Attenuation of Sensory and Affective Responses to Heat Pain: Evidence for Contralateral Mechanisms

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Gallez, Ariane, Marie-Claire Albanese, Pierre Rainville, and Gary H. Duncan. Attenuation of sensory and affective responses to heat pain: evidence for contralateral mechanisms. J Neurophysiol 94: 3509–3515, 2005; doi:10.1152/jn.01006.2004. Attenuation of responses to repeated sensory events has been thoroughly studied in many modalities; however, attenuation of pain perception has not yet benefited from such extensive investigation. Described here are two psychophysical studies that examined the effects of repeated exposure to thermal stimuli, assessing potential attenuation of the perception of pain and its possible spatial specificity. Twenty-two subjects were presented thermal stimuli to the volar surface of the right and left forearms. Twelve subjects in study 1 received the same stimuli and conditions on each of five daily experimental sessions, whereas 10 subjects in study 2 received thermal stimuli, which were restricted to one side for four daily sessions and then applied to the other side on the fifth session. Ratings of warmth intensity, pain intensity, and pain unpleasantness were recorded while the subjects performed a thermal sensory discrimination task. Results of study 1 demonstrate that repeated stimulation with noxious heat can lead to long-term attenuation of pain perception; results of study 2 extend these findings of attenuation to both pain intensity and unpleasantness and show that this effect is highly specific to the exposed body side for both aspects of the pain experience. We suggest that the functional plasticity underlying this attenuation effect lies in brain areas with a strong contralateral pattern of pain-related activation.

INTRODUCTION

Many studies have demonstrated a reduction in the perception of a given stimulus over time. The gradual reduction of sensation or neuronal/receptor activity during sustained stimulation of constant intensity is usually defined as “adaptation” (Price 1992; Theunissen et al. 2000). The time span of perceptual adaptation is usually said to be very short, a phenomenon considered to occur over a period of a few seconds. Perceptual adaptation has been observed in virtually all modalities including vibratotactile touch (Hollins et al. 1990), taste (Theunissen et al. 2000), smell (Dalton 2000), and heat pain (Price et al. 1977). Habituation, sometimes used as a synonym for adaptation, most often involves repeated exposure to the stimulus. The context and time frame for observing the effects of habituation may vary from the reduction in responsiveness to regular rates of stimulation presented within a single testing period (Thompson and Spencer 1966) to the reduced perception of odors presented over a period of several weeks—referred to by the authors (Dalton and Wysocki 1996) as both adaptation and habituation. A further distinction is sometimes made between peripheral mechanisms of adaptation and central mechanisms of habituation (Dalton 2000). Given the lack of clarity in the psychophysical literature concerning the use of physiological terms such as “adaptation” and “habituation,” we have chosen to use a more general term “attenuation” when referring to the gradual decrease in the perception of stimuli that are administered repeatedly over a number of days.

A number of studies have investigated changes in pain perception evoked by noxious stimuli. The temporal frame of comparison has ranged from a few seconds (Chudler et al. 1990) or a few minutes (Becerra et al. 1999; Valeriani et al. 2003), to several days or weeks (Greenspan and McGillis 1994; Rosier et al. 2002; Yarnitsky et al. 1995, 1996); however, results of these studies are inconsistent and allow no clear consensus. Considering the paucity of information concerning the time-dependent modulation of pain perception, and its cerebral correlates, we developed psychophysical paradigms to investigate in detail potential changes in the perceived intensity and unpleasantness of heat stimuli presented over a period of several weeks. To maintain the subjects’ arousal and motivation during this extended period of study, stimuli were presented within the context of psychophysical training in a sensory-discriminative detection task with periodic perceptual ratings of the different stimuli. Presented here are results of these psychophysical studies concerning attenuation of the perceptual aspects of the stimuli over the period of training. Some of these results have been presented previously in abstract form (Gallez et al. 2002, 2003).

METHODS

Subjects

Twenty-two normal volunteers (12 women and 10 men, aged 21–47) participated in these experiments; 12 took part in experiment 1 and 10 in experiment 2. None suffered chronic pain, neurological symptoms, or psychiatric disorders. All gave informed consent acknowledging that the methods and risks were clearly explained and understood and that they were free to withdraw from the study at any time without prejudice. All procedures were approved by the Health Science Research Ethics Committee at the University of Montreal.

Stimuli

All experiments were conducted in a sound-attenuated, temperature-controlled anechoic testing chamber. Thermal stimuli were presented on the volar surface of the forearms with two custom-built...
Each condition (innocuous condition, to minimize local sensitization by the noxious stimuli. In experiment 1, forearm were used during the course of the eight experimental blocks. This approach using two thermodes allowed us to maximize the temperatures between 47.5 and 48.7°C. Noxious stimuli in both experiments shared the same range of temperatures from 38.5 to 41.7°C. Innocuous stimuli varied from 40 and 42.4°C to better produce an unambiguous warm sensation in all trials. N\’Xous stimuli in both experiments shared the same range of temperatures between 47.5 and 48.7°C.

Each experimental session was divided into eight blocks of 16 trials with innocuous and noxious stimuli presented separately in alternate blocks (a total of 64 trials each of innocuous and noxious stimuli); during each block, trials alternated between the two thermodes, which were positioned on the same forearm in a distal/proximal orientation. This approach using two thermodes allowed us to maximize the interval between consecutive stimuli presented to the same spot of skin, without movement of the thermodes between trials. During experiment 1, eight evenly distributed stimulation sites on the single forearm were used during the course of the eight experimental blocks to minimize local sensitization by the noxious stimuli. In experiment 2, the paradigm was simplified to 4 (rather than 8) stimulus sites tested on a single forearm during the course of an experimental session.

Experimental protocol

**EXPERIMENT 1.** Each subject participated in five experimental sessions, spaced between 1 and 6 days apart. To assess the temporal evolution of perception and sensory-discriminative ability, subjects performed a temperature-discrimination task (see Fig. 1) repeated during each training session. In each trial, the temperature increased to a 4-s plateau (T1 = 38.5°C in innocuous trials, 47.5°C in painful trials) from which the comparison temperature was presented (T2, 2 s) before returning to baseline. Based on preliminary studies, four increments of temperature change (ΔT’s = 0.0, 0.8, 1.6, and 3.2°C; noxious condition, ΔT’s = 0.0, 0.3, 0.6, and 1.2°C). Each experimental session consisted of four blocks of 16 painful trials and four blocks of 16 innocuous trials. ΔT’s and stimulation sites were counterbalanced within each 16-trial block, and blocks of noxious and innocuous stimuli were alternated between the two forearms.

The subjects’ task was to detect T2 and compare it to T1 by pressing the appropriate mouse button (left/right, T2 “same as”/“different from” T1, respectively). Four seconds were allowed for the response, starting from return of the temperature to baseline. Feedback (correct/incorrect) was provided after each trial. Responses and response latencies were recorded. A subjective numerical rating of overall pain intensity was requested at the end of each block on a pain intensity scale, relative to its defined extremes (0: no pain, 100: extremely intense pain) and intermediate measures (25: slightly intense, 50: moderately intense, 75: very intense)—slightly modified from Rainville et al. (1992).

**EXPERIMENT 2.** Duration and presentation of stimuli were similar to those of experiment 1. To better equate the difficulty of the noxious and innocuous tasks in this second experiment, a smaller range of temperatures (ΔT’s = 0, 0.6, 1.2, and 2.4°C) was chosen for the innocuous task. Only one forearm was stimulated on training sessions 1–4; the opposing forearm was stimulated on day 5, using the same psychophysical task. Stimulation of left and right forearms was counterbalanced across the 10 subjects.

To simplify the same/different discrimination task in experiment 2, the subject was asked to respond as soon as possible to any detected increase from T1 to T2 by pressing a mouse button. Thus a detection button-press corresponds to an implicit “different” response, whereas the absence of a detection button-press corresponds to an implicit “same” response. Responses occurring earlier than 200 ms after the onset of T2 were disallowed (insufficient time for the subject to have detected a real temperature change); those made >4 s after return of the temperature to baseline were considered too late and not included in the analysis. Regardless of the subject’s response, stimuli continued for the full duration of the stimulus period, to maintain a standard basis from which to judge the perceptual qualities of stimulation. Blocks of innocuous and noxious stimuli were presented alternately. After each trial in the first block of each condition, and at the end of every block, subjects were asked to evaluate pain intensity, warmth intensity, and pain unpleasantness. The pain intensity scale was identical to that used in experiment 1; the warmth intensity scale was graded from 0 (no sensation) to 100 (extremely intense, not quite painful) with intermediate marks at 25 (slightly intense), 50 (moderately intense) and 75 (very intense); and the pain unpleasantness scale was graded from 0 (not at all unpleasant) to 100 (extremely unpleasant, not at all unpleasant), with intermediate marks at 25 (slightly unpleasant), 50 (moderately unpleasant) and 75 (very unpleasant).
Data analysis

SENSORY-Discriminative Ability. Same/different responses were categorized as hits (correct responses: different when ΔT > 0°C) or false alarms (different when ΔT = 0°C). For each session, the percentage of hits and false alarms (FA = 100% − correct responses at ΔT = 0°C) was calculated for every ΔT. Discriminative ability ("discriminability", A’) was calculated with signal detection theory (Brown Grier 1971), according to the following formula:

A’ = 0.5 + \left(\frac{1}{2}\right) \left[1 + \frac{1}{2} \left(1 - x \frac{y}{1 - x}\right)\right]

where x = FA rate and y = hit rate. Discriminability is random when A’ is equal to 0.5 and is maximal when equal to 1.

Response speed was obtained by calculating the inverse of correct response latencies (measured in ms), multiplied by 1000, yielding a value of 1 for a latency of 1 s, and values from 0.25 to 5.0 for latencies of 4 s to 200 ms. The median response speed was calculated for every ΔT.

Ratings. Mean daily ratings for each condition were obtained by averaging those given after each block within each training session. Individual trial ratings in the first block of each condition in experiment 2 were averaged across ΔT’s in every session.

Statistics

Performance, discriminability, and subjective ratings were compared across stimulus conditions (warm vs. heat pain), ΔT’s, and sessions, using ANOVA with repeated measures by subjects. In experiment 2, neither the main effect of block nor any interaction with this variable was observed in our analyses of subjective ratings. Therefore the block variable was eliminated, and results of ANOVAs in each condition are presented with ratings averaged across the four blocks. Planned Student’s t-tests were also used to examine specific differences.

Results

In experiment 1, one male subject did not finish the experiment because a thermode calibration problem resulted in temperatures outside the predetermined range; hence all analyses for the first experiment were carried out on a total of 11 subjects. In experiment 2, during the first session, two subjects failed to meet the minimum criterion for subject ratings (i.e., mean ≥10% for the maximum level stimuli): one subject felt only weak or no pain for the strongest stimulus intensities, whereas the second subject showed low and inconsistent ratings of warmth stimuli. These two subjects were therefore excluded from the analysis of ratings in which they specifically showed floor effects (mean 1st-session ratings were too low to allow an unbiased test of a 2-tailed hypothesis for changes in perception). Hence nine subjects were included in the rating analyses of each condition in experiment 2. However, because these two atypical subjects did not show abnormal performance levels, all 10 subjects were included in the performance analyses.

Stimulus-response characteristics

SENSORY-Discriminative Ability. We first assessed the subjects’ ability to attend to and detect small changes in thermal intensity. In both experiments 1 and 2, the magnitude of the change in temperature (ΔT) had a highly significant effect on the percentage of detected ΔT’s, the discriminability index A (Brown Grier 1971), and the response speed in both the noxious and the innocuous conditions (ANOVAs, all Ps < 0.001). Neither floor nor ceiling effects were present as discriminability increased significantly at each ΔT (see Fig. 2; t-test, all Ps < 0.004). These results provided the necessary validation of the experimental task and ensured that subjects closely attended to the stimuli in both experiments.

Ratings of Warmth and Pain. Although no ratings of individual stimuli were collected during experiment 1, results of the discrimination tasks suggest that different intensities of innocuous and noxious T2 stimuli were perceived as increasingly more intense than the respective T1 standards as indicated by the increased ease of discriminability over the full range of stimulus intensities presented within each task (described in the preceding text). This interpretation was tested in experiment 2, where subjects rated warmth, pain intensity, and pain unpleasantness after each stimulus in the first block of trials presented during the two conditions of each experimental session. ANOVA analyses confirmed a significant effect of stimulus intensities on ratings in the two tasks (Fig. 3; F > 50.0, P < 0.001), thus providing additional validation of the rating procedure.

To assess the subjects’ capacity to distinguish sensory from affective aspects of pain, we tested for differences between ratings of pain intensity and unpleasantness. The subjects’ evaluations of individual stimuli during the first block of trials of each experimental session showed that the perception of pain unpleasantness was consistently lower than that of pain intensity (F = 6.4, P < 0.05). Likewise, global evaluations recorded at the end of each block also indicated a significant difference between ratings of pain intensity and unpleasantness (F = 5.1, P = 0.05). These results are consistent with previous psychophysical studies showing systematic differences between sensory and affective aspects of phasic thermal pain (Price et al. 1992; Rainville et al. 1992) and confirm the subjects’ understanding of the meaning of the two pain dimensions and their efforts to rate them separately.

Training-related changes in pain and warm ratings

ATTENUATION (EFFECTS OF REPEATED EXPOSURE). Experiment 1. In the first experiment, ratings of pain intensity markedly decreased with successive experimental sessions (Fig. 4A; F =...
ANTENESS RATINGS (F = 7.0, P = 0.005) and warmth intensity (F = 50.2, P < 0.001), pain intensity (F = 70.2, P < 0.001), and unpleasantness ratings (F = 70.8, P < 0.001).

Ratings declined between sessions 1 and 2 (t-test, t = 4.5, P < 0.005) and stabilized thereafter (Fig. 4A; ANOVA day 2–5: t = 0.7). These results indicate that repeated exposure to the stimuli resulted in a significant attenuation of pain perception by the second experimental session and that this effect persisted for the rest of the 5-day training period.

Experiment 2. In the second experiment, ratings of innocuous and noxious heat stimuli showed a robust and generalized effect of attenuation to warmth, pain intensity, and pain unpleasantness across the first four sessions (Fig. 4, B and C, Table 1; warm: F = 6.0, P < 0.005; pain intensity: F = 6.5, P < 0.005; pain unpleasantness: F = 6.0, P < 0.005). Planned contrasts between sessions 1 and 4 confirmed the session-related decrease of both warmth (t-test, t = 2.99, P < 0.01) and pain ratings (pain intensity: t = 4.1, P < 0.005; pain unpleasantness: t = 4.2, P < 0.005). Analysis of the individual trial ratings in each session’s first experimental block suggested that the attenuation effect was consistent across all ΔT’s for the intensity ratings but not for the unpleasantness ratings, for which a ΔT-session interaction was observed (F = 2.5, P < 0.05). Indeed, only the unpleasantness ratings for the larger ΔT (1.2°C) were subject to a significant attenuation, a result reflecting the trend toward stronger attenuation effects at larger ΔT’s.

These results closely replicate the attenuation of pain intensity observed across successive experimental sessions in experiment 1, and extend those findings to include attenuation of both the unpleasantness of noxious thermal stimuli, as well as the perception of warmth associated with innocuous heat stimuli.

ATTENUATION SPECIFICITY (EFFECTS OF TRANSFER). Noxious heat. The design of experiment 2, in which the site of stimulation was transferred to the opposite forearm for the final experimental session, allowed a direct evaluation of the possible spatial restrictions (or generality) of the perceptual attenuation initially observed in experiment 1. After the transfer of thermal stimuli to the opposite forearm in session 5 of experiment 2, overall ratings of pain intensity and unpleasantness increased significantly compared with those of session 4 (Fig. 4, B and C, Table 1; t-test of mean postblock ratings, pain intensity: t = 3.2, P < 0.01; pain unpleasantness, t = 2.6, P < 0.05), returning to levels indistinguishable from those reported in the initial baseline session (session 1 vs. session 5: pain intensity: t = 0.4, P = 0.67; pain unpleasantness: t = 0.06, P = 0.94). Analysis of the individual ratings obtained for each stimulus in the first block of each session also indicated that perception of pain intensity and unpleasantness during session 5 was significantly greater than that of session 4 (main effect of session; intensity: F = 13.7, P < 0.01; unpleasantness: F = 6.5, P = 0.01).

FIG. 4. Evolution of the mean ± SE ratings across 5 successive sessions. A: changes in pain intensity observed in experiment 1. B: changes in pain intensity (●), pain affect (○), and warmth intensity (C) observed in experiment 2. Pain intensity and affect ratings display similar patterns of statistical significance (*P < 0.05; NS: P > 0.7; see Table 1 for all values).

FIG. 3. Mean ± SE ratings of pain (A; intensity: ●; affect: ○) and warmth intensity (B) for the 4 different stimulus magnitudes used (ΔT0–3) in experiment 2. Individual trial ratings confirmed that larger ΔT’s led to higher warm (F = 50.2, P < 0.001), pain intensity (F = 70.2, P < 0.001), and unpleasantness ratings (F = 70.8, P < 0.001).
More recently, Rosier et al. (2002) described a study in which subjects’ pain sensations were assessed across four sessions conducted 1 wk apart; but in contrast to our findings of attenuation, Rosier et al. observed variable responses among subjects and between measurement scales.

Several factors may have contributed to the consistency of our results and the significant attenuation seen in our own two studies, compared with the variable results reported in previous studies. To reduce spurious effects of environmental factors, all our experiments were conducted in a thermostatically controlled, anechoic testing chamber. Additionally, we addressed problems in scaling reliability, noted by Rosier et al. (2002), by using numerical rating scales anchored by both terminal and intermediate verbal descriptors. This combined category-ratio scaling method was first described by Marks et al. (1983), who demonstrated its use in reducing variability and response bias. We have previously used these scales for minimizing both inter-subject and between-session variability in ratings (Rainville et al. 1992) and further validate the procedure here for warmth, pain intensity, and unpleasantness ratings (Fig. 3; F > 50.0, P < 0.001). The most important difference between our studies and those noted in the preceding text may be our use of a psychophysical discrimination task to avoid an overt focus on pain ratings, per se. Active involvement in a discrimination task may help in stabilizing the subjects’ level of attention; likewise, pain evaluations elicited within the context of a discrimination experiment may reduce the potential for bias, which is inherent to experiments the sole purpose of which is to monitor pain perception. Finally, assuming that perceptual attenuation reflects changes in neuronal processing, then intense psychophysical training—rather than periodic ratings—may be more likely to produce systematic changes in pain perception. In primate studies, the active engagement of perceptual processes in the context of sensory-discriminative training with vibrotactile stimuli has been shown to promote plastic changes within CNS regions involved in the encoding of that afferent sensory information (Buonomano and Merzenich 1998). In our studies, engagement in an attention demanding thermal-discrimination task may have facilitated a neuronal plasticity leading to the perceptual attenuation of pain.

**Neuronal correlates of attenuated pain ratings**

A long-term reduction or attenuation of thermal pain sensation most likely reflects a decrease in the activity of cerebral
areas implicated in the encoding of pain intensity (see Coghill et al. 1999, 2001, 2003; Derbyshire et al. 1997); however, one cannot rule out the possibility that such modulation in cerebral activity is in part a reflection of changes in afferent activity through peripheral or spinal nociceptive pathways. The absence of a generalization of the attenuation to the opposite arm suggests that the process underlying pain attenuation likely occurred in cerebral areas that show lateral specificity and/or some degree of somatotopic organization. Using stimulation sites and temperatures similar to those of our present study, Coghill et al. (2001) demonstrated that pain intensity-related activation of somatosensory and insular cortices was restricted to the side contralateral to the site of stimulation, a finding replicated by Bingel and colleagues (2003) and extended to lateral thalamus. Numerous studies have implicated SI in the sensory-discriminative aspect of pain perception (Bingel et al. 2003; Kenshalo 1991; Kenshalo and Isensee 1983; Kenshalo et al. 1988, 1989; Ploner et al. 1999; Timmermann et al. 2001), and the small contralateral receptive fields of nociceptive neurons described in primate SI (Kenshalo et al. 2000) are consistent with the possibility that functional plasticity in this area may have contributed to the spatially specific attenuation affects observed in our study.

Our results also show that the emotional aspect of pain was subject to attenuation. A reduction in the emotional impact of a stimulus has previously been observed in the treatment of phobia. Exposure therapy, the aim of which is the extinction or attenuation of fear and anxiety through repeated exposure to the phobic stimulus, has proven efficient in reducing self-reported anxiety in spider phobia (de Jong et al. 2000) and fear of flying (Maltby et al. 2002). Cerebral structures involved in emotional processing have likewise displayed attenuation after repeated exposure to phobic (Paquette et al. 2003) or emotionally salient visual stimuli (Breiter et al. 1996; Phan et al. 2003; Wright et al. 2001). However, these effects are generally found bilaterally (e.g., amygdala and hippocampus) or lateralized to one hemisphere within structures involved in the attentional or emotional processing of stimuli (e.g., anterior cingulate or prefrontal cortices), independent of their position in the visual field.

Interestingly, in the present study the attenuation of pain affect was spatially specific rather than bilateral. One explanation for the similar evolution of intensity and affect ratings in our study could be the difficulty in separating these two pain dimensions—both psychophysically and functionally. However, we and others have previously shown that pain intensity and affect are indeed two distinct and dissociable facets of the pain experience (Price 2000; Rainville et al. 1992, 1999), even though their magnitudes are often strongly correlated. In the present study, the consistent difference observed between ratings of intensity and affect indicate that subjects were able to discriminate these two aspects of the pain experience. Although cerebral areas classically associated with pain affect (e.g., medial thalamus, insula and cingulate cortex) often exhibit bilateral pain-evoked activity (see, for example, Bingel et al. 2003), one can nevertheless interpret our findings of spatially selective affect in accordance with a direction of causation between pain intensity and pain affect established by Rainville et al. (1999) and the serial and parallel pain pathways proposed by Price (2000). In our study, it is plausible that the temporal changes in pain unpleasantness may have been a direct consequence of attenuation of pain intensity rather than reflecting an independent modulation of activity within the structures subserving pain affect. Consequently, according to this unidirectional relationship between the two, the evolution of pain affect would accompany that of pain intensity, following both its temporal and spatial properties of attenuation.

### Attenuation to innocuous warmth

In the innocuous heat condition, evaluations of warmth intensity demonstrated a significant attenuation across the first four experimental sessions but failed to show a significant reversal of attenuation after change of the stimulation site in the fifth session. However, considering the evaluations of warmth closely mirrored the ratings of pain and showed a strong trend ($P = 0.08$) on day 5 toward returning to preattenuation values, one cannot conclude that the processes subserving attenuation within the two modalities are entirely independent. Our failure to document a significant spatial specificity for attenuation of warmth perception may be explained from the substantial inter-individual variability in the ratings of warmth perception, perhaps reflecting the subjects' difficulty to rate warmth intensity consistently. Alternatively, innocuous thermal stimuli may, indeed, activate a range of brain areas with a weaker lateralization bias, which could lead to a more generalized attenuation affect. Future studies will be required to clarify this issue.

### Conclusion

This study investigated attenuation in heat pain perception. Both sensory and affective components of pain showed attenuation, and it was highly specific to the repeatedly exposed body side. We suggest that the probable plasticity underlying these perceptual changes occurred in brain areas that display at least a contralateral bias if not a strict pattern of contralateral activation. We also suggest that attenuation of pain unpleasantness is the result of a serial interaction of the lateral and medial pain systems. In addition, these results give support to the exploration of noninvasive, medication-free therapies for the relief of pathological pain, through behavioral manipulations (Flor et al. 1995, 2001) designed to induce adaptive plastic changes within the nociceptive system.

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