solomon & Corbit (1974, p. 128) with permission.

intervention (innocuous cooling) following the noxious heat stimulus to investigate whether pleasant pain relief may be modulated by factors other than a reduction in pain intensity.

Materials and methods

Overview

Three experiments were conducted during this investigation (see Fig. 2 for an overview of methods and results). The methods shared by all studies are outlined in this section. The experiment-specific methods are described in more detail in the following sections. All experiments had local ethics committee approval (Oxford Research Ethics Committee; OxREC) and conformed to the guidelines of the Declaration of Helsinki (1996).

Subjects

Subjects for all three studies were healthy right-handed adult volunteers. Of the 27 subjects recruited, 11 participated in two or more of the three experiments. All subjects gave informed consent

Relief measurements

Brief noxious thermal stimulation was used to elicit relief. Subjects rated relief at the end of each painful heat stimulus. To explain to the subjects the relief sensation that we were measuring, we asked them to imagine the relief that they would feel when, after holding onto a painfully hot cup for some seconds, they were finally able to put the cup down. Subjects moved a mechanical slider to indicate the level of relief that they had felt after the cessation of each noxious heat stimulus using a visual analogue scale (VAS) with the anchors 'no relief' and 'intense relief'. In Experiment II, subjects indicated their maximal level of relief, whereas Experiments I and III required subjects to give continuous ratings of relief, tracking the entire period that they experienced relief. Before each experiment, subjects were given two to three practice stimuli to help to familiarize them with the rating procedure. We defined the onset of relief ratings as the first time-point after the beginning of each heat stimulus, where relief ratings exceeded 0 on the 11-point relief VAS. Similarly, the end of relief was defined as the last point where relief ratings > 0. As all noxious heat stimuli returned promptly to a non-painful baseline temperature, we computed pain intensity reduction as the difference between the level of reported pain (e.g. 7/10) and no pain (0/10). Subjects did not report any burns or skin injury following participation in any of the experiments described below.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, USA). Correction for multiple comparisons was performed using the Greenhouse-Geisser correction algorithm.

Experiment I

Temporal relationship between pain and relief

Subjects

Ten healthy right-handed adult volunteers (age 28.6 ± 7.1 years, mean ± SD, seven females, three males) were recruited for this experiment. One dataset was incomplete due to technical difficulties. One other subject failed to comply with experiment instructions. Both datasets were excluded from analysis, giving a final study group size of 8.

Stimulus presentation

We used an in-house-developed thermal resistor with a 15 × 20 mm thermode to deliver noxious thermal stimulation (3 s at destination temperature) to the back of the subject's left hand. The same device has been used in several previous studies by our group (Wise *et al.*, 2002; Brooks *et al.*, 2005; Fairhurst *et al.*, 2007). The device has a fast rise time (30°C rise in 0.8 s) and is internally self-calibrating, which ensures that the correct temperature is delivered. For each subject, we determined a temperature corresponding to a rating of seven on the 11-point pain intensity scale. The average temperature of the noxious stimuli was 55.6 ± 2.8°C (mean ± SD). The study was divided into two runs of 10 stimuli with an inter-stimulus interval of 60 s. The two runs were separated by a short gap of ∼5 min.

Behavioural measurements

Subjects gave continuous ratings of pain intensity in one run and of relief intensity in the other. Consistent with the relief VAS, the VAS for pain had the anchors 'no pain' and 'intense pain'. The order of presentation of the two runs was counterbalanced across subjects.

Statistical analysis

To test for a significant difference between pain intensity and relief ratings, we extracted the maximum intensity of each continuous pain and relief rating, and entered each subject's mean ratings into a paired *t*-test. To characterize the temporal profile of pain and relief, we measured the time-points of onset, peak and end of the continuous ratings for each subject. In addition, we used Matlab 7.1 (The Mathworks Inc., Natick, MA, USA) to calculate the first derivative of the mean pain ratings for each subject. From this, we identified the time-point of greatest decrease in pain intensity. A paired *t*-test was used to test for significant differences between the temporal measures.

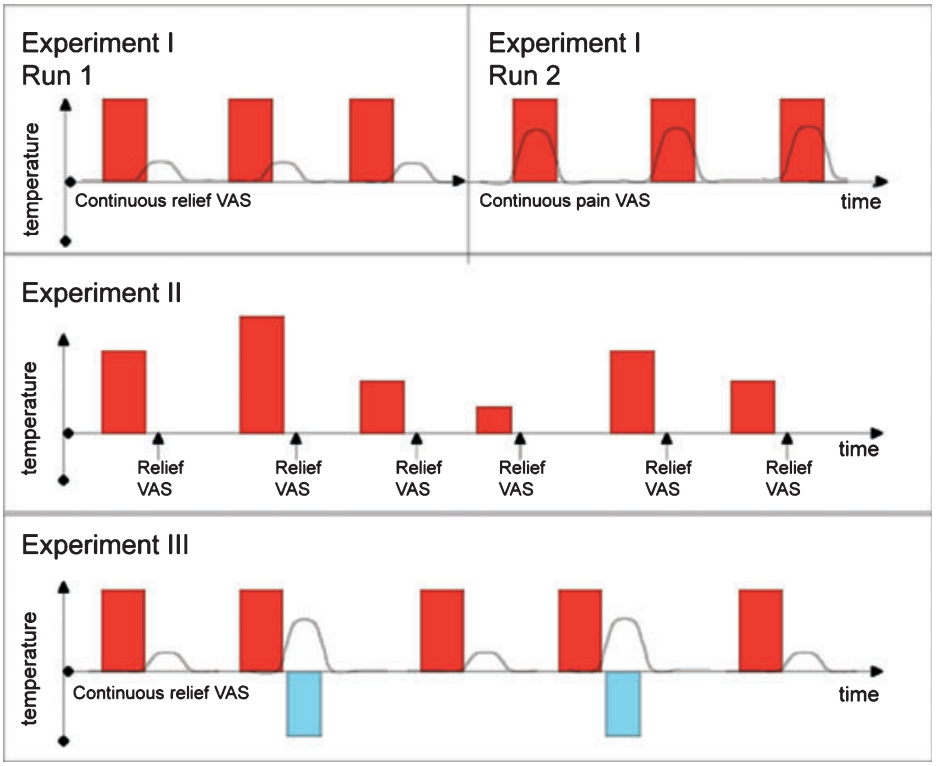

FIG. 2. Overview of experimental design for Experiments I-III. In Experiment I, the two near-identical runs differed only in whether relief or pain intensity was being rated. In Run 1, subjects gave continuous ratings of relief perception, whereas in Run 2 they rated pain in a similar fashion. The order of the two runs was counterbalanced. Experiment II employed a parametric design with four pain intensities. Non-continuous (VAS) relief ratings were obtained after each event. Although the temperature of the noxious stimulus was kept the same in Experiment III, relief was modulated by additional innocuous cooling of the skin. After every other heat stimulus, the capsaicin-treated skin was cooled to 25°C for 3 s. Subjects rated relief continuously after each heat event.

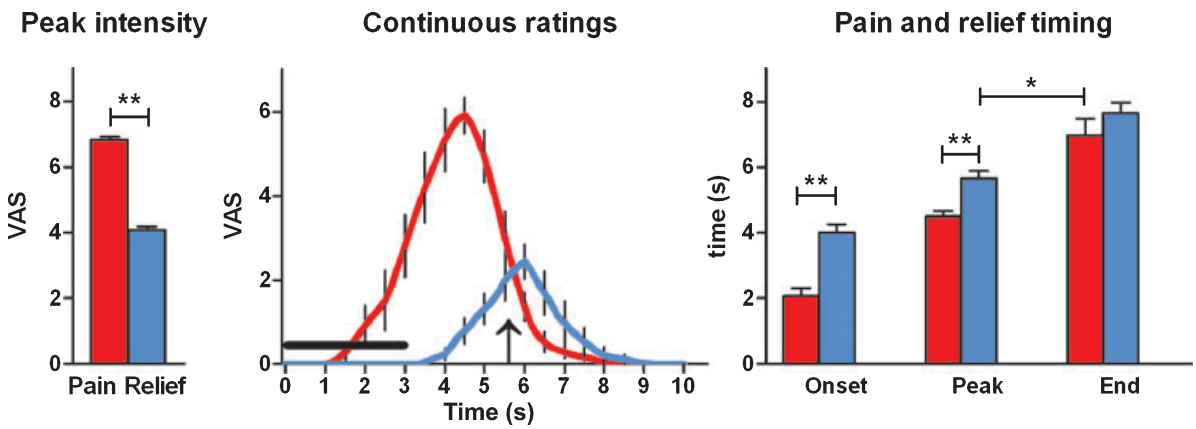

FIG. 3. Continuous pain and relief intensity ratings. Pain measurements are depicted in red and relief measurements in blue. The left panel shows the mean peak intensity of the pain and relief ratings, which were significantly different ($P < 0.001$). The average continuous ratings are shown in the middle panel. Note that the averaging of each subject's ratings in this graph has resulted in smoothing of the onset and peak timing information. The horizontal black bar indicates the presence of the noxious stimulus. The arrow illustrates the time when the pain intensity reduction was fastest, as calculated from the first derivative of the pain intensity ratings. The bar chart to the right summarizes the temporal aspects of pain and relief ratings. As the chart illustrates, relief started significantly after the onset of pain and also peaked significantly later than the maximum pain rating (but before the end of the pain sensation). Note that relief onset was not significantly different from the time of the maximum pain. $^{**}P < 0.001$, $^{*}P < 0.05$. All bars denote SEM.

Results

Peak pain intensity and relief ratings

The mean peak pain intensity rating was 6.3 ± 1, significantly higher (paired *t*-test, $P < 0.001$) than the average maximum relief intensity rating (2.6 ± 0.9, mean ± SD, see Fig. 3). The mean pain and relief ratings were significantly correlated (Pearson's $r = 0.82$, $P = 0.012$). A repeated-measures ANOVA showed that the pain ratings did not change as a function of time during the course of the experiment ($F_{9,63} = 1.63$, $P = 0.20$). The same result was found for relief ratings ($F_{9,54} = 1.39$, $P = 0.27$).

Relative timing of pain and relief ratings

The temporal characteristics of the pain and relief ratings are summarized in Fig. 3. As expected, relief began after pain (mean lag 1.9 s, $P < 0.001$) and the maximum relief occurred significantly later than the peak in pain intensity (paired *t*-test, $P < 0.001$). Relief sensation reached its maximum before the end of the reported pain sensation (mean lag 1.3 s, $P = 0.036$). The point at which maximum relief occurred was not significantly different from the time of maximum pain intensity reduction, as calculated from the minimum of the first derivative of each subject's mean pain rating ($P = 0.104$). On average, relief began 0.5 s before the maximum pain intensity report but this difference was not significant ($P = 0.07$) (Fig. 3).

Experiment II

Correlation between pain intensity and relief magnitude

Subjects

Sixteen healthy right-handed adult volunteers (age 30.3 ± 5.9 years, mean ± SD, nine males, seven females) were recruited for this experiment.

Stimulus presentation

We used the thermal resistor described above for Experiment I to deliver noxious thermal stimulation (3 s at destination temperature) to the volar aspect of the subject's left arm. The experiment consisted of four conditions: pain threshold, mild pain, moderate pain and intense pain. For each subject, we determined four temperatures of the thermal resistor that provoked pain intensity ratings of 1, 3, 5 and 7 on the 11-point numerical scale. The average four temperatures used in these four pain intensity conditions were 50.1 ± 3.4, 52.3 ± 2.7, 54.3 ± 2.2 and 56.0 ± 2.1°C, respectively (mean ± SD). Each condition consisted of six repetitions of one of the four temperatures. The 24 stimuli were presented in a pseudo-randomized order. The inter-stimulus interval was pseudo-randomized (range 45–75 s, mean 60 s). Each stimulus was preceded by a 3 s visual cue.

Behavioural measurements

At 10 s after the termination of each heat stimulus, the relief VAS was displayed on a screen for 5 s. Subjects were specifically instructed to rate only the relief elicited by the cessation of the stimulus. This was to avoid interference from any relief that they might have felt simply because the heat stimulation was not of the highest intensity during that particular trial. After rating relief intensity subjects made a written note of the pain intensity of the heat stimulus using the standard 11-point numerical rating scale. The relief and pain intensity rating scales were made as different from each other as possible to ensure that subjects treated the two ratings as independent.

Physiological measurements

The galvanic skin response is considered a measure of general arousal. Skin conductance changes with the activation of the sweat glands, mediated by the sympathetic nervous system (Critchley *et al.*, 2002). Galvanic skin responses were recorded at 100 Hz throughout the experiment using a Data Lab 2000 (Lafayette Instruments Company, Loughborough, UK). The electrodes were fastened securely on two fingers on the subject's left hand. The physiological data were pre-processed (smoothing, peak detection) in MATLAB 7.1. Galvanic skin responses were computed for an 8 s period following the onset of each heat stimulus. The baseline was defined as the duration from the end of the rating period until the onset of the next event cue. Two physiological datasets were incomplete due to technical difficulties and were excluded from the physiological data analysis.

Statistical analysis

For pain intensity and relief ratings as well as galvanic skin responses, repeated-measures ANOVAs were used to test for main effect of condition and for linear increases across the four temperature conditions. We also tested the correlation between pain intensity and relief ratings across the pain intensity spectrum by using each subject's mean ratings from each of the four conditions.

Results

Pain and relief intensity perception

The mean pain intensity and relief ratings are summarized in Fig. 4. Both pain intensity and relief ratings increased across the four separate pain intensity conditions (repeated-measures ANOVA, linear trend, $P < 0.001$). Because we wanted to measure relief from pain, those events that failed to elicit pain were excluded from analysis (average number of events excluded per subject: 1.0 ± 1.0, range 0–3). The ratings of pain intensity and relief were significantly correlated (Spearman's $r = 0.80$, $P < 0.001$, see Fig. 4). Repeated-measures ANOVAs showed that the pain and relief ratings in the pain threshold, moderate and intense pain conditions did not change significantly as a function of time during the course of the experiment (pain: $P > 0.06$; relief: $P > 0.1$). Ratings in the mild pain condition, however, did differ significantly over time (pain: $F_{5,75} = 3.10$, $P = 0.03$; relief: $F_{5,75} = 5.30$, $P < 0.01$).

Autonomic measures

As illustrated in the top right-hand panel of Fig. 4, galvanic skin response changes increased across conditions (repeated-measures ANOVA, linear trend, $P < 0.001$). The galvanic skin response changes were significantly positively correlated with both pain ($r = 0.51$, $P < 0.001$) and relief ($r = 0.39$, $P = 0.003$).

Experiment III

Manipulating relief pleasantness

Subjects

Fourteen healthy right-handed adult volunteers (age 29.2 ± 6.9 years, mean ± SD, seven females, seven males) were recruited for this experiment. One dataset was incomplete due to technical difficulties and was excluded from analysis, giving a final study group size of 13.

Induction of thermal hyperalgesia

This experiment employed the heat/capsaicin model (Petersen & Rowbotham, 1999; Dirks *et al.*, 2003) to create primary and secondary thermal hyperalgesia. A 30 × 30 mm area of the skin was heated to 45°C for 5 min before application of capsaicin cream (0.075% Axsain; Bioglan Laboratories Ltd, Hitchin, UK). The cream was removed after 45 min.

Stimulus presentation

We used a thermal stimulator with a 30 × 30 mm thermode (TSA-II; Medoc Advanced Medical Systems, Haifa, Israel) to deliver noxious heat (5 s at destination temperature) to the base of the thumb of the subject's left hand. This device was also used to cool the skin to 25°C

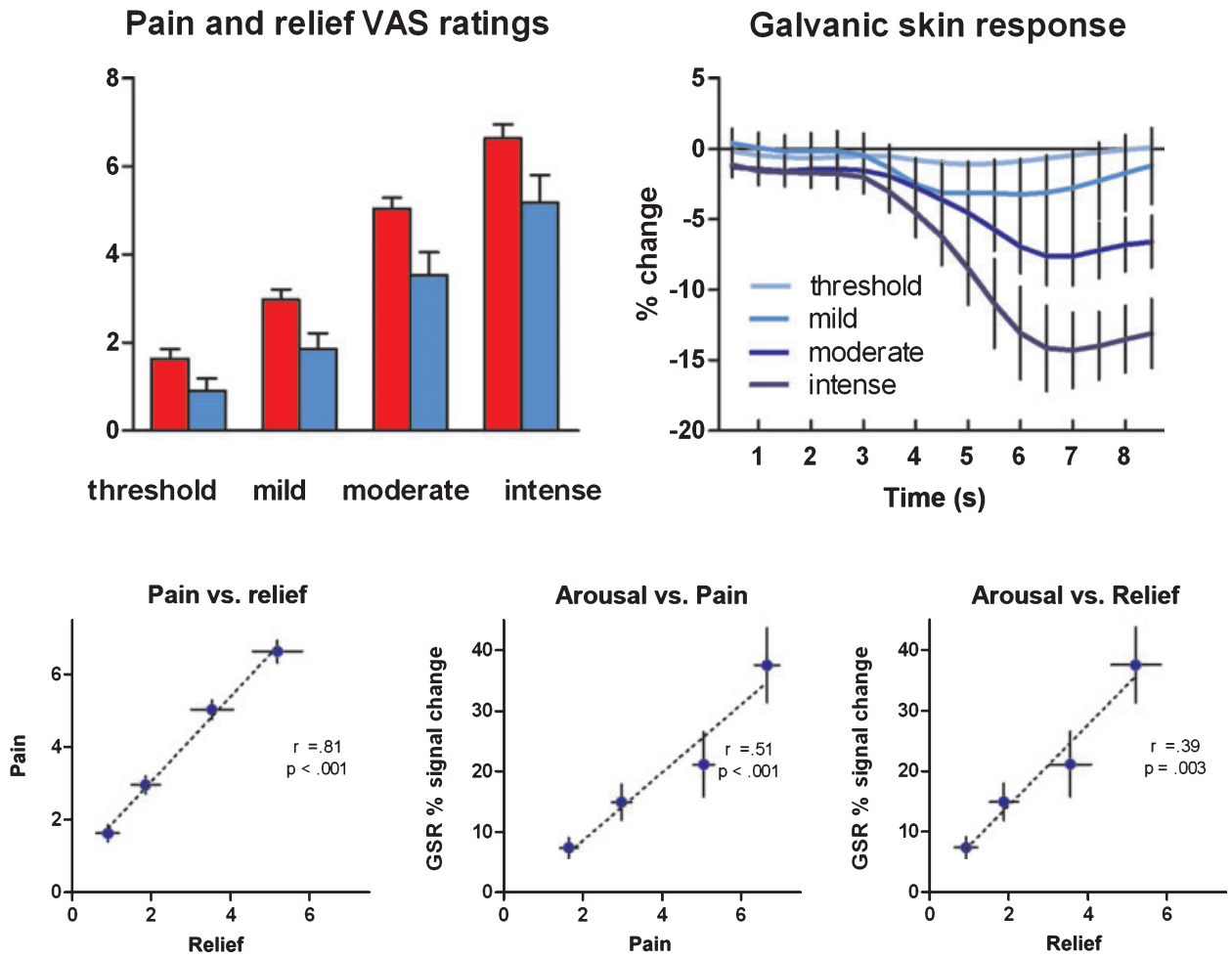

FIG. 4. Experiment II. Pain and relief intensity ratings and autonomic measures. The top left panel depicts pain (red) and relief (blue) ratings across the four conditions. The top right panel shows the mean galvanic skin response for each condition over time. The three bottom panels show the significant correlations between relief and pain intensity, and between pain and relief ratings and arousal, as measured by galvanic skin response changes. All bars denote SEM.

(3 s at destination temperature). The temperature ramp rate was set to 9°C/s. For each subject, we determined a temperature corresponding to a rating of seven on the 11-point pain intensity scale on the same patch of skin both before and after applying the heat/capsaicin model. Before the application of the heat/capsaicin model, the average stimulus temperature corresponding to a rating of 7/10 on the 11-point pain intensity scale was 48.4 ± 1.9°C (mean ± SD). The temperature required to yield the same pain intensity post-capsaicin treatment was significantly lower (46.0 ± 3.4°C, mean ± SD, $P = 0.035$), confirming the existence of capsaicin-induced primary thermal hyperalgesia.

The post-capsaicin treatment temperature was presented for 5 s a total of 20 times during the experiment to the area of primary hyperalgesia. An inter-stimulus interval of 30 s was used. There were two conditions. After every other noxious heat stimulus, the temperature of the thermode returned to baseline (35°C; baseline condition). After the other heat stimuli the thermode was cooled to 25°C for 3 s before returning to baseline (cooling condition). Subjects were informed that cooling would occur after every other heat stimulus. Pilot data indicated that cooling capsaicin-treated skin after applying noxious heat increased the pleasantness of relief. This cooling relief effect was much weaker in untreated skin heated to the same pain intensity level (data not shown).

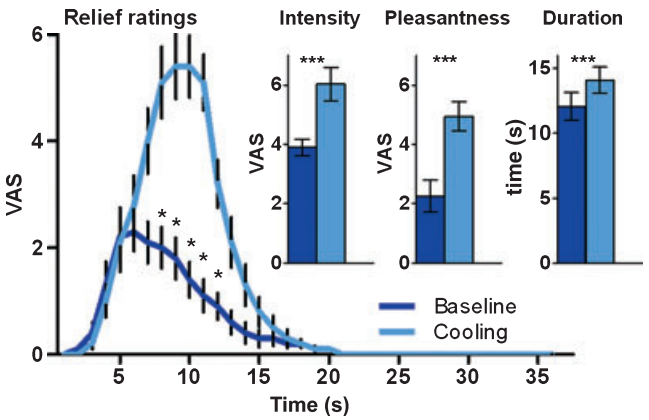

FIG. 5. Ratings of relief elicited by the return to baseline temperature from noxious heat (baseline condition) and from innocuous cooling (cooling condition). The average continuous ratings of cooling and non-cooling (baseline) relief are depicted in the main line graph (*$P < 0.05$, Bonferroni corrected). The bar charts illustrate significant increases in peak relief intensity, relief pleasantness and relief in the cooling condition. 0 s is defined as the time-point that marks the end of each heat plateau. ***$P < 0.001$. All bars denote SEM.

Behavioural measurements

Subjects were instructed to rate relief continuously after each painful heat stimulus. After the end of the relief sensation, but before the next stimulus, subjects gave verbal ratings of pain intensity and relief pleasantness on 11-point numerical rating scales. Consistent with the relief and pain intensity scales, the relief pleasantness scale had the anchors 'not pleasant' and 'intensely pleasant'. Stimulus pleasantness ratings are commonly used to measure the reward value of a stimulus (e.g. Gottfried *et al.*, 2003). After completion of the study, subjects reported average background pain sensation during the between-stimulus rest periods over the entire experiment on the standard 11-point pain intensity scale.

Statistical analysis

To test for significant differences between cooling and baseline relief, we extracted the maximum intensity of each continuous relief rating and entered each subject's mean ratings into a paired *t*-test. Mean pain intensity and relief pleasantness ratings from each relief condition were also compared using a paired *t*-test. To characterize the temporal profile of relief in the two conditions, we measured the time-point of maximum relief and the end of the continuous ratings for each subject. A paired *t*-test was used to test for significant differences between the temporal measures. Additional tests were applied to investigate the correlation between relief intensity and pleasantness ratings within each relief condition and across conditions (Pearson's correlation test).

Results

Relief ratings

All subjects reported finding pain relief with cooling more pleasant than pain relief without cooling (Fig. 5). The mean pleasantness rating in the cooling condition was 5.0 ± 1.8 (mean ± SD) vs. 2.3 ± 1.9 in the baseline condition (paired *t*-test, $P < 0.001$). The peak relief ratings were also higher during cooling (6.0 ± 2.1) than during baseline (3.9 ± 1.6, paired *t*-test, $P < 0.001$). Relief ratings in the two conditions first diverged after the peak of the baseline relief ratings, 8 s after the heat stimulus began ramping down (paired *t*-test, $P < 0.05$, Bonferroni corrected for multiple comparisons). At this point, the temperature had started to ramp up from the cooling stimulus but was still 9°C below the baseline of 35°C. The between-condition differences remained significant for 5 s. The time of the maximum relief was also increased with cooling (paired *t*-test, $P < 0.001$) and the duration was prolonged ($P < 0.001$). The level of relief intensity correlated with pleasantness ratings within both conditions (baseline condition: $r = 0.56$, $P = 0.048$; cooling condition: $r = 0.61$, $P = 0.027$) but not with pain intensity reduction (baseline condition: $r = 0.265$, $P = 0.38$; cooling condition: $r = 0.45$, $P = 0.12$). Across both conditions there was no significant correlation between relief measures and pain intensity reduction (relief intensity: $r = 0.38$, $P = 0.06$; relief pleasantness: $r = 0.104$, $P = 0.615$; relief duration: $r = 0.02$, $P = 0.90$). A repeated-measures ANOVA showed that the relief ratings did not change as a function of time during the course of the experiment (baseline condition: $F_{9,108} = 0.33$, $P = 0.866$; cooling condition: $F_{9,108} = 0.24$, $P = 0.869$).

Pain ratings

The mean pain intensity in the cooling condition was 7.1 ± 0.7 compared with 7.0 ± 0.7 in the baseline condition. A paired *t*-test showed that the small difference in pain intensity ratings between conditions (the mean difference in ratings was 0.18) was nevertheless significant ($P = 0.025$). A repeated-measures ANOVA showed that the pain ratings did not change as a function of time during the course of the experiment ($F_{19,228} = 1.49$, $P = 0.21$). In addition, six subjects also reported feeling mild tonic background pain at the baseline temperature (35°C) during the experiment (group average 1.7 ± 2.1 on the 11-point pain intensity scale, mean ± SD). The subjects who reported background pain did not differ from the other seven subjects in any measures of relief or in pain intensity elicited by the thermal heat stimulus (unpaired *t*-tests, $P > 0.24$).

Between-experiment comparison

Pain and relief ratings to intense pain

The three experiments described above used thermal heat pain to the dorsum of the hand, volar surface of the arm and thenar eminence of the hand, respectively. Furthermore, whereas the two first experiments stimulated normal skin for 3 s per stimulus, Experiment III stimulated capsaicin-treated hyperalgesic skin for 5 s. The rating scales also differed between studies. Experiment I used continuous pain and relief intensity ratings, whereas Experiment II utilized visual analogue (relief) and numerical rating (pain) scales after each stimulus. Experiment III employed continuous ratings for relief and a numerical rating scale for pain. Despite these methodological differences, the pain intensity ratings did not differ significantly between Experiments I and III or between those studies and the intense pain condition ratings in Experiment II (Experiment I: 6.3 ± 1.0; Experiment II: 6.6 ± 1.2; Experiment III: 7.0 ± 0.7; unpaired *t*-tests, $P > 0.66$ for all three comparisons). Relief ratings after intense pain stimulation (and no cooling) were also of similar intensity across the three experiments (Experiment I: 2.6 ± 0.9; Experiment II: 5.2 ± 2.5; Experiment III: 3.9 ± 1.6; unpaired *t*-tests, $P > 0.12$ for all three comparisons).

Discussion

The results from this series of experiments demonstrate that relief from brief experimental pain may be better understood within an opponent process framework than as a phenomenon accurately measured by pain intensity reduction. According to the opponent process theory, a pleasant sensation of pain relief should follow any rapidly terminated painful stimulus. The existence of such a sensation at the end of pain was confirmed in all three experiments reported here. The model also predicts that relief should be less intense than the initial pain sensation, as demonstrated in Experiment I, and that relief should increase as pain intensity is augmented, as confirmed by the results from Experiment II. The continuous rating data from Experiment I also suggest that the relief sensation is closely linked to the efficacy of the pain intensity reduction. A final prediction of the opponent process model tested here was that relief should be of opposite emotional valence from the pain. The relief pleasantness ratings from Experiment III confirmed this prediction, demonstrating clearly the close link between relief and reward. Note that this study employed the heat/capsaicin-sensitization model of central sensitization, suggesting that our findings on relief from experimentally induced pain may extend to some clinical pain situations. Although the temperature of painful stimuli was identical across conditions in Experiment III, the temperature following noxious heat was varied. That this intervention (cooling) significantly impacted on the magnitude and duration of

relief ratings provides further evidence that pain relief encapsulates more than a reduction in pain intensity.

The continuous relief ratings recorded in Experiment I show a striking resemblance to the positive affective peak following pain in the opponent process model (see Figs 1 and 3). As expected, the maximum relief intensity ratings were significantly lower than the pain intensity ratings. The continuous ratings obtained in this experiment also allowed for investigation of the temporal interrelationship between pain and relief. We found that subjects started reporting relief near to the time of maximum pain intensity and that the maximum relief corresponded closely to the time at which pain intensity decreased the most rapidly. Thus, it is possible that the relief ratings mirrored the efficacy (i.e. speed) of the pain intensity reduction, as predicted by homeostatic theories (Cabanac, 1979). It should be noted, however, that the duration of the noxious stimuli was not varied and the early onset of relief ratings may also reflect a learned expectation of pain intensity reduction. In Experiment II, subjects received four levels of brief noxious thermal heat stimulation, corresponding to pain threshold, mild, moderate and intense pain. The measures of pain intensity, arousal and relief intensity were all correlated, supporting the idea that the subjective utility of removing a severe and threatening pain should be higher than the utility of ending a milder pain.

Similarities in the brain's processing of relief and reward have been reported by functional and molecular imaging studies investigating the placebo effect (de la Fuente-Fernandez *et al.*, 2001; Scott *et al.*, 2007) and reward learning (Seymour *et al.*, 2005). In Experiment III, we used relief pleasantness ratings as a measure of the reward value of relief from pain. An established model of central sensitization, the heat/capsaicin model (Petersen & Rowbotham, 1999; Dirks *et al.*, 2003), was used to induce thermal hyperalgesia in the subject's skin. Pilot data using cooling after noxious heat in normal and sensitized skin suggested that the pleasantness of cooling increased during hyperalgesia. The subjective sensation in the sensitized skin is akin to that of moderate sunburn. Innocuous cooling is thought to reduce pain perception by inhibiting central pain processing in addition to hastening the return of the skin to a non-harmful temperature (Craig, 1998; Nahra & Plaghki, 2005). Prompt cooling is widely recommended as a treatment for burns (Davies, 1982; Nguyen *et al.*, 2002). We hypothesized that applying cooling to hyperalgesic skin would increase relief independently of the reduction in pain intensity, thus demonstrating that pain relief encompasses more than mere pain intensity reduction. Confirming this, both relief intensity and pleasantness significantly increased when the skin was cooled to 25°C. As expected, the two measures were highly correlated: when relief intensity increased, so did pleasantness ratings. The duration of relief was also increased by cooling the sensitized skin. It is possible that the increased pain relief reported in the cooling condition is a direct consequence of a faster pain intensity reduction facilitated by skin cooling.

A putative neurobiological mechanism for the opponent process of pain is the endogenous opioid system. It is well established that the brain releases endogenous opioids in response to painful stimulation (Zubieta *et al.*, 2001, 2005). Interestingly, a recent positron emission tomography study reported opioid activation of brain regions after pain, in what may be the first demonstration of opioid-driven pleasant relief after pain (Sprenger *et al.*, 2006). Interestingly, an opponent process-like pattern of opioid pain relief followed by opioid-induced hyperalgesia is commonly observed, which resembles the hyperalgesic effects of mu opioid antagonism (Koppert *et al.*, 2003). According to Solomon & Corbit (1974), opponent processes are more pronounced when the primary process ends abruptly, as may be the case with acute pain and during intravenous opioid analgesic drug treatment but not commonly the case in chronic pain. Opponent process theory is therefore more relevant for acute pain and fast onset analgesia, and it is within these areas that pain relief appears to be a more useful concept than pain intensity reduction (Farrar *et al.*, 2000, 2001).

The use of brief, experimental heat pain with fast and complete pain intensity reduction is a limitation of this study, as it is not clear from our results how pain relief would be affected in clinical situations, when pain intensity reduction is often slow and/or incomplete. The opponent process model predicts significantly less pleasant relief in response to a slow reduction in pain levels. Similarly, it is conceivable that the pleasant opponent process elicited by partial pain intensity reduction may be cancelled out by the remaining pain sensation. That relief measures were similar across the three experiments, however, despite their differing use of capsaicin-sensitized vs. normal skin and the difference in the area of stimulation (volar forearm, dorsum of hand and thenar), suggests that we have measured a robust phenomenon that may extend to clinical situations where pain intensity reduction is rapid. Two further limitations of the studies are the fixed order of pain and relief ratings in Experiments II and III (relief was always measured before pain) and that background pain ratings were only acquired at the end of Experiment III.

Overall, our results concur with the growing clinical awareness that pain relief seen as a mere reduction in pain is insufficient to capture the utility of pain relief for the individual (Farrar *et al.*, 2001; Jensen *et al.*, 2005). In this study, we show that when healthy subjects are asked to rate their relief from pain, these ratings are not equal to the drop in pain intensity that caused the relief, although this drop is commonly used as a measure of pain relief. Importantly, the pain-reduction definition of relief misses the important role of homeostatic utility and reward for pain relief. Both intensity and pleasantness of relief appear to increase with the subjective utility of the pain reduction. The results reported here strongly suggest that there is more to pain relief than a simple reduction in pain intensity.

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Abbreviation

VAS, visual analogue scale.

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