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Effects of odors on pain perception: deciphering the roles of emotion and attention

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Abstract

Emotions have been shown to alter pain perception, but the underlying mechanism is unclear since emotions also affect attention, which itself changes nociceptive transmission. We manipulated independently direction of attention and emotional state, using tasks involving heat pain and pleasant and unpleasant odors. Shifts in attention between the thermal and olfactory modalities did not alter mood or anxiety. Yet, when subjects focused attention on the pain, they perceived it as clearly more intense and somewhat more unpleasant than when they attended to the odor. In contrast, odor valence altered mood, anxiety level, and pain unpleasantness, but did not change the perception of pain intensity. Pain unpleasantness ratings correlated with mood, but not with odor valence, suggesting that emotional changes underlie the selective modulation of pain affect. These results show that emotion and attention differentially alter pain perception and thus invoke at least partially separable neural modulatory circuits.

Keywords: Pain modulation; Attention; Emotion; Odors; Heat; Experimental pain

1. Introduction

Pain is a complex experience, shaped both by the intensity of noxious stimulation and by psychological variables, such as emotional state and mood. Emotional states and attitudes of patients affect pain perception associated with chronic diseases (Haythornthwaite and Benrud-Larson, 2000; Schanberg et al., 2000). In laboratory studies, improving mood by presenting pleasant stimuli such as music or humorous films usually reduces pain perception (Cogan et al., 1987; Zelman et al., 1991; Good, 1996; Weisenberg et al., 1998; de Wied and Verbaten, 2001; Meagher et al., 2001; Marchand and Arsenault, 2002). Conversely, manipulations that affect mood negatively increase pain perception (Zelman et al., 1991; Weisenberg et al., 1998; de Wied and Verbaten, 2001; Meagher et al., 2001). Nevertheless, the interpretation of these studies is difficult, because they did not control for associated changes in attention, a variable known to alter nociceptive transmission and affect the pain experience (Villemure and Bushnell, 2002). Pain modulation attributed to mood changes could in fact originate from alteration in attention, since emotional state itself can directly influence attention (Ohman et al., 2001), including attention to pain (Keogh et al., 2001). In fact, studies that systematically varied direction of attention and either pain-relevant or pain-irrelevant anxiety levels found that attentional focus, not anxiety, influenced pain perception (Arntz and de Jong, 1993; Arntz et al., 1994).

Odorants provide a simple and elegant tool for modifying emotions and for examining the interaction between attentional and emotional influence on pain. Odors can alter or even induce emotional responses and evoke memories with considerable emotional content (Herz and Engen, 1996; Keogh et al., 2001). In fact, mere exposure to odorants may have effects functionally equivalent to natural mood states or mood states induced with elaborate methods (Rotton et al., 1978; Ehrlichman and Halpern, 1988; Baron, 1990; Ehrlichman and Bastone, 1992). Odorants are particularly useful in inducing mood changes because they are almost always experienced as clearly pleasant or unpleasant, and experiencing odors requires little or no symbolic transformation or cognitive mediation (Ehrlichman and Bastone, 1992).

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In contrast, listening to music or viewing films requires higher cognitive processes to alter emotions (Ehrlichman and Bastone, 1992). Odors, or emotional states induced by odors, can influence the affective evaluation of stimuli such as the attractiveness of people and artistic value of paintings (Rotton, 1983; Ehrlichman and Bastone, 1992). Importantly, odor-induced emotional responses occur rapidly, with exposures of less than 2 min inducing significant mood changes (Ehrlichman and Bastone, 1992; Chen and Haviland-Jones, 1999). Finally, odorants can serve as attentional targets, as can painful stimuli (Miron et al., 1989; Spence et al., 2001).

The current study controlled and manipulated independently direction of attention and hedonic value of odors, to determine whether brief exposure to odorants could produce mood states that modulated the pain experience and, more importantly, to determine if these emotional modulations could be dissociated from attentional effects.

2. Methods

2.1. Subjects

Fifteen subjects (five males) between 18 and 34 years of age (mean age was 24) completed the study and were paid for their participation. The study was approved by the McGill University Institutional Review Board, and written informed consent was obtained from each subject. Potential subjects were excluded if they presented any of the following conditions: broncho-pulmonary or neurological disease, chronic pain, pregnancy or breastfeeding, current cold or allergy symptoms, smoking, allergy to perfume, current use of analgesic medication including non-prescription drugs, use of alcohol within 12 h of the experimental procedure, and failing the olfactory screening. In addition, subjects were instructed not to wear scented products.

2.2. General procedure

Subjects' consent was obtained, olfactory function was evaluated, and olfactory and thermal stimuli were chosen for each subject. The specific temperatures were individually determined for each subject to produce moderate pain, and odorants were individually chosen to insure highly pleasant and unpleasant valences. Subjects then underwent psychophysical testing in which they performed an intensity discrimination task involving either the olfactory or thermal stimuli, in order to direct attention to the thermal or olfactory modality, while simultaneously manipulating odor hedonics.

2.3. Olfactory screening

A screening of gross olfactory dysfunction was undertaken using full-strength phenyl ethyl alcohol and distilled water in a two-alternative forced choice paradigm requiring four consecutive correct choices. On each trial subjects smelled both liquids in random order and, indicated which bottle contained the strongest smell.

2.4. Experimental task

Subjects were seated in a dentist chair in a ventilated room. During each trial, both painful heat and an odorant were simultaneously presented, but on some trials subjects performed a heat discrimination task, whereas on other trials they performed an odor discrimination task, thus ensuring that they attended to one or the other sensory modality. Besides direction of attention, the hedonic value of the odorant (pleasant or unpleasant) was controlled and manipulated independently. Fig. 1 provides a graphic depiction of the paradigm. Each subject received four separate 5-min conditions with 12 discriminations in each. In one condition subjects attended to the intensity of the noxious heat in the presence of the pleasant odorant, and, in another, in the presence of the unpleasant odorant. A third and fourth condition involved attending to the intensity of the pleasant or unpleasant odorant in the presence of noxious thermal stimuli. The order of the conditions was counterbalanced across subjects. In 50% of cases (pseudo-random), both stimuli of the pair were the same intensity. In order to maximize the attentional demand of the discrimination tasks, we chose stimulus intensity differences that led to a sub-maximal performance. Following the 12th discrimination of each condition, subjects provided the experimenter with ratings of the overall pain intensity, pain hedonics, odor intensity, odor hedonics, mood, anxiety/calmness, anger, fear, happiness, disgust and sadness felt during the immediately preceding trial using the visual analog scales (VAS) described below.

2.5. Measures

VAS were presented to the subjects, to evaluate the intensity and hedonic quality (pleasantness/unpleasantness) of the odor and painful stimuli. We stressed the differences between stimulus intensity and pleasantness/unpleasantness using explanations taken from Price et al. (1983). VAS for mood and emotional state were also presented. Because the affective component of pain has been shown to be influenced by many emotions, including anxiety, anger, fear, sadness, disgust, and happiness in chronic pain patients (Wade et al., 1990; Fernandez and Milburn, 1994), each of these emotions was evaluated using separate VAS. Visual analog scales were chosen over questionnaires evaluating mood and its sub-components, such as the Profile of Mood State, because VAS are rapid and simple to administer and because they represent a suitable alternative to the longer inventories (Wade et al., 1990; Fernandez and Milburn, 1994). In addition, such inventories evaluate sub-components of mood, such as depression, vigor/energetic

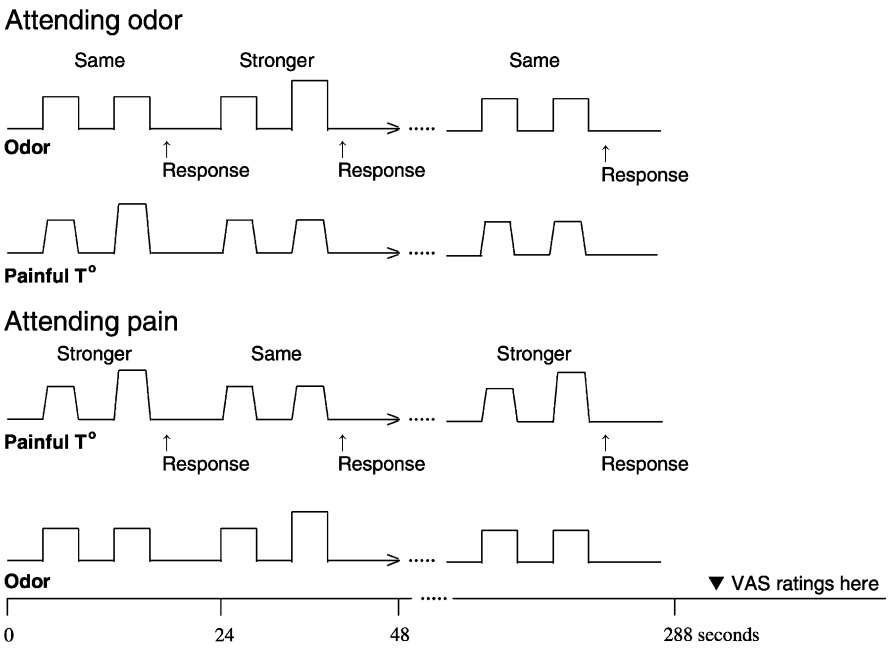

Fig. 1. Graphic depiction of the intensity discrimination task. This task was introduced to ensure that subjects were attending to the prescribed modality. Odors and painful temperatures were presented simultaneously. In one condition (top panel), subjects attended to odor stimuli, in another (bottom panel) they attended to noxious heat (order counterbalanced across subjects). Inter-stimulus interval was 4 s while inter-pair interval was 8 s. After each stimulus pair, subjects indicated whether the intensity of the second stimulus was the same or stronger than the first (equal probability; pseudo-random order). Subjects received feedback regarding the accuracy of their judgment. To ensure that the task was sufficiently difficult to engage subjects' attention, the difference in temperature and odor intensities were determined individually so that performance approximated 80% correct responses. Subjects kept their eyes closed to avoid distraction from the experimental task. A total of 12 discriminations per condition were performed. Following the last discrimination, subjects provided the experimenter with ratings of the overall pain intensity, pain hedonics, odor intensity, odor hedonics, mood, anxiety/calmness, anger, fear, happiness, disgust and sadness felt during the immediately preceding trial using VAS.

arousal, fatigue and confusion, that were less likely to be affected by our experimental conditions. The 100-mm odor intensity scale was anchored with 0 (no odor) and 100 (extremely intense). The 200-mm heat/pain intensity scale was anchored with 0 (no heat) and 200 (most intense pain tolerable) with a mid-point of 100 defined as the pain threshold (Morin and Bushnell, 1998). The 200-mm hedonic scale used for both the odor and thermal/painful stimuli was anchored with −100 (extremely unpleasant) and 100 (extremely pleasant) with a mid-point of 0 labeled neutral. Similarly, the 200-mm mood scale was anchored with −100 (extremely bad) and 100 (extremely good) with a mid-point of 0 labeled neutral. The 200-mm anxiety scale was anchored with −100 (extremely anxious) and 100 (extremely calm) with a mid-point of 0 labeled neutral. The 100-mm scales for anger, fear, sadness, disgust, and happiness were anchored with 0 (not at all) and 100 (extremely). Because of the subjects' reclined position and the presence of the thermode and olfactory stimulation devices, subjects were presented the VAS visually and asked to report a number indicating where they would place a mark on the VAS.

2.6. Painful heat stimuli

A temperature that evoked moderate pain in the absence of the experimental odors was first chosen for each subject, by presenting two ascending series of discrete temperatures ranging from 36 to 47°C to three areas of the volar forearm using a 9-mm^2 contact thermode (Medoc TSA II Neuro-Sensory analyzer, Medoc Ltd. Advanced Medical System, Israel). Each stimulus had a plateau time of 2 s and a rise/fall time of 10°/s leading to an approximate stimulus length of 4 s. After each heat pulse, subjects rated stimulus intensity and pleasantness/unpleasantness, and a temperature was identified which the subject rated as 130–150 on the 200-mm heat/pain intensity scale. Subjects then practiced the thermal discrimination task (Fig. 1), and a second heat stimulus was identified that subjects could distinguish from the first with approximately 80% accuracy. This second temperature was between one and two degrees above the moderately painful temperature, depending on the discriminative capabilities of each subject.

2.7. Odor stimuli

In a separate room from that used for the main experiment, subjects evaluated 27 odors diluted to 0.1–3% v/v in an appropriate inodorous solvent (distilled water or mineral oil). Different types of odors were presented, including pyridine (Sigma-Aldrich Canada Ltd, Ont., Canada), commercial perfumes, and cosmetic grade fragrance oils with food, floral, greenery, and woody scents (K & W Specialties Ltd, Ont., Canada). The diluted

fragrances (10 ml) were presented in 60 ml amber bottles that were identified only with numbers. Using the pleasantness/unpleasantness ratings, two subsets of odors were created – one including the most preferred odors (highest pleasantness ratings) and the other including the most disliked (highest unpleasantness ratings). From these subsets, two experimental odorants were chosen (the most liked and disliked) using a consecutive two-alternative forced choice paradigm.

During the odor discrimination task (Fig. 1), 4-s odor pulses were delivered by a computer-controlled odor generator (Knosys olfactometers, Bethesda, MD). A Time-To-Live (TTL) pulse from the thermode triggered the opening of the appropriate control valve of the olfactometer, resulting in a synchronized presentation of the thermal and olfactory stimuli. An air flow of 1600 cc/min was used. The odorized air from each independent channel reached the subjects through a 3 m long Teflon-lined tube. Each tube was connected to a separate leg of a glass manifold whose central opening connected to an exhaust fan that operated between presentations to prevent lingering odors. A Y-shape glass piece was inserted in the subject's nostrils for bi-rhinal stimulation. Subjects were instructed to close their mouth and breath normally through the nose. Depending on the odorant chosen, the stronger concentration ranged from 1% (pyridine and commercial perfumes), to full strength (other odors) while the weaker concentration typically ranged between 0.1 and 3% v/v, depending on the discrimination capacity of the subject. The weaker concentration was used as the first stimulus of the pair while the stronger concentration appeared pseudo-randomly in 50% of cases as the second stimulus of the pair. None of the odors used were judged as pungent or irritating.

2.8. Statistical analyzes

All statistical analyzes were performed with Statistica 6.0 (StatSoft, Inc, OK, USA). A significance level of $P < 0.05$ was adopted for all analyzes. A paired sample *t*-test was used to evaluate whether the performances on the heat and odor intensity discrimination tasks differed. We used the general linear model for separate analyzes of the dependent variables pain intensity, pain unpleasantness, mood, anxiety, and disgust with one between factor (SEX) and two repeated measures with two levels each (ATTENTION: to pain or to odor; ODOR VALENCE: pleasant or unpleasant). The Tukey Honest Significance Difference was used for post-hoc analyzes when appropriate. Pearson correlations were used to address the relationship between the different relevant dependent variables. Differential scores were used for these correlations and the critical *P* value was adjusted for the number of comparisons. For each factor, we subtracted the ratings given in the presence of the unpleasant odorant from the ratings obtained in the presence of the pleasant odorants.

3. Results

Subjects chose temperatures between 44 and 47°C as moderately painful. All subjects chose pyridine as the highly unpleasant odorant, but they chose a variety of floral, greenery, woody and food scents as the highly pleasant odorant. Subjects' performance accuracy on the two-alternative forced-choice task did not significantly differ between the odor and pain discrimination tasks (Heat pain: 76% ± 3, Odor: 81% ± 3; $t = 1.27$, $P = 0.225$), thus suggesting similar attentional demands for the two tasks.

Although SEX was used as a variable in the following analyzes, there was no significant effect of this factor in any of the analyzes and therefore these results are not reported here. The 5-min exposures to the pleasant and unpleasant odorants altered subjects' mood and anxiety states, both when the subjects were required to attend to the odors and when they were required to attend to the pain. As shown in Figs. 2 and 3B, independent of attentional state, the pleasant odors produced a positive mood and a calm state, whereas the unpleasant odor produced a negative mood and a state of mild anxiety (For mood: Effect of Odor $F(1, 13) = 8.14$; $P = 0.014$, no interaction between Attention and Odor $F(1, 13) = 2.27$; $P = 0.156$; For anxiety/calmness: Effect of Odor $F(1, 13) = 7.34$; $P = 0.018$, no interaction between Attention and Odor $F(1, 13) = 0.71$; $P = 0.413$). Subjects also reported disgust while exposed to the unpleasant odor (Pleasant odor = 0.2 ± 0.2, Unpleasant odor = 25 ± 5, $F(1, 13) = 21.88$; $P < 0.001$) and the disgust was greater when subjects attended to the unpleasant odor then when they attended to the heat pain (Odor × Attention interaction: $F(1, 13) = 9.07$; $P = 0.01$, Attention unpleasant odor = 33 ± 7, Attention pain with unpleasant odor present = 17 ± 5, Tukey HSD $P < 0.001$). Four subjects reported happiness when the pleasant odor was present despite the presence of pain. Anger, fear and sadness were reported even less frequently. For this reason, these emotions were not submitted to statistical analysis. Direction of attention had no effect on mood or anxiety (Fig. 3A).

Subjects also rated the intensity and unpleasantness of the noxious heat stimuli after each 5-min condition. As shown in Fig. 3A, subjects perceived the noxious heat as being more intense when they attended to it then when they attended to the odor ($F(1, 13) = 6.17$; $P = 0.027$). A similar trend was observed for pain unpleasantness, but it did not reach statistical significance ($F(1, 13) = 4.02$; $P = 0.066$). This effect of attention on pain ratings occurred in the presence of either the pleasant or unpleasant odor (non-significant interactions between attention and odor valence for intensity: $F(1, 13) = 0.40$; $P = 0.539$ and unpleasantness: $F(1, 13) = 0.03$; $P = 0.875$).

In contrast to the effects of attention, odor valence altered pain unpleasantness without significantly affecting pain intensity (Fig. 3B) [For intensity: $F(1,13) = 2.16$; $P = 0.165$; For unpleasantness: $F(1,13) = 5.71$; $P = 0.033$)]. This preferential effect of odor valence on the affective

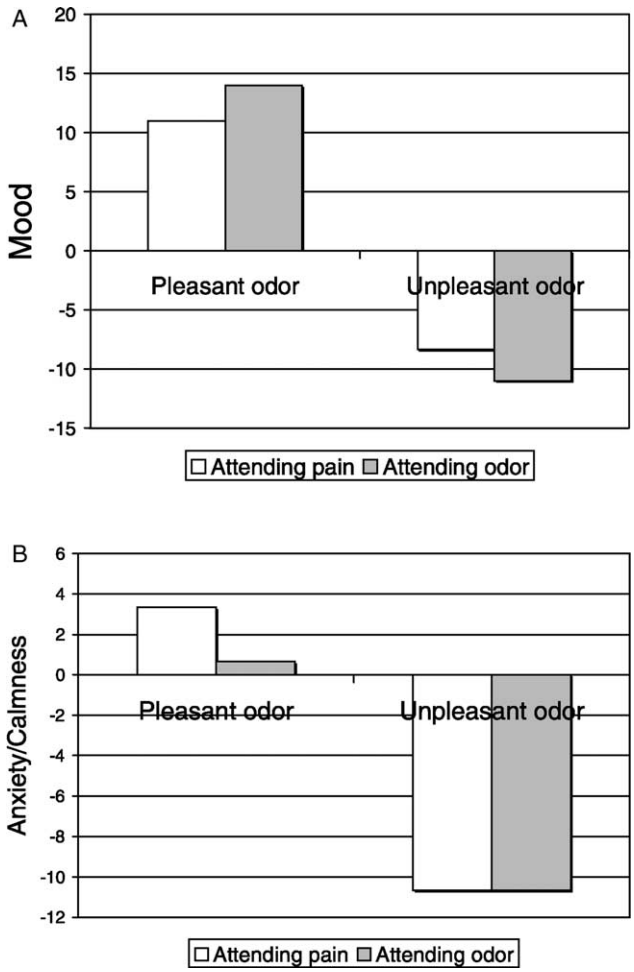

Fig. 2. Mood and anxiety changes induced by odorants as a function of experimental conditions. (A) The presence of a pleasant odorant resulted in a positive mood state whether subjects were attending to the odor or to pain. Conversely, the presence of an unpleasant odorant led to negative mood ratings whether subjects were attending to the odor or attending to pain. (B) The presence of a pleasant odorant resulted in a calmer state, whether subjects were attending to the odor or attending to pain. The presence of an unpleasant odorant resulted in a more anxious state, whether or not subjects attended the odor.

(unpleasantness) dimension of pain occurred whether or not the subject was required to attend to the odor.

Since odor valence altered mood, anxiety level (see Fig. 3B) and disgust, the effect of odor valence on pain unpleasantness could be either the direct consequence of the odorant or could result from associated emotional changes. To differentiate these factors, we performed correlation analyzes between pain hedonics ratings and odor valence, mood, anxiety levels and disgust. For each factor, we used differential scores (we subtracted the ratings given in the presence of the unpleasant odorant from the ratings obtained in the presence of the pleasant odorant). Fig. 4 shows a significant correlation between mood and pain hedonics differential scores ($r = 0.64$, $P = 0.010$; still significant when adjusting for the number of correlations (critical $P < 0.0125$)). The more the pleasant and unpleasant odorants had opposite effects on mood, or in other words, the more effective the odors were to modulate mood, the more pain hedonics was modulated. In contrast, there was no direct correlation between pain hedonics differential scores and anxiety ($r = 0.13$, $P = 0.654$), odor hedonics ($r = 0.26$, $P = 0.343$), or disgust differential scores ($r = -0.21$, $P = 0.462$), suggesting that the effect of odors on pain hedonics is an indirect effect of associated mood changes. We also examined the relationship between pain *intensity* differential scores and odor valence, mood, anxiety and disgust differential scores. Neither odor valence nor mood nor anxiety nor disgust showed a significant correlation with pain intensity differential scores ($r < 0.39$, $P > 0.152$), further suggesting that these variables did not influence the sensory aspect of pain perception.

4. Discussion

Our results show that odors can produce mood states that modulate the pain experience and that these emotional modulations are dissociable from attentional effects. Direction of attention had no effect on mood or anxiety, but altered perceived pain intensity and, to a lesser degree, pain unpleasantness (non-significant trend). Odor valence, on the other hand, altered mood, level of anxiety and pain unpleasantness, but did not significantly affect perceived pain intensity. Further, pain unpleasantness ratings correlated with mood, but not with odor valence, suggesting that emotional changes underlie the selective modulation of pain affect. The observation that emotional manipulations modulate pain unpleasantness more than pain intensity, whereas the reverse is true for attention, suggests that the two effects are dissociable and that different neural modulatory circuits are involved. Furthermore, it provides evidence for the existence and measurability of these two dimensions of the pain experience contrary to what has been previously suggested (Chapman et al., 2001).

Another important observation is that the presence of pleasant and unpleasant odors can lead to very rapid changes in emotional state. Using intermittent exposures to an odor within the 5-min tasks, we observed clear oscillations in both mood and anxiety that were accompanied by changes in the hedonic aspect of pain perception. An imaging study has recently implicated the entorhinal cortex in the aggravation of pain by anxiety (Ploghaus et al., 2001). Direct projections from the main olfactory bulb to the lateral entorhinal cortex have been identified (McLean and Shipley, 1992). The rapid modulation of mood and anxiety level by odors may be mediated by these projections.

The correlation data indicate that odor valence modulates pain unpleasantness indirectly through its effect on mood, rather than through a direct effect of odor hedonics on pain perception. It is not how much an odor is liked that is important, but rather how much this odor alters the general

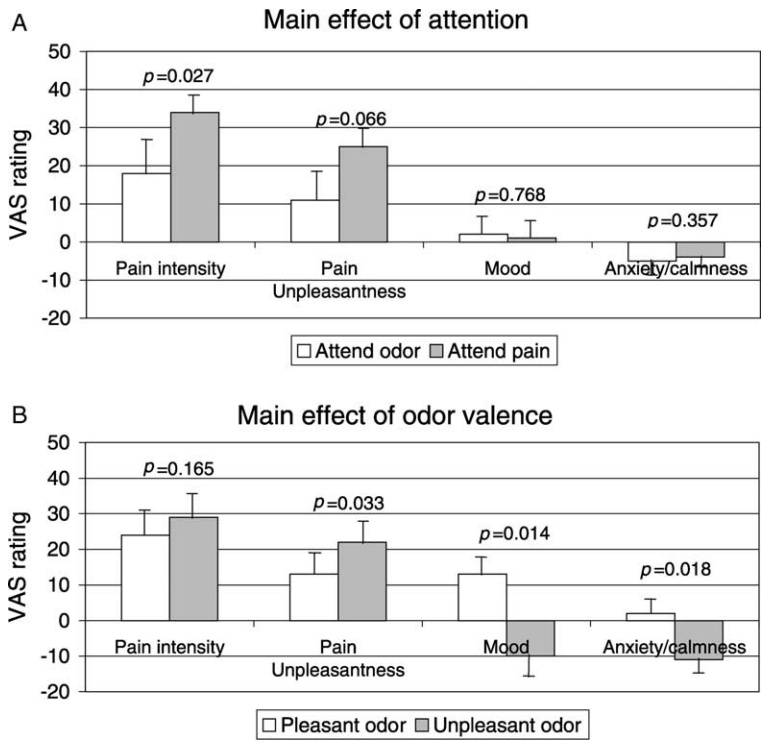

Fig. 3. Main effects of attention and odor valence on pain intensity, pain unpleasantness, mood and anxiety VAS ratings. Because as a group subjects rated the thermal stimuli as painful and unpleasant, the original scales of pain intensity and hedonics were transformed for more clarity so that '0' represents pain threshold/neutral and '100' the most intense pain tolerable/extremely unpleasant. For mood, '0' is neutral, '100' is extremely good and ' − 100' is extremely bad. For anxiety/calmness, '0' is neutral, '100' is extremely calm and ' − 100' is extremely anxious. (A) Direction of attention had no effect on mood and anxiety, but altered both perceived pain intensity and unpleasantness. (B) Odor valence altered mood, anxiety and pain unpleasantness ratings but did not significantly affect perceived pain intensity.

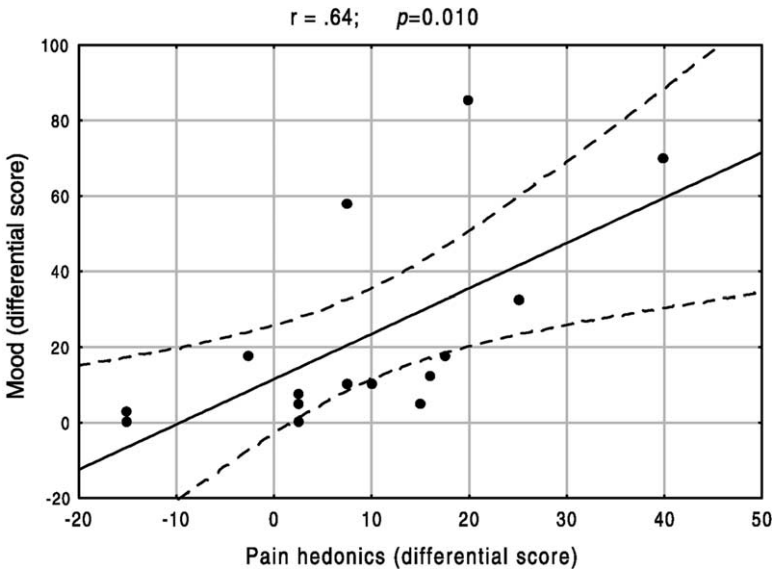

Fig. 4. Correlation between mood and pain hedonics differential scores. For each factor, we subtracted the ratings given in the presence of the unpleasant odorant from the ratings obtained in the presence of the pleasant odorants. There was a significant correlation between mood and pain hedonics differential scores. This indicates that the more the pleasant and unpleasant odors have opposite effect on mood, the more pain hedonics is modulated. It might appear that this significant correlation is due to the top three points, however, when removing those data points we still obtain a significant correlation ($r = 0.68$; $P = 0.014$). The dashed lines represent 95% confidence interval.

mood state. This finding is consistent with those of Baron (1990), Rotton (1983) and Ehrlichman and Halpern (1988) showing that odor experiences influence cognition and behavior in ways similar to those produced by affective states. However, our results contrast with those of Marchand and Arsenault (2002), who found that odors modulated mood of both men and women, but only altered pain in women, thus suggesting that emotional factors were not responsible for the pain modulation. In that study, the relationship between odors and mood and that between odors and pain were evaluated on separate days, so it is not clear how the odors affected emotional state during the pain session. Their results might be attributable to an attentional effect since in their study pain intensity and unpleasantness were modulated in parallel, which is similar to the modulatory effects of attention observed in the present and previous studies (Bushnell et al., 1985; Miron et al., 1989; Bushnell et al., 1999) and since in the absence of clear instructions men and women focus differentially on pain (Keogh et al., 2000; Keefe et al., 2000). In our study, there was no effect of the variable SEX. However, this could be due to a lack of power caused by our small sample size. Another study, specifically addressing this issue, is now underway.

Our finding that pain is perceived as less intense when subjects attend to an alternate modality is similar to results of previous studies that used hedonically neutral distracting stimuli, such as white lights, pure tones, or vibratory stimuli (Miron et al., 1989; Bushnell et al., 1999; Longe et al., 2001; Rode et al., 2001). Thus, the addition of hedonic value to the distracting stimulus does not appear to alter the modulatory effects of attentional state. Further, as we previously found using emotionally neutral distracters (Bushnell et al., 1999), pain intensity was significantly modulated, with a lesser (non-significant) modulation of pain unpleasantness. This consistently stronger effect of cross-modality attention on pain intensity suggests that the primary modulation is of sensory structures, which in turn secondarily alters affective regions. Brain imaging studies have observed attention-related modulation in brain structures thought to be primarily sensory or affective in nature (Bushnell et al., 1999; Bantick et al., 2002). However, using attentional manipulations similar to those of the current study, pain-evoked activity in primary somatosensory cortex (sensory regions) showed the most pronounced modulation by attentional state (Bushnell et al., 1999).

4.1. By what mechanisms do emotion and attention modulate pain?

Psychological modulation of pain can be mediated by opiate-sensitive descending inhibition of nociceptive input to the brain involving regions such as the periaquaductal gray matter (PAG) and rostral ventral medulla (Fields and Basbaum, 1999; Fields, 2000), as well as by direct effects of opioids in cortical nociceptive-related areas, including the anterior cingulate cortex (Zubieta et al., 2001; Petrovic et al., 2002). Further, some psychological pain modulation, such as that produced by conditioning, appears to be mediated by non-opioid systems (Amanzio and Benedetti, 1999). Recent human functional magnetic resonance imaging (fMRI) evidence of Ploghaus et al. (2001) suggests that pain modulation by anxiety is associated with activation changes in the entorhinal cortex, but it is not known whether there is further involvement of opioid systems. There is evidence, however, that attentional modulation of pain may at least partially be mediated by an opioid system. Tracey et al. (2002) observed activation in PAG when subjects were distracted from pain, and the degree of increase in activation predicted the magnitude of the decrease in pain intensity ratings. Studies in awake monkeys show that attentional state modulates nociceptive transmission in both the spinal cord dorsal horn and thalamus (Bushnell et al., 1984; Bushnell and Duncan, 1989; Bushnell et al., 1993), further supporting the idea that descending modulatory systems are engaged. The results presented here indicate that the perception of pain affect is integrated with the emotional dimension of other sensory modalities. Brain regions integrating multimodal inputs would therefore be expected to be involved in the perception of this dimension of pain.

In conclusion, these results show that brief repeated exposures to odorants modulate emotional state and that emotional factors can in turn alter pain perception. This emotional modulation of pain is separable from that produced by distraction, suggesting that emotion and attention invoke at least partially different neural modulatory circuits.

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