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Pain additivity, diffuse noxious inhibitory controls, and attention: A functional measurement analysis

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Abstract

This study utilized the methodology of Functional Measurement theory to investigate the additivity of painful and non-painful thermally induced experiences at one body site with those produced by brief noxious and innocuous electrical stimuli at another. Forty healthy young subjects were tested, using a Peltier thermode to induce tonic pain and an electrocutaneous stimulator for presenting phasic pain, under conditions of either full attention or visual/cognitive distraction (counting numerous light signals) in order to evaluate whether the summed effects are attributable to refocused attention. Six levels of intensity were combined in a factorial design for both tonic and phasic pain. Subjects indicated the overall strength of their dual perception on a visual analog scale. Stimuli showed complex patterns of interaction. Two stimuli were generally rated as greater than one, but the summation was far from additive and greatly influenced by the intensity of the stronger stimulus, suggesting inhibitory action. In general, tonic heat pain strongly affected the perception of phasic electrocutaneous pain whereas the reverse was only partly true. Distraction had a very small effect, suggesting that the "pain inhibits pain" phenomenon attributable to diffuse noxious inhibitory controls (DNIC) is not due to attentional processes. Our data also relate to issues regarding spatial summation across dermatomes and to adaptation level effects in pain, in which a strong painful experience serves as an anchor or comparison point by which others are judged. The psychophysical findings provide a perceptual foundation for clinical phenomena in which patients face with comorbid pain disorders.

Keywords: *Pain, integration, functional measurement, summation, heat, electrical stimulation, psychophysics*

Introduction

Psychophysical and clinical pain studies usually ask the observer or patient to provide details about a single source of discomfort. The task may require a judgment of pain intensity or unpleasantness using magnitude estimation, verbal descriptors, or a visual analog scale, but the focus is almost always on one bodily area.

This somewhat simplifies real world conditions. While patients may tell their health professional that they have pain in, for example, the back, the face, the abdomen, or the head, a careful clinical examination often discovers other locations and sources of pain. Even a simple technique such as the use of an outlined body map (Parker et al. 1995; Escalante et al. 1996; Carr 1997), combined with a visual analog scale for each site (Lautenbacher et al. 1999), indicates that individuals can specify the locus and intensity of multiple, simultaneous pains. How do such multiple pains interact?

Do multiple pains influence each other?

Pain sensations at multiple body sites can influence one another. In the laboratory, interactions between two concurrent noxious stimuli have been investigated in both lower animals and humans within the framework of a phenomenon known as "heterotopic noxious conditioning stimulation" (HNCS) (Plaghki et al. 1994; Lautenbacher et al. 2002) or

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"diffuse noxious inhibitory controls" (DNIC) (Willer 1977; Le Bars et al. 1979a, 1979b). Typically, in such studies, a strong tonic stimulus at one body site reduces the perceived pain (Talbot et al. 1989) or the size of a noxiously induced reflex or evoked response (Andersen et al. 2001; Motohashi and Umino 2001) produced by a brief, phasic stimulus at another location on the body. This effect appears to be generated, in large part, by the action of a potent descending inhibitory pain control system, principally modulated by opiate mechanisms (Willer et al. 1990; Le Bars et al. 1992).

In DNIC studies, the tonic conditioning stimulus is generally both greater in intensity and longer in duration than the test stimulus. Only rarely have researchers investigated the nature of the interaction between two noxious stimuli close in perceived intensity and duration or the combination of a painful and non-painful stimulus.

Svensson et al. (1999) explored whether both painful (hypertonic saline) and non-painful (vibration) conditioning stimuli would influence the perceived pain intensity of an electrocutaneous test stimulus at a different body site. Both forms of the conditioning stimulus caused significant decreases in the perceived pain intensity of the test stimulus. The noxious stimulus caused a reduction of 26–37% in the experienced intensity of the electrical test pulse, while the vibration reduced the intensity by 15–25%, the higher end of each range occurring for ipsilateral stimulation and the lower for contralateral. Watanabe et al. (1999) found that tonic muscle pain reduced both cortical evoked potential amplitudes and perceived pain intensity for cutaneous electrical pulses presented extra-segmentally, but non-painful vibration affected neither.

Kosek and Hansson (1997) reported that non-painful vibration on the forearm increased pressure pain thresholds, warmth thresholds, and heat pain thresholds on the thigh, but had no effect on the perceived intensity of more noxious thermal pulses. Lautenbacher and Rollman (1997) found concurrent thermal stimulation on the foot, at both painful and non-painful levels, significantly increased electrical pain threshold on the forearm in healthy controls (but not in fibromyalgia patients). Lautenbacher et al. (2002), however, in a study involving phasic heat stimuli at the cheek and tonic conditioning stimuli at either the hand (hot water) or forearm (thermode) discovered that only painful levels of the conditioning stimulus increased the heat pain threshold.

Findings such as these, which show that non-painful conditioning stimuli can sometimes modulate the perceived intensity of moderately and even strongly noxious test presentations, suggest that, under appropriate conditions, the notion that "pain inhibits pain" (Melzack 1975) needs to be expanded. As well, they raise the likelihood that such interactions are not exclusively the result of an ascending and descending spino-bulbo-spinal inhibitory control system involving depression of nociceptive inputs (Villanueva and Le Bars 1995) and, in particular, suggest that other somatosensory mechanisms, attentional factors, or situational influences on relational judgments (how one stimulus compares to another) may determine the perceptual response to multiple noxious and non-noxious signals (Svensson et al. 1999).

Functional measurement

Anderson's (1970) theoretical and empirical work on psychophysical integration of several simultaneously or successively presented stimuli provides an excellent framework for studying multi-signal interactions. Anderson, who emphasized that perception should be viewed as the integration of stimulus information into a unitary percept, developed information integration theory and the functional measurement paradigm as a means of establishing the rules which subjects use in forming perceptions or judgments. This "cognitive algebra" approach (Anderson 1976) avoids the traditional technique of scaling single stimuli in favor of one which requires the judgment of a set or combination of stimuli yielding, at the same time, functional scales of each of the component stimulus dimensions.

Typically, each of two sets of stimuli is combined in a factorial design and subjects assign a single magnitude estimation response reflective of their subjective impression of the joint pair. The characteristics of the judgment functions, showing perceived magnitude as a function of the intensity of one stimulus, with intensity of the other stimulus as a parameter, permit a determination of the interaction between the two signals, particularly noting, from examination of slopes, whether they are additive.

Several investigators have used functional measurement to study the underlying characteristics of pain integration. Algom et al. (1986) undertook a multimodal test of discomfort, combining six levels of electric shock and six levels of loud tones. Asking "Is overall pain equal to the simple sum of the component painful sensations", they had subjects make magnitude estimates of the discomfort produced by a very brief electrical shock that was presented during a 3.5 s auditory tone. The roughly parallel nature of the psychophysical functions (plotting perceived pain vs current intensity, with stimulus–response functions for each auditory level as a parameter) caused them to conclude "overall pain equals the linear sum of the component electrocutaneous and auditory pain".

In a subsequent study (Algom et al. 1987), this group replicated their findings, using a longer train of square wave pulses combined with the same auditory sequence. Again, "a given increase in the level of any one of the noxious variables increased overall nociception by a constant amount regardless of the level of the other variable". The authors proposed a functional theory of pain in which the outputs of separate pain-related psychophysical transformations are projected onto a central cognitive space where they are integrated according to simple algebraic rules.

Jones (1980) had subjects judge the intensity of a pair of successive electrical shocks on a 20-point rating scale. In one session, the four different intensities were each weak, while in a second session they were each noxious. Their data suggested that perceived magnitude increased nonlinearly when the shocks were painful, since more intense stimuli had a disproportionate influence on the ratings. A later study (Jones and Gwynn 1984), using a wider range of intensities, displayed integration of stimulus pairs at both low and high levels of painfulness. Gracely and Wolskee (1983) extended the functional measurement approach to verbal descriptors of pain, showing that subjects could combine different levels of tooth pulp stimulation with words such as "mild", "moderate", or "intense" to yield a set of parallel, monotonically increasing functions of perceived averaged intensity or unpleasantness.

These findings suggest that observers are able to quantitatively evaluate the perceptual experiences created by multiple simultaneous or successive stimuli, that noxious stimuli may have a disproportionate effect in influencing the combined perception, and that the functional measurement model can be used to describe the effects of such presentations. Still, by focusing on restricted ranges of intensities and utilizing brief stimuli, identical or homologous sites, verbal descriptors, or auditory presentations, they are restricted in their ability to inform us about the nature of more common pain interactions, whether they are clinical (such as a new pain added against a mosaic of existing discomfort) or experimentally induced.

The nature of such interactions is often not additive. In the DNIC phenomenon, a lengthy tonic stimulus appears to inhibit the representation of a severe but brief phasic input, but there are several studies where non-noxious as well as noxious stimuli have produced DNIC-like effects (Lautenbacher et al. 2002; Xu et al. 2003).

Bidirectional interactions have also been described. Studies of the so-called "touch gate", have shown that induced pain or clinical pain can suppress the perception of non-noxious stimuli (Apkarian et al. 1992, 1994; Hollins et al. 1996; Bolanowski et al. 2001; Stohler et al. 2001) while another investigation indicated that phasic pain, perhaps through an alerting function, can facilitate tactile processing (Ploner et al. 2004).

The study we are presenting in this report involves a careful examination of the interaction between simultaneously delivered somatosensory inputs, controlling body sites, stimulus modalities, intensities, and durations. By using the functional measurement methodology, manipulating the parameters of both a tonic heat conditioning stimulus located on the thigh and a phasic train of electrical pulses presented on the forearm, we are able to illustrate the psychophysical characteristics of pain integration and to shed light on the mechanisms underlying the DNIC phenomenon. Moreover, by testing this integration under two attentional conditions, full attention and distraction created by a visual task, we can investigate whether the effects of the conditioning stimulus are attributable to its attentional role as a distracter.

Materials and methods

Subjects

Twenty women and 20 men (age: 25 ± 2 years for women and 26 ± 2 years for men) took part in the study. Criteria for inclusion were no acute and chronic disease or pain, no disturbance of somatic sensation and, for women, no pregnancy. Subjects were asked to remain free of any analgesics, sedatives, or cough medication for 1 week prior to the two experimental sessions and to drink no alcohol for the 12 h preceding each session. Ten of the women used oral contraceptives. All subjects gave informed consent and were paid for participation. The experimental protocol was approved by the human ethics committee of the University of Marburg's School of Medicine.

Protocol and procedures

All subjects took part in two sessions within a period of 5 days or less. One session tested subjects under a condition of no distraction of attention away from experimental pain; the other session involved distraction. The order of these sessions was randomized. Sessions began at 9:30 a.m., 1:30 p.m., or 5:30 p.m. The time of day was equivalent for the two sessions within each subject. Session 1 lasted 3.5 h while Session 2 was 3 h long; the first took somewhat longer due to instructions and practice trials.

Each session consisted of 35 experimental blocks. In each block, one of the combinations of six preset intensities of tonic stimulation and six preset intensities of phasic stimulation was applied. The factorial combination of 6×6 intensities would have led to 36 experimental blocks; however, the combination of zero/zero intensities was not administered. The intensities for tonic heat stimulation were zero stimulation, stimulation at -1.0, -0.5, 0.0, 0.5, and 1.0°C relative to each participant's heat pain threshold. The intensities for phasic electrical stimulation were zero stimulation, stimulation at -0.6, -0.3, 0.0, 0.3, and 0.6 mA relative to the individually determined electrocutaneous pain threshold. The 35 combinations of intensities were arranged randomly for use in the same order for all subjects.

Tonic heat stimuli were delivered by use of a Peltier thermode (Phywe Systeme, Goettingen, Germany) of 6 cm^2 contact area attached by a contact pressure of 0.4 N/cm^2 to the skin at the thigh. The tonic stimulus consisted of a series of short heat pulses, which were tailored to the individual pain threshold and reached, at peak, the temperature as specified: -1.0, -0.5, 0.0, 0.5, and 1.0°C relative to pain threshold (see Figure 1). The base of the pulses was always 1.0°C below peak. These brief pulses were delivered at a frequency of 30 pulses per min over 2 min. Such stimulation triggers slow temporal summation and results in a highly effective and safe noxious input when applied above pain threshold (Lautenbacher et al. 1995).

The phasic electrical stimuli were supplied by a constant current stimulator (Frederic Haer and Company, Brunswick, ME, USA) and delivered to the skin on the volar surface of the forearm by means of surface electrodes of 0.4 cm diameter. A stimulus consisted of a train of 15 pulses of 4 ms duration applied with a frequency of 100 Hz. When paired with the heat stimulus, six of these phasic electrical stimuli were delivered at intervals of 20 s, starting 20 s after the onset of the heat (see Figure 1). When presented alone, the same temporal pattern was utilized.

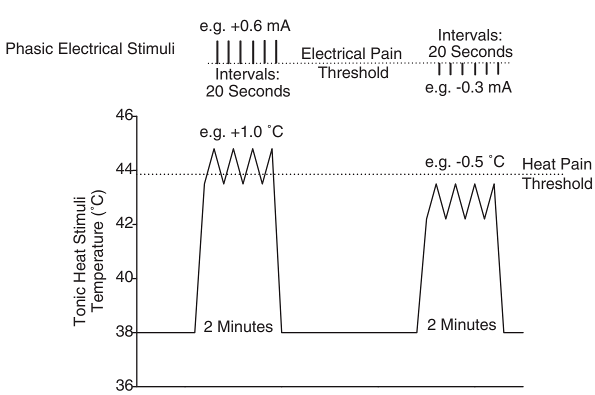


Figure 1. Schematic description of the experimental procedure. As examples 2 out of 35 combinations of phasic stimulation (electrical current) and tonic stimulation (heat) are presented.

Pain ratings

A visual warning began 1 s prior to each phasic electrical stimulus onset, overlapped the pulses, and remained on for a total of 2 s. At the offset of the visual signal, subjects were asked to rate the combined intensities of the tonic heat and the phasic electrical stimuli that they had just experienced. This approach of assessing two concurrent stimuli by a single rating was adopted from the established functional measurement methodology (see Introduction). For the rating of the combined intensities, an open visual analog scale (VAS) with a length of 140 mm was used. The scale was marked at 20 mm with "no sensation", at 70 mm with "very slightly painful sensation", and at 120 mm with "extremely painful sensation". Each experimental block consisted of six ratings which were averaged to obtain the value for that particular combination of phasic and tonic stimulation.

Attentional distraction

The visual display, besides signaling the delivery of the stimulus and the time when the subject should provide a rating, was used for experimental manipulation of attentional distraction. The display consisted of 16 small signal lights arranged in a square configuration (4×4). In the attentional distraction condition, six to nine lights were activated on each trial, the exact number of which was randomized. The subjects were required to count the lights and, after providing a pain rating, to report their number. Since the lights were on during phasic stimulation, concurrent attentional distraction from the noxious inputs was guaranteed. In the condition with no attentional distraction, all lights were illuminated and no counting instruction was given. Pilot testing indicated that the distraction task was sufficiently difficult to produce significant error rates but not so demanding as to frustrate observers or prevent them from performing the psychophysical rating task.

Testing protocol

Since all thermal and electrical stimuli were defined relative to pain threshold, assessment of pain threshold for each body side preceded experimental stimulation on each testing day. Heat pain thresholds were determined on each thigh by asking subjects to adjust a temperature starting from 38°C, using heating and cooling buttons, until they obtained a level which was barely painful. There were seven such trials; averages of the last six were used as the measure of pain threshold. For assessment of the electrical pain thresholds, discrete stimuli of increasing intensities from zero were administered on each arm. Current levels were increased in steps of 0.15 mA until subjects indicated that they were experiencing pain. There were four runs; averages of the last three were used as the pain threshold.

Subjects sat in a comfortable armchair and placed their feet on an adjustable footrest. Two adjacent electrodes were centered on the volar side of each forearm. At the appropriate times, according to the experimental protocol, either the left or the right pair was connected to the stimulator. The thermode was attached, also according to the experimental protocol, at one of nine varying sites on the dorsal surface of each thigh. The site of heat stimulation was changed after each experimental block until the last of the nine sites was tested (in order to control for the effects of local sensitization), then the body side was switched. Half of the subjects began with stimulation at the left body side; the others were stimulated starting on the right. Tonic thermal and phasic electrical stimuli were always applied ipsilaterally.

At the beginning of their first session, subjects received standard instructions, were made familiar with the procedure by exposure to phasic electrical stimuli and concurrent tonic heat stimuli at pain threshold level, and were trained to rate the total sensation produced by the two stimuli by giving one combined rating. Heat stimulation during this practice phase was presented at the calf in order to avoid premature sensitization of the thigh region.

Data analysis

The main interest in the present study focused on the perceptual interaction of tonic and phasic stimuli. It is clearly established that perceived intensity of tonic heat or phasic electrically induced pain will be enhanced as the intensity of each stimulus, presented alone, increases. Of prime interest in this study, however, is the interaction between these two stimuli presented together. Is there additivity between phasic and tonic stimuli, causing an increase in sensation, or a DNIC-like inhibition of the former by the latter, resulting in sensation reduction? Are effects of one stimulus on another reciprocal; if A affects B, does B affect A? As well, since each of the two stimuli can be greater, equal, or less intense perceptually than the other, is there a more complex interaction between the two, reflecting mediation by relative intensity?

Accordingly, the data were examined specifically for interactions by means of an analysis of variance with repeated measurement factors, one for the intensities of phasic electrical stimulation and one for the intensities of tonic heat stimulation. A further repeated measurement factor was added to assess the effects of attentional distraction. Finally, a group factor was added to control for the effects of gender, which is not emphasized in the present study and will not be reported here.

The result was a 2 (gender) $\times$ 2 (attention) $\times$ 6 (levels of phasic stimulation) $\times$ 6 (levels of tonic stimulation) analysis of variance (ANOVA), with the rating of the combined stimuli as the dependent variable. This analysis allowed us to assess both the combined effects of phasic and tonic stimuli and the effect of each stimulus by itself (intensity level "zero" for one of the two stimuli). Since the combination of zero/zero intensities for phasic and tonic stimulation is meaningless and was not administered, this cell of the analysis of variance was filled by estimates of 0 for all subjects.

In order to assess the effect of only combined stimulation, a second analysis was computed which did not include the "zero" intensity levels. This creates a 2 (gender) $\times$ 2 (attention) $\times$ 5 (phasic stimulation levels) $\times$ 5 (tonic stimulation levels) ANOVA. Where it was appropriate, a posteriori analyses were conducted by means of *t*-tests for paired samples. Alpha level of significance was set to 0.05 throughout.

Results

Pain thresholds

The assessment of pain thresholds was undertaken in order to tailor the phasic electrical and the tonic heat stimulation in the experimental trials. Pain thresholds were assessed for both body sides during both sessions (separated by a maximum of 5 days). The averaged pain thresholds on the left body side were 44.2 ± 1.4°C for heat and 2.45 ± 1.19 mA for electrical current; those on the right body side were 44.4 ± 1.2°C for heat and 2.60 ± 1.19 mA for electrical current. The side difference for heat was not significant ($p > 0.050$), while the difference for electrical current was small but significant ($p \leq 0.050$). The latter finding does not create difficulties regarding phasic stimulation, since both the left and the right body sides were used in all subjects and the intensity of phasic stimulation was tailored separately to pain threshold on each body side. The pain thresholds in Session 1 were

44.2 ± 1.4°C for heat and 2.48 ± 1.17 mA for electrical current and those in Session 2 were 44.4 ± 1.2°C for heat and 2.57 ± 1.20 mA for electrical current. Both differences were non-significant (both $p > 0.050$).

Effects of combined stimulation

Before looking for combined effects, we tested whether increasing intensity levels of both phasic electrical and tonic heat stimulation led to increasing ratings on the VAS. This criterion was clearly fulfilled as evidenced by the highly significant main effects of stimulation in both analyses of variance, both with and without zero level stimulation included (see Table I).

The key question is whether, in addition to the main effects of both thermal and electrical intensity, there is an interaction effect between the two. Such a significant interaction was found in each analysis of variance, with and without zero level stimulation included (see Table I).

Figure 2(a) illustrates the interaction, as slopes describing the effects of phasic electrical stimulation upon the ratings become markedly shallower at the three highest intensity levels of tonic heat stimulation, particularly at the uppermost one. Corroborating this inspection, ratings for adjacent levels of electrical intensity were always significantly different from one another at the lower levels of tonic heat stimulation (zero stimulation, 1.0 and 0.5°C below heat pain threshold) but failed to differ once at pain threshold, twice at 0.5°C above heat pain threshold, and four times out of five comparisons at 1.0°C above heat pain threshold (see Table II). It is important to note that the impact of the tonic heat stimulation upon the perceptual effects of phasic electrical currents was clearly not confined to the electrical pain range; it is obvious also below electrical pain threshold (see Figure 2(a) and Table II).

We did not obtain an equivalent impact of phasic electrical stimulation upon the perceptual effects of tonic heat stimulation. Only the highest level of phasic electrical stimulation markedly reduced the distances between the VAS ratings for the various intensity levels of tonic heat stimulation (see Figure 2(b)). In confirmation, adjacent levels of tonic heat stimulation were not significantly different in four out of five comparisons at the highest level of phasic electrical stimulation (see Table II). At lower levels of phasic electrical stimulation, this happened very rarely and without dependence upon the intensity of the current. As was the case above, the strongest phasic electrical stimuli influenced the subjective ratings of both initially painful and non-painful tonic heat stimuli.

Effects of attention

There was a main effect of attention in both analyses of variance, with and without zero level stimulation included (see Table I). Still, the reduction by distraction was extremely modest, bringing the ratings for all stimulus combinations down from 73.6 ± 11.2 to 70.9 ± 12.1 and those for stimulus combinations not including zero levels from 79.6 ± 12.0 to 77.1 ± 12.9.

There is a significant ($2 \times 2 \times 5 \times 5$ analysis) and nearly significant ($2 \times 2 \times 6 \times 6$ analysis) interaction between the effects of attentional condition and the effects of intensity of phasic electrical stimulation (see Table I). As Figures 3(a) (for lower heat levels) and (b) (for higher heat levels) depict, the increase in ratings associated with the increase in phasic electrical stimulation is smaller in the condition with distraction than in that without distraction. Accordingly, at the level of 0.6 mA below electrical pain threshold, the difference between the ratings without distraction, averaged over all intensity levels of tonic heat stimulation (68.3 ± 15.1), and those with distraction (67.5 ± 15.4) was not significant

Table I. Results of the analyses of variance of the effects of the phasic stimuli (intensity levels of electrical current), tonic stimuli (intensity levels of heat), and attentional distraction upon the ratings on a visual analog scale for 40 subjects.

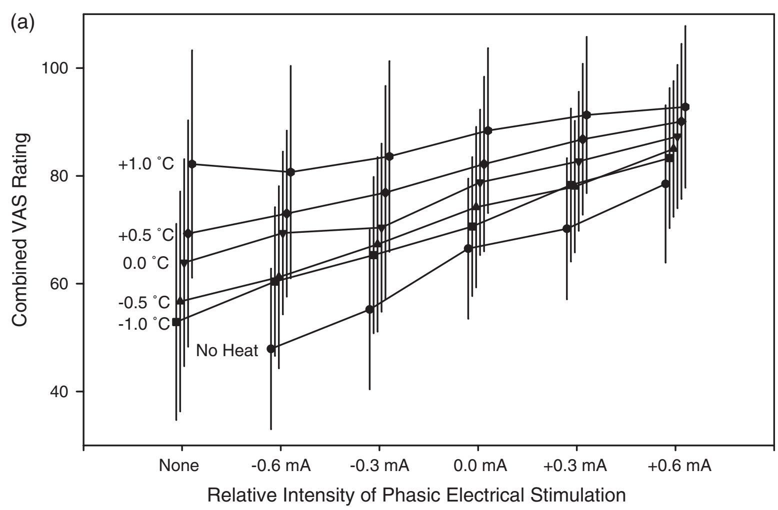
	$2 \times 2 \times 5 \times 5$ Analysis[a]		$2 \times 2 \times 6 \times 6$ Analysis[b]	
Source of variance	F	p	F	p
Phasic stimulus (P)	76.55	<0.001	148.03	<0.001
Tonic stimulus (T)	55.48	<0.001	120.56	<0.001
P × T	2.63	0.001	42.92	<0.001
Attention (A)	5.34	0.026	6.36	0.016
A × P	2.61	0.038	2.20	0.056
A × T	1.00	0.407	2.31	0.046
A × P × T	1.39	0.141	1.83	0.008

[a]Analysis which includes five intensity levels of phasic and of tonic stimuli and no zero levels of these stimuli. [b]Analysis which includes six intensity levels of phasic and of tonic stimuli and zero levels of these stimuli.

($p > 0.050$), whereas at the level of 0.6 mA above electrical pain threshold, there was a highly significant difference between the ratings without distraction (90.1 ± 11.3) and those with distraction (85.0 ± 13.0, $p \leq 0.001$). The differences in between gradually shifted from non-significant to significant (at 0.3 mA below pain threshold 71.6 ± 16.7 without distraction and 71.9 ± 15.9 with distraction ($p > 0.050$), at pain threshold 80.1 ± 12.7 without distraction and 76.3 ± 14.1 with distraction ($p \leq 0.050$), 0.3 mA above pain threshold 84.5 ± 12.4 without distraction and 81.5 ± 12.3 with distraction ($p \leq 0.050$)). These findings indicate that attentional distraction affects only the perceptual effects of painful phasic electrical stimuli, but not those of non-painful ones. This effect occurred whether the electrical pulses were presented in isolation or paired with thermal stimulation.

A different finding emerged when we examined the effects of distraction on thermal stimuli. For tonic heat, the interaction between the effects of attentional condition and the effects of intensity level in the $2 \times 2 \times 5 \times 5$ ANOVA (zero level stimulation not included) was not significant, whereas in the $2 \times 2 \times 6 \times 6$ analysis (zero level stimulation included) the interaction was significant.

The reason for this becomes clear in Figures 3(a) and (b). Only in the condition in which tonic heat stimulation was applied alone (zero level stimulation for phasic electrical stimulation) was the effect of attention dependent on the level of tonic heat stimulation; distraction appeared to have no effect on the subjective ratings of non-painful heat levels but markedly reduced the rating of painful intensities. In this instance, the averaged ratings in the conditions with and without distraction were



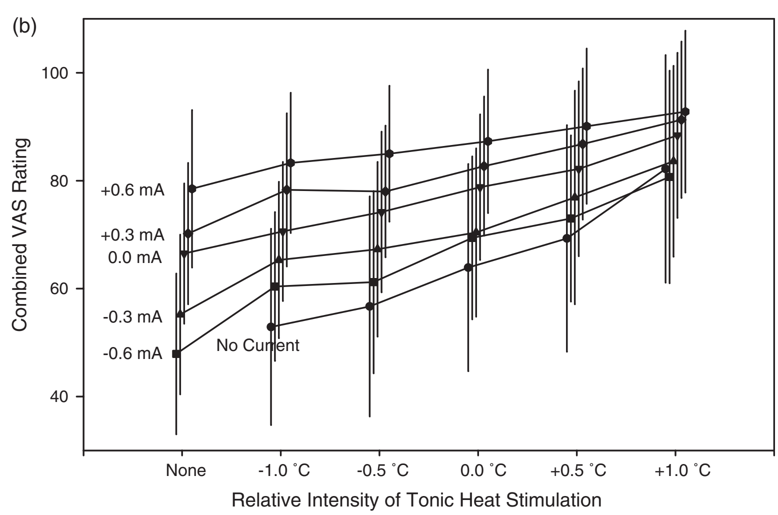


Figure 2. Means and standard deviations of the visual analog scale ratings as function of the intensity levels of phasic electrical stimulation (a, with level of concurrent heat as a parameter) and tonic heat stimulation (b, with level of concurrent electrical stimulation as a parameter) in 40 subjects averaged over the two attentional conditions (with and without distraction).

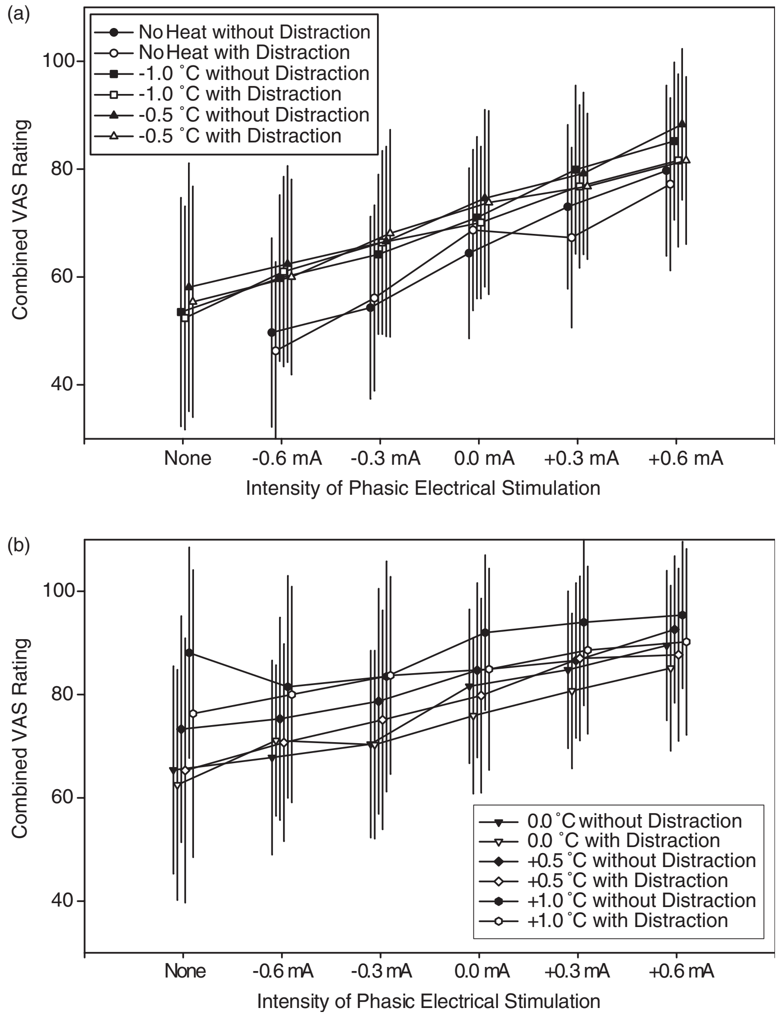


Figure 3. Means and standard deviations of the visual analog scale ratings as function of the intensity levels of phasic stimulation (electrical current) and tonic stimulation (heat) in 40 subjects separately for the attentional condition with (open symbols) and that without distraction (closed symbols). "None" is used for the conditions when the thermal stimuli were presented alone. (a) The conditions with the lower intensities of tonic heat stimulation. (b) The conditions with the higher intensities.

Table II. Means and standard deviations of the common visual analog scale ratings for the combinations of tonic heat stimuli (rows) and of phasic electrical stimuli (columns) averaged over the two attentional conditions with and without distraction ($n = 40$); asterisks ($^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$) and "ns" symbols describe the significance of t-test results (paired samples) for differences between cells.

	No heat		−1.0°C		−0.5°C		0.0°C		0.5°C		1.0°C
No current	0.0 ± 0.0	***	52.9 ± 18.2	ns	56.7 ± 20.4	**	63.9 ± 19.2	ns	69.3 ± 21.0	***	82.2 ± 21.1
	***		**		*		*		ns		ns
−0.6 mA	47.9 ± 14.9	***	60.4 ± 13.8	ns	61.2 ± 16.9	***	69.4 ± 15.1	ns	73.0 ± 15.4	***	80.7 ± 19.7
	**		*		***		ns		ns		ns
−0.3 mA	55.2 ± 14.8	***	65.3 ± 14.5	ns	67.3 ± 16.2	ns	70.4 ± 15.6	**	76.9 ± 19.8	***	83.6 ± 17.7
	***		**		***		***		*		**
−0.0 mA	66.5 ± 13.0	ns	70.6 ± 12.9	ns	74.2 ± 14.9	**	78.8 ± 13.5	ns	82.2 ± 16.2	***	88.4 ± 15.3
	*		***		*		**		*		ns
0.3 mA	70.2 ± 13.1	***	78.3 ± 14.2	ns	78.0 ± 12.2	*	82.7 ± 12.9	*	86.8 ± 14.0	**	91.3 ± 14.5
	***		**		***		**		*		ns
0.6 mA	78.5 ± 14.6	*	83.3 ± 13.0	ns	85.0 ± 12.6	ns	87.3 ± 13.3	ns	90.1 ± 14.4	ns	92.8 ± 15.0

53.9 ± 21.2 and 52.4 ± 20.7 ($p > 0.050$) at the level of 1.0°C below heat pain threshold, 58.1 ± 23.0 and 55.4 ± 21.4 ($p > 0.050$) at the level of 0.5°C below heat pain threshold, 65.4 ± 20.1 and 62.5 ± 22.3 ($p > 0.050$) at the level of heat pain threshold, 73.3 ± 21.9 and 65.3 ± 25.6 ($p \leq 0.050$) at the level of 0.5°C above heat pain threshold, and 88.1 ± 20.4 and 76.3 ± 27.8 ($p \leq 0.001$) at the level of 1.0°C above heat pain thresholds. This shift from non-significant to highly significant differences means that attentional distraction lowered the ratings of the tonic heat stimulation only at the higher, mainly painful levels when thermal stimulation was presented alone.

The fact that there is no similar combination-specific effect of attentional distraction upon the perception of phasic electrical stimulation (distraction affects painful electrical pulses both when alone and in combination with thermal stimuli) forms the basis for the significant interaction of Attention × Phasic Stimulus × Tonic Stimulus in the $2 \times 2 \times 6 \times 6$ analysis of variance (zero level stimulation included) (see Table I). If the suppressive effects of the tonic stimulus on the perception of the phasic one (as suggested by the DNIC phenomenon) depended upon attentional distraction, it should have become manifest by a significant interaction of Attention × Phasic Stimulus × Tonic Stimulus in the $2 \times 2 \times 5 \times 5$ analysis of variance (no zero level stimulation included). However, in this analysis no significant three-way interaction appeared.

Discussion

The data presented in this report provide a number of insights regarding the way in which multiple stimuli interact in order to produce a percept of overall sensation. First, we have shown that two stimuli, whether innocuous or noxious, produce joint effects, which are greater than either presented alone but the combined perceptual effect is far from additive. Second, when one of the stimuli is intense and/or prolonged, it has a disproportionate effect on the combined rating. Third, the lack of additivity and the moderate contribution of a second stimulus to an intense one suggest that the strong stimulus causes a DNIC-like suppression of the experience produced by the weaker signal, greatly muting its normal effect. Finally, attentional distraction produces a reliable but modest decline in the ratings for these stimuli. The absence of a three-way interaction of attention with electrical and thermal intensity in the decisive analysis of variance denotes that the suppressive DNIC-like effects of stimulation are not dependent upon distraction. We will consider these effects separately below.

Additivity of pain

Figure 1 and Table II, which present the ratings of perceived intensity for all combinations of tonic and phasic stimulus levels, allow us to confirm and quantify the conclusion that "two pains are greater than one". The striking nature of this relationship deserves careful examination.

On a 140 mm scale that spans the pain range, with 70 standing for "very slightly painful sensation", observers demonstrated appropriate use of the scale. The average rating for the phasic electrical stimulus at pain threshold was about 67; for the tonic thermal stimulus, it was 64.

What happens when you simultaneously present the two stimuli? You get a total pain experience that is far less than the sum of the two values individually. To take a few examples from Table II, (i) an electrical pulse rated as 67 and a thermal stimulus rated as 64 combine to produce a pain experience rated as 79; (ii) combining levels of electrical and thermal signals that are each slightly painful (70) yields a combined experience that is notably painful (87), but still much less than an algebraic sum; (iii) once you have a quite intense level of a thermal stimulus (rated 82), adding the electrical stimulus has relatively little effect. In fact, adding a non-noxious electrical stimulus (rated 48) has no effect, adding one that is barely painful (67) takes the combined rating to 88, and adding the most intense stimulus (rated 79) still only produces a total pain rating of 93. In essence, slightly to moderately noxious stimuli combine far from additively to produce a quite painful perception. Strongly painful experiences, particularly when induced by tonic heat, are only moderately influenced by the addition of a second stimulus.

Interactions between perceived intensity of stimuli

Rather steep individual stimulus–response functions become increasingly flatter or shallower as an increasingly strong stimulus is applied concurrently, highlighting two trends. First, adding a stimulus to a moderately or strongly intense stimulus has relatively little effect. Second, there is an asymmetry or imbalance in the perceptual relationship between the tonic and phasic stimuli, such that summing the phasic to an intense tonic stimulus has less effect than the reverse. The analyses reported earlier confirmed this by demonstrating, in an examination of the significant interaction effect between the two stimuli (in addition to separate main effects), that the addition of the electrical stimulus had a less deleterious effect on the discrimination of adjacent levels of heat stimulation than vice versa.

Several other features merit attention. The data for the electrocutaneous or the heat pulses presented alone, as well as those signals presented in combination, produce relatively flat psychophysical functions which span the range from clearly non-painful to moderately painful. There is a smooth transition between the innocuous and noxious ranges of these continua.

Not surprisingly, one can enhance a pain experience by either raising the intensity of a single stimulus or combining it with another one. Increasing a single electrical train from 0.3 mA above pain threshold to 0.6 mA above threshold changes the rating from 70 to 79. Adding an innocuous tonic heat pulse (1.0°C below pain threshold) to the threshold plus 0.3 mA stimulus does the same. This means that concurrent somatosensory stimulation can enhance the sensation of overall pain in an extra-segmental interaction, even if one of these sources of sensation produces non-painful experiences.

These conclusions are based upon the assumption that the trained subjects were capable of concurrently following two requests in using our scale. They had (i) to use the line length on the VAS in a proportional way to express the intensity of sensation and (ii) to appropriately regard the verbal markers on the VAS for the ranges of painful and non-painful sensations. Conflicts between the two task demands could, perhaps, distort the use of line lengths. Likewise, we note that the tonic thermal stimuli were always presented at the forearm and the phasic electrical ones at the thigh. Thus, the stimuli differ in terms of modality, duration, locus, and peripheral and central neural representations. Practical considerations did not allow for a parametric evaluation of all these characteristics, but such fixed combinations are often utilized in psychophysical studies in general and pain ones in particular.

Implications for the DNIC effect

Earlier studies have suggested that the DNIC phenomenon involves a pain-induced attenuation in the neural or behavioral representation of a separate noxious test stimulus (Talbot et al. 1989; De Broucker et al. 1990; Kakigi 1994). Willer et al. (1989) found that the reduction of the R_{III} nociceptive flexion reflex in humans was directly related to the intensity of a tonic thermal conditioning stimulus within the pain range but was not affected by innocuous stimuli. Other reports (Svensson et al. 1999; Lautenbacher et al. 2002), however, have demonstrated circumstances where non-painful conditioning stimuli can reduce the perceived pain intensity of phasic test pulses.

In this study, moderately high levels of tonic heat stimulation tended to make different levels of phasic electrical stimulation, both above and below pain threshold, relatively indistinguishable. In contrast, only very intense electrical stimulation had a comparable effect on the perception of thermal stimuli. Hence, although there are combinations which create mutual, bidirectional interactions between tonic and phasic stimuli, generally the tonic heat stimulus, even when equivalently painful, has a greater effect in reducing the contribution of the phasic electrical one than is the reverse case. It is unlikely that these effects reflect the operation of a ceiling effect; examination of the figures indicates that subjects had considerable room for higher pain ratings in all conditions and combinations.

While this study is not a test of the DNIC paradigm in the traditional sense (in which subjects only describe their perception of the phasic stimulus in the presence of an intense tonic masker), the fact that a weak stimulus adds little to the joint perception of itself and a concurrent very noxious signal, particularly when the stronger stimulus is a tonic thermal one, suggests that the masker provides a neural or cognitive inhibition of the weaker pulse.

Cognitive factors have been considered to play a role in the DNIC effect before. Numerous studies (Boureau et al. 1991; Peters et al. 1992; Dar et al. 1995) have suggested that a perceptual adaptation level model would predict the incomplete additivity of two stimuli, particularly when one of them is intense. Adaptation level theory applied to pain (Rollman 1979, 1989) proposes that one painful experience can serve as an anchor or comparison point by which others are judged. The perceived painfulness of, say, an intense heat stimulus may make the presence of a simultaneous electrical pulse seem rather modest. Consequently, the net effect of the second stimulus is weak and the judgment of the combined pair is not considerably greater than that of the stronger one alone. Adaptation level theory places emphasis on a simultaneous comparison process in which two stimuli are processed. Such, was also the case in the functional measurement task presented here.

Relationship to spatial summation

The finding that noxious stimulation at two bodily sites gives rise to a joint sensation that is greater than either one presented alone raises questions about the nature and locus of the integration process. The psychophysical data do not directly address the role of peripheral and central sensory effects or higher order cognitive ones, but the large separation between the stimulation sites at the thigh and forearm make it unlikely that we are dealing with peripheral spatial summation effects.

Green (1991) showed that a chemical irritant (methyl salicylate) applied to one forearm could inhibit a weaker one applied contralaterally but had no effect on the perception of warmth or pain elicited 10 cm away by a thermal stimulus. In the reverse case, noxious heat, at that distance, could reduce the level of chemical irritation. A rather different pattern of interaction occurred when the chemical counter-irritant was applied immediately adjacent to the thermal stimulus. Then, the perceived warmth of the latter increased in what seemed to be local summation or integration.

Others have also identified manifestly different effects when two somatosensory stimuli are presented near to one another or far away. Bolanowski et al. (2000) found that heat-induced or cold-induced pain elevated tactile thresholds when applied in close proximity, but had no effect contralaterally. Dowman and Zimmer (1996) discovered that painful heat can increase the perceived magnitude of an innocuous electrical stimulus when applied nearby but not contralaterally. Likewise, Nahra and Plaghki (2003), who presented subjects with brush strokes on the left arm or right foot while stimulating the left arm with brief CO_2 laser pulses, found that segmental brushing interfered with the detection of low amplitude laser pulses but that the extra-segmental interactions between the foot and arm were negligible.

Spatial summation studies of pain, using two identical forms of noxious stimulation, have typically found effects only when the distance between the probes is 10 cm or less (Price et al. 1989; Defrin et al. 2006; Staud et al. 2007). There are studies, however, that have shown at least weak interactions over greater distances. Staud et al. (2004) found considerably more spatial summation of pain within a single dermatome than across several ones while Nielsen and Arendt-Nielsen (1997) reported spatial summation effects on both pain threshold and suprathreshold perception for both separation conditions.

Martikainen et al. (2004), however, found a more complex pattern of interaction depending upon spatial conditions; one presentation of cold pressor pain would enhance another cold pressor pain at an adjacent site but suppress it at a distant locus, suggesting the convergence of nociceptive signals in pain-relay neurons for the former condition and a DNIC-related supraspinal inhibition for the latter. Pud et al. (2005), on the other hand, noted DNIC-like inhibition both homotopically (the conditioning and test stimuli were adjacent) and heterotopically (they were presented on opposite hands). It seems likely that both the physical nature of the noxious stimuli and their experimental parameters (area, site, temporal pattern, etc.) influence their summation, so we cannot rule out that the interactions between the two stimuli in this study involve neural mechanisms similar to those underlying some of the reported effects.

Effects of attentional distraction

Our data indicated that the distraction task had a statistically significant but small effect on overall ratings. Moreover, the effect of distraction became manifest only at painful levels, a finding also reported elsewhere (Bushnell et al. 1985; Lautenbacher et al. 1998). There was a significant interaction effect, such that the ratings of weak phasic electrical trains, alone or in combination with thermal pulses, were unaffected by distraction, but those for intense electrical pulses, alone or paired, were reduced by about five units on our VAS.

It is noteworthy that distraction had a small effect upon the perception of strong electrical current, whether or not a concurrent thermal stimulus was presented, but that it affected tonic heat only when that stimulus was presented alone. It seems likely that the unique characteristics of the electrical stimuli (both their sharp, pricking nature and their emotional threat potential) themselves are distracting. Thus, the effect of an additional distracter (counting light signals) on the ratings of tonic heat becomes salient only in conditions without electrical stimulation. It should be noted that the thermal stimuli were always presented on the forearm and the electrical ones were always presented at the thigh; it is conceivable that visual distraction affects the perception of isolated noxious signals more on the forearm than the thigh, although this seems somewhat improbable.

The most important finding is the lack of a significant three-way interaction between the factors "attention", "tonic stimulus", and "phasic stimulus", given the significant two-way interaction between the latter two factors. The two-way interaction is strongly suggestive of a DNIC-like suppressive effect. The critical addition of attentional state in the three-way ANOVA ($2 \times 2 \times 5 \times 5$ analysis) allowed us to examine whether the perceptual interplay between the thermal and electrical stimuli depends upon attentional allocation. Since it did not matter, in this analysis, whether our subjects were attentionally absorbed by counting the light signals or whether they were able to focus their full attention on the pain stimuli, our data provide one of the few pieces of direct evidence that DNIC-like effects observed in humans are not simply due to attentional distraction.

Clinical implications

In the real world, pains rarely occur in isolation. Certainly fibromyalgia (Gracely et al. 2003; Neumann and Buskila 2003) and other forms of "generalized" or "widespread" pain (Koelbaek Johansen et al. 1999; Croft et al. 2003; John et al. 2003) are characterized by multiple pain sites, but even patients suffering from so-called "regional pain" often experience numerous other areas of serious discomfort (Dao et al. 1997; Henriksson 1999; Maleki et al. 2000; Whitehead et al. 2002; Aaron and Buchwald 2003). Pain sufferers generally seem to focus on that area that is most intense or causes the greatest functional limitation. Other bodily pains, which can be identified during careful examination, seem small by contrast and are deemphasized when the patient initially describes the nature and location of his or her complaints.

Our data reflect similar conditions. Phasic pain signals produce weak effects in the presence of strong tonic ones. In many respects, this is adaptive. The addition of new sources of discomfort in a patient who is already in pain does not increase the individual's perceived pain or distress as much as it would in someone who is pain free. In keeping with this hypothesis, there is evidence in some pain conditions (Callaghan et al. 1978; Rollman 1992) that successful treatment of the primary pain complaint causes patients to rate experimentally induced stimuli as more intense than they did earlier when they were likely comparing them to their endogenous discomfort. In consequence, the cure of one pain problem might lead to the unmasking of another one, a fact that requires clinical consideration because patients who are not prepared for such a development might show distress and frustration at the unexpected appearance of new pains.

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