PAIN® 151 (2010) 489–495

PAIN®

www.elsevier.com/locate/pain

The interactions between spatial summation and DNIC: Effect of the distance between two painful stimuli and attentional factors on pain perception

Ruth Defrin [a,*], Irit Tsedek [a], Inbal Lugasi [a], Irit Moriles [a], Gideon Urca [b]

[a] Dept. of Physical Therapy, Sackler Faculty of Medicine, Tel-Aviv University, 69978, Israel
[b] Dept. of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel-Aviv University, 69978, Israel

ARTICLE INFO

Article history:
Received 4 May 2010
Received in revised form 8 July 2010
Accepted 6 August 2010

Keywords:
Spatial summation of pain
DNIC
Attention
Instructions

ABSTRACT

The ability of a painful stimulus to suppress pain in another, remote area (DNIC) has been intensely studied. However, the effect of the distance between the two painful stimuli and the attentional factors during the measurement of pain perception received minimal treatment. We evaluated the effect of these factors on DNIC and on the interaction between DNIC and spatial summation (SS) of pain. Subjects rated the intensity of a test stimulus (applied to one hand) alone and simultaneously with conditioning stimuli applied to four different locations; 5 and 30 cm from the test stimulus on the same hand, the contralateral hand and contralateral leg. In each location, ratings were performed under three different instructions: summation, attention to test stimulus, attention to conditioning stimulus. The distance between the conditioning and test stimulus significantly affected pain perception ($p < 0.01$) regardless of the instructions; SS occurred only at a distance of 5 cm and DNIC occurred only in the remaining distances. DNIC's magnitude increased as the distance between the two stimuli increased ($p < 0.01$). However, the instruction to summate attenuated DNIC and the DNIC instruction attenuated SS of pain. Attention to the conditioning stimulus induced a stronger DNIC than attention to the test stimulus ($p < 0.001$). We conclude that (1) DNIC and SS of pain appear to be antagonistic processes. (2) DNIC is affected by the distance between two noxious stimuli and to a lesser extent, by attention. (3) The interaction between DNIC, SS and attention is complex and reflects the role of sensory–cognitive integration in pain perception.

1. Introduction

That pain in one body region can inhibit pain in another body region is a well-known phenomenon since ancient times [26]. Le Bars et al. (1979) termed this phenomenon as "diffuse noxious inhibitory controls" (DNIC) [22,23] and it was found to exist in both animals and humans [6,7,21,43]. In a standard DNIC experiment, a noxious stimulus is delivering to one body region ("conditioning stimulus" – CS) while measuring the pain evoked by another stimulus ("test stimulus" – TS) administered to another region [5,31]. A decrease of the latter is indicative of DNIC.

Although DNIC is extensively studied, several issues require further investigation. The critical distance between the TS and CS allowing for DNIC is one such issue. No consistent relationship was found between CS localization and its efficacy in attenuating the perceived intensity of the TS. The intensity of the TS has been shown to increase [19,38] and decrease [1] when the CS is administered to the ipsilateral homotopic site indicating either spatial summation of pain or DNIC, respectively. In other instances the intensity of the TS did not change [17,46].

The few attempts to study different, extra-segmental locations for the CS also yielded inconsistencies. While DNIC was stronger when the CS was applied to the ipsilateral heterotropic region compared with the contralateral [1,38], in another study DNIC was stronger in the contralateral-heterotropic region compared with the homotopic [40] and in another study, DNIC did not differ between homotopic and heterotopic regions [30]. Therefore studying the extent to which DNIC is affected by the distance between the test and conditioning stimulus is called for.

In the majority of DNIC experiments, as in those mentioned above, the characteristics of the TS are different than those of the CS in terms of modality, intensity and timing. Usually a combination of modalities such as electrical and thermal [5,20,21,39], hypertonic saline and electrical or mechanical [17,38,46] or heat and cold [16] is used. The intensity of the TS and CS is usually different as well [e.g. 28,48,49] as is their timing [e.g. 38,40]. The different stimulation parameters for TS and CS might produce an attentional bias towards one of them making it more prominent. Hence, DNIC might result from the changes in subjects' attention

* Tel.: +972 3 6405431; fax: +972 3 6405436.
E-mail address: rutidef@post.tau.ac.il (R. Defrin).

0304-3959/$36.00
doi:10.1016/j.pain.2010.08.009

leading to a decreased rating capability. In order to test such a hypothesis the parameters of the CS and TS must be identical.

The variable results led us to conduct a systematic study of DNIC in which all sensory cues associated with differences between the TS and CS are eliminated and in this "neutral" condition (identical modality, relative intensity, stimulation area, and timing), to test the effect of the distance between them and the effect of attention. This condition also allowed us to further examine the interactions between DNIC and between the seemingly opposite phenomenons, i.e. spatial summation of pain. More specifically, we asked how spatial inhibition (DNIC) and spatial summation of pain are affected by the distance between the two stimuli and the instructions given to subjects.

2. Methods

2.1. Subjects

Seventeen healthy volunteers, eight males and nine females (mean age 27 ± 6 years), participated in the study by attending three testing sessions, separated by at least 1 week.

Subjects suffering from pain, diseases causing potential neural damage (e.g. diabetes), systemic illnesses, skin lesions of any kind, language problems, hearing or speech disorders and mental disorders were excluded. Informed consent was obtained from all subjects after receiving a full explanation of the goals and protocols of the study. The institutional review board of Tel-Aviv University approved the experiments.

Testing took place in a quiet room. Temperature in the room was maintained at 22 ± 2 °C. The subjects were seated in a comfortable armchair with the hands and legs supported. Measurements were conducted on the hands and legs. All subjects were trained in perceived pain intensity (PPI) measurements prior to the experiments. The results obtained in the training sessions were discarded.

2.2. Thermal stimulator

Thermal stimuli were delivered using two Peltier-based computerized thermal stimulators (TSA 2001, Medoc Ltd., Israel), with a 3 × 3 cm contact probes. The principles of the Peltier stimulator were already described [11,42,47]. Briefly, a passage of current through the Peltier element produces temperature changes at rates determined by an active feedback system. As soon as the target temperature is attained, probe temperature actively reverts to a preset adaptation temperature by passage of an inverse current. The adaptation (baseline) temperature was set to 35 °C. The two TSA machines were synchronized via a communication cable and special software and could be operated simultaneously.

2.3. Determination of the test and conditioning stimuli

Our purpose was to establish, for each subject and in each testing session, identical test and conditioning stimuli in terms of modality, intensity, and timing. Test and conditioning stimuli were determined at the beginning of each testing session by matching the temperature level to a score of 5 in a 0–10 visual analog scale (VAS). These temperatures were interpolated from stimulus–response functions created for each subject in each of the four body regions tested (the three regions of the hand and the leg).

For the stimulus–response functions, subjects received a series of heat stimuli and were asked to rate the intensity of perceived pain following each stimulus on the (VAS) by moving the inner slider of a 15 cm plastic ruler with end points set as "no pain sensation" and "the most intense pain sensation imaginable". The stimulus intensities used for these magnitude estimations rose from a baseline temperature of 35 °C to a destination temperature ranging between 37 °C to the temperature eliciting eight on the VAS at which it remained for 3 s and then returned to baseline. An inter-stimulus interval of at least 30 s was maintained to avoid any changes in skin sensitivity and to allow for adequate VAS scoring. We repeated this procedure in each of the three testing sessions for each subject.

2.4. Procedures

The study comprised of two separate experiments.

2.4.1. Experiment I (n = 7)

The aim of experiment I was to evaluate the effect of distance between test and conditioning stimulus and the instructions on DNIC and on spatial summation. As previously mentioned, the test and conditioning stimuli were identical in terms of modality (contact heat-pain), intensity (VAS 5), stimulation area and shape (3 × 3 cm) and duration (3 s in destination). The locations of the test and conditioning stimuli are depicted in Fig. 1. The test stimulus was always on the distal part of the forearm and the conditioning stimuli were placed in four different body regions with varying distances; (1) 5 cm from the test stimulus on the same arm (ipsilateral homotopic), (2) 30 cm from the test stimulus on the same arm (ipsilateral heterotropic), (3) on the distal part of the contralateral forearm (contralateral-homotopic) and (4) on the lower lateral part of the contralateral leg (contralateral-heterotropic). The test and conditioning stimuli were always administered simultaneously.

Subjects were asked to rate the amount of pain perceived as produced by the test stimulus (applied to the distal part of the forearm) in the absence and in the presence of the conditioning stimulus. The conditioning stimulus was administered to the four body regions three times, following three different instruction: (1) "rate the *total* amount of pain evoked by the two stimuli together" (a "spatial summation instruction"), (2) "concentrate only on the *test stimulus* (pointed out by the examiner) and rate the amount of pain caused by it" ("DNIC-A instruction" = attention to the test stimulus), (3) "concentrate only on *the conditioning* stimulus (pointed out by the examiner) and rate the amount of pain caused by the test stimulus" ("DNIC-B instruction" = attention to the conditioning stimulus). The order of the instructions was random.

As a control condition, subjects also rated the test stimulus in the presence of an innocuous conditioning stimulus (36 °C) applied to the four body regions.

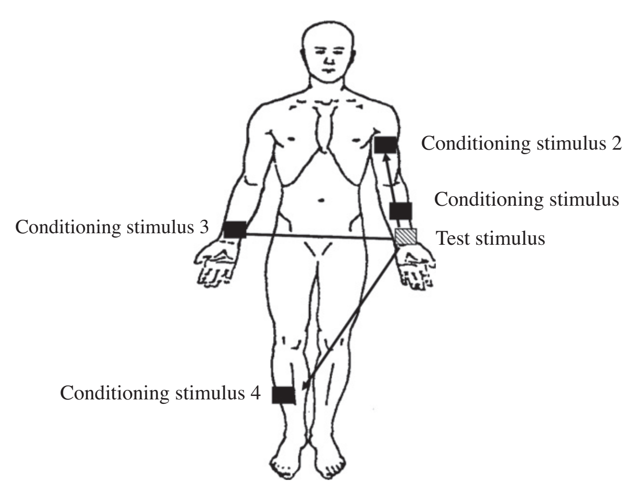

Fig. 1. The locations of the test and conditioning stimuli.

In summary, each subject underwent three testing sessions. In each session subjects rated the test stimulus five times (test stimulus alone + following application of noxious conditioning stimuli with the three different instructions + following application of innocuous conditioning stimulus) and this was repeated at the four different locations. In total, subjects rated the test stimulus 20 times in each session.

2.4.2. Experiment II (n = 10)

The aim of experiment II was to further evaluate the effect of attention on DNIC. Stimulation parameters were identical to those of experiment I. In this experiment, the location of the test stimulus was on the distal part of the forearm and the conditioning stimulus was on the lower lateral part of the contralateral leg. This stimulation configuration was chosen because in experiment I it yielded DNIC at all times. The test and conditioning stimuli were always administered simultaneously. Subjects were asked to rate the amount of pain evoked by the test stimulus four times as following; (1) in the absence of the conditioning stimulus, (2) in the presence of the conditioning stimulus with no special instruction, (3) in the presence of the conditioning stimulus with the instruction DNIC-A as used in experiment I (attention to the test stimulus) and (4) in the presence of the conditioning stimulus with the instruction DNIC-B as used in experiment I (attention to the conditioning stimulus). We decided to repeat the DNIC instructions used in experiment I in order to learn whether pain ratings under these instructions are different than under no specific instruction and also to learn whether these instructions evoke consistent results as those obtained in experiment I even though they are administered in a somewhat different experimental setup.

2.5. Data analysis

Data were analyzed with the SAS software. Mixed effects models for repeated measures were applied to test the effect of several factors on the pain ratings (VAS scores) of subjects. In experiment I the factors were: distance between test and conditioning stimulus (5 and 30 cm, contralateral hand and leg) and instructions (summation, DNIC; attention towards or away from conditioning stimulus). In experiment II the factor was instruction (attention towards or away from conditioning stimulus, no instruction). Interactions between the factors were also calculated. Pair wise comparisons were also calculated between conditions within each distance and correction for multiple comparisons was done with the FDR procedure. $p < 0.05$ was considered significant.

3. Results

3.1. Experiment I

3.1.1. Main effects

Pain ratings (VAS) of the test stimulus were significantly affected by the distance between the test and conditioning stimuli ($F(3377) = 4.5$, $p < 0.01$) and by the instruction given to subjects ($F(4377) = 7.11$, $p < 0.0001$). The interaction distance $*$ instruction was significant ($F(15, 377) = 2.85$, $p < 0.001$), namely the different instructions evoked different outcomes for the four distances.

3.1.2. The effect of the distance between the test and conditioning stimulus on DNIC

Fig. 2 presents the change in perceived pain (VAS) between the ratings of the test stimulus alone and the rating of the test stimulus in the presence of the conditioning stimuli applied to four different locations under instructions two (DNIC-A) and three (DNIC-B) combined, namely the two "DNIC instructions". A significant reduction in perceived pain evoked by the test stimulus occurred

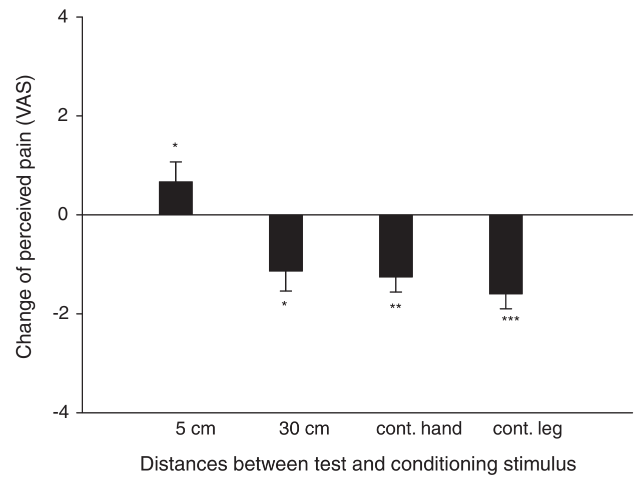

Fig. 2. Perceived pain intensity decreased significantly in the presence of the conditioning stimulus (relative to the rating of the test stimulus alone) at 30 cm separation ($^*p < 0.05$), contralateral hand ($^{**}p < 0.01$) and leg ($^{***}p < 0.0001$), indicating DNIC at these distances. At 5 cm, perceived pain increased ($^*p < 0.05$) indicative of spatial summation of pain despite the instruction. Values are group means of the differences of ratings ±SE.

when the conditioning stimulus was at a distance of 30 cm on the same arm (perceived pain decreased from 6.14 ± 1 to 5 ± 2, $p < 0.05$), on the contralateral hand (from 6.26 ± 1.2 to 5 ± 2, $p < 0.01$) and on the contralateral leg (6.3 ± 1–4.7 ± 2, $p < 0.0001$). The larger the distance, the larger was the decrease in PPI (1.14, 1.26 and 1.6, respectively $p < 0.01$) i.e. the stronger was DNIC.

At a distance of 5 cm on the same arm, there was no DNIC. On the contrary, at that distance, perceived pain significantly increased from 5.7 ± 1 to 6.4 ± 1 ($p < 0.05$) despite the "DNIC instruction" (Fig. 2).

3.1.3. The effect of the distance between test and conditioning stimulus on spatial summation of pain

Fig. 3 presents the change in perceived pain (VAS) between the ratings of the test stimulus alone and the rating of the test stimulus in the presence of the conditioning stimuli applied to four different

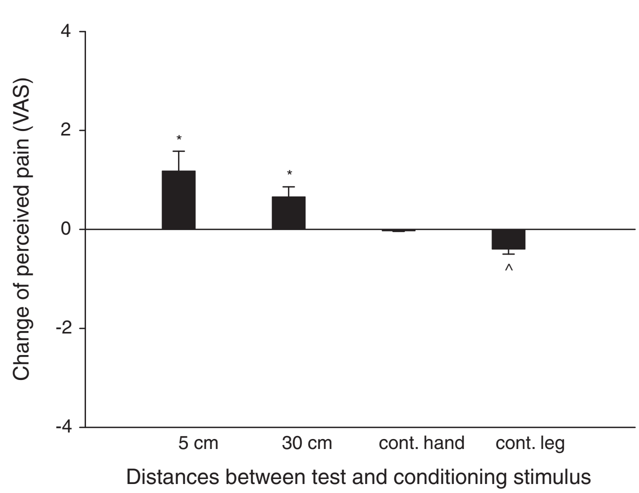

Fig. 3. Perceived pain intensity increased significantly in the presence of the conditioning stimulus (relative to the rating of the test stimulus alone) at 5 cm separation on the same hand ($^*p < 0.001$), indicating spatial summation of pain. At 30 cm, pain intensity slightly increased ($^*p = 0.05$), at the contralateral hand pain intensity did not change significantly, and at the contralateral leg pain intensity slightly decreased ($\hat{}p = 0.07$). Values are group means of the differences of ratings ±SE.

locations under instructions one namely under the "summation instructions". There was a significant global effect of the "summation instruction" on the distance between the test and conditioning stimulus ($p < 0.01$). At separation of 5 cm on the same arm, perceived pain significantly increased from 5.2 ± 1.3 to 7 ± 1.3 ($p < 0.01$), indicating spatial summation of pain. At separation of 30 cm on the same arm, perceived pain slightly but significantly increased from 6.14 ± 1.4 to 6.8 ± 1.4 ($p = 0.05$). In contrast, no spatial summation was observed when the CS was applied to the contralateral hand (6.26 ± 1.2–6.23 ± 1.3, respectively) and to the contralateral leg (6.3 ± 1–5.9 ± 1) despite the "summation instruction" (Fig. 3).

3.1.4. The effect of attention

Fig. 4 depicts the reduction in perceived pain produced by the test stimulus during application of the conditioning stimulus, in the two "DNIC instructions" separately; DNIC-A (focus your attention on the test stimulus) vs. DNIC-B (focus your attention on the conditioning stimulus) for all separation distances combined. The type of DNIC instruction significantly affected perceived pain ($p < 0.01$) and the interaction type of instruction $*$ distance was insignificant ($p = 0.7$), namely that the two instructions produced the same differential effect in all distances; attention towards the conditioning stimulus caused a significantly larger reduction in the pain evoked by the test stimulus compared to attention towards the test stimulus i.e. it strengthened the DNIC effect (Fig. 4).

Attention to the conditioning stimulus led to a greater reduction in pain than attention to the test stimulus at 30 cm separation on the same hand (5.24 vs. 4.82, respectively, $p < 0.05$) and at contralateral hand (5.8 vs. 4.9, $p < 0.05$). With the CS on the contralateral leg, both instructions produced a similar and significant DNIC. At stimulus separation of 5 cm there was no DNIC for either instruction, rather perceived pain increased despite the "DNIC instruction" indicative of spatial summation of pain (not shown).

3.1.5. The effect of a nonnoxious conditioning stimulus

A non-noxious conditioning stimulus produced a significant reduction in pain evoked by the test stimulus only when the conditioning stimulus was on the contralateral leg (from 6.3 ± 1.5 to 4.8 ± 2, $p < 0.05$). In the other conditions, perceived pain did not change compared to the pain ratings of the test stimulus alone (not shown).

3.1.6. Experiment I – summary of results

Table 1 summarizes the effects tested here: (1) the instruction of spatial summation induced spatial summation in the smallest separation distance (5 cm) and slightly in the next separation distance (30 cm) and never in the larger separation distances. (2) The instructions of DNIC induced DNIC only at separations of 30 cm, contralateral hand and contralateral leg and never in the smallest separation (5 cm). (3) Attention towards the conditioning stimulus produces stronger DNIC than when attention was towards the test stimulus.

3.2. Experiment II

A significant main effect was found for the condition ($F(3149) = 13.2$, $p < 0.001$). Fig. 5 presents the change in perceived pain (VAS) between the ratings of the test stimulus alone and the rating of the test stimulus in the presence of the conditioning stimuli applied to the contralateral leg, under no specific instruction, when attention was directed to the test stimulus and when attention was directed to the conditioning stimulus. Perceived pain decreased significantly during application of the conditioning stimulus under no specific instruction (from 5.68 ± 3 to 4.7 ± 2, $p < 0.05$) indicative of DNIC. Attention directed to either the test or the conditioning stimulus further increased the DNIC effect (from 5.68 ± 3 to 4.2 ± 3, $p < 0.01$ and to 3.2 ± 32, $p < 0.001$, respectively) compared to no specific instruction, with the latter condition yielding a greater DNIC than the former ($p < 0.05$).

Table 1
Summary of the interactions between the distance between two noxious stimuli and the instructions given to subjects.

Instructions	Distances			
	Same hand		Contralateral	
	5 cm	30 cm	Hand	Leg
Spatial summation	+	^1	–	–
The two DNIC instructions combined	–	+	+	+
DNIC-A (directed attention to test stimulus)	–	^2	^1	+
DNIC-B (directed attention to conditioning stimulus)	–	+	+	+

'+' = The effect is significant ($p < 0.05$–0.0001), ^ = the effect is borderline (^1, $p = 0.05$; ^2, $p = 0.07$); – = no effect.

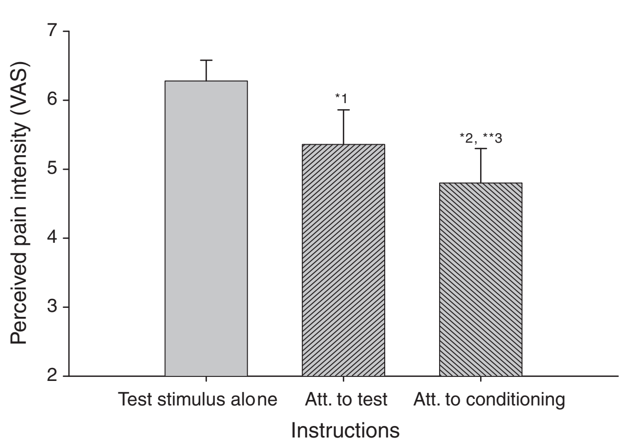

Fig. 4. Perceived pain intensity induced by the test stimulus alone and by the test stimulus in the presence of the conditioning stimulus, under the two "DNIC instructions": attention to the test stimulus" vs. "attention the conditioning stimulus". Both instructions induced a significant reduction in pain compared with test stimulus alone ($^{*1}p < 0.05$, $^{*2}p < 0.01$) but the latter induced a larger decrease in pain, i.e. a larger DNIC compared with the former ($^{*3}p < 0.01$). Values are group means ± SE.

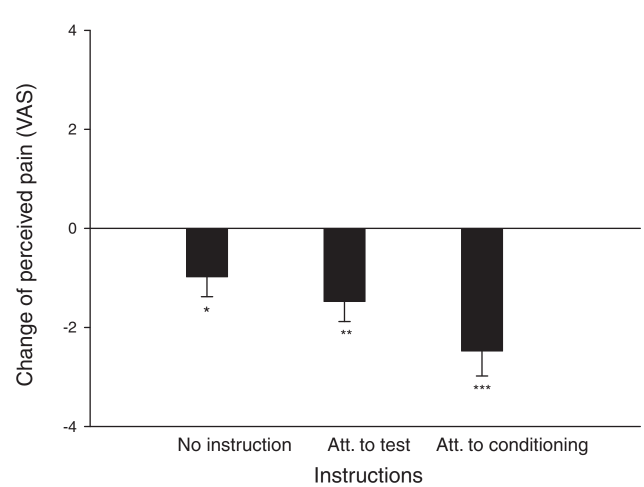

Fig. 5. Perceived pain intensity decreased significantly in the presence of the conditioning stimulus (relative to the rating of the test stimulus alone) under no instruction ($^{*}p < 0.05$) and more so when attention was directed to the test ($^{**}p < 0.01$) and to the conditioning ($^{***}p < 0.001$) stimulus. Counting backwards did not yield DNIC. Values are group means of the differences of ratings ±SE.

4. Discussion

Results revealed that at a small separation distance DNIC cannot occur regardless of the instructions given to subjects, rather spatial summation (SS) of pain occurs. In contrast, at large separation distances only DNIC occurs and it is stronger at larger separation distances and when attention is directed to the conditioning stimulus.

4.1. The effect of distance on SS and DNIC

That two adjacent noxious stimuli summate and generate increased pain intensity or deceased pain-threshold, are well established [8–10,27,29]. SS of pain reflects a central phenomenon occurring in spinal or supraspinal levels [10,29]. In the present study SS occurred at separation of 5 cm, below the previously proposed 10 cm boundary for SS [9,10]. Surprisingly, slight SS occurred at 30 cm separation, only when subjects received an instruction to summate. Recently, SS occurred at 30 cm separation in the leg but to a lesser extent than in smaller separations [33] suggesting that SS may be affected by conditions other than the distance between the stimuli, as discussed below.

The magnitude of DNIC increased with the increase in the separation distance between the test and conditioning stimulus being largest for the contralateral-heterotropic region (the leg). Stronger DNIC was previously reported when the conditioning stimulus was applied to a contralateral-heterotropic compared with contralateral-homotopic site [38,40]. In addition, stronger DNIC was found in more remote than in closer ipsilateral-heterotrpic site [17,46]. Although there are studies in which the magnitude of DNIC was similar regardless of the conditioning stimulus location [30] it appears that DNIC has reciprocal relations with the distance between the test and conditioning stimulus.

4.2. Interactions between DNIC and SS of pain

The interaction between DNIC and SS with regard to the distance between two noxious stimuli is evident by the finding that when subjects summate they are unable to produce DNIC and vice versa. Moreover, if subjects are instructed to perform contrary to what is expected to occur according to the separation distance, the instruction attenuates the expected effect; SS occurs to a lesser extent at 5 cm separation when subjects are ''urged'' to produce DNIC, and DNIC occurs to a lesser extent at the large distances when subjects are ''urged'' to summate. It therefore appears that DNIC and SS of pain are antagonistic but both are affected by cognitive processes.

The cognitive influence on SS and DNIC may be limited by the spatial constraint these processes have. SS cannot occur beyond and DNIC cannot occur below a certain separation distance despite the instructions subjects receive. Namely, that the cognitive role is less dominant when conditions are ''optimal'' in terms of spatial configuration. The correlation found between DNIC magnitude and the distance between two stimuli, and the lack of effect of directed attention on DNIC in the largest separation distance may support this suggestion.

SS is thought to occur when information from two adjacent nociceptive inputs converge and summate within a receptive field of one central neuron, inducing increased neuronal discharge frequency. Alternatively but not mutually exclusive is the possibility that SS occurs when two stimuli increase the number of activated neurons as compared with activation induced by one stimulus [29]. Both the mechanisms result in an increased nociceptive output of central neurons, consequently increasing pain ratings. It seems that at large enough separation between two stimuli, convergence of information and/or recruitment of adjacent neurons can no longer occur due to the spatial arrangement of the receptive fields and/or a more efficient surrounding inhibition each stimulus evokes [13]. At such distances, the system regards each stimulus separately and conditions allow for mutual inhibition (DNIC).

Upon less ''optimal'' conditions when spatial constraints are minimal, instructions/attention may increase or decrease the amount of SS and DNIC reflecting the cognitive effect on these processes. Note that the test and the conditioning stimulus were identical in modality, intensity and timing, in order to control for the possibility that DNIC results from unintentional bias to one of the stimuli or from judging one stimulus relative to the other, as suggested by the adaptation level theory [34] as previously reported [20]. Under these conditions attention does indeed reinforce DNIC. Nevertheless, we cannot discard the possibility that interactions between SS and DNIC might be affected by the rating capabilities of subjects. Providing an overall pain rating for two stimuli (SS) might be easier than concentrating on one of two active stimuli (DNIC). Perhaps using an electrophysiological measure of pain would have overcome this difficulty.

4.3. The effect of attention on DNIC

The effect of attention on DNIC did not receive much attention. Kakigi [18] found no differences in the amount of DNIC when subjects received no instructions compared with instruction to direct attention towards the test stimulus. Staud et al. [37] observed an increased DNIC when subjects directed attention to the test or conditioning stimulus only in fibromyalgia patients. We, on the other hand, found that directed attention evoked stronger DNIC in all subjects. Quevedo and Coghill [32] found that directing attention to either one of two stimuli separated by 10 cm abolished their summation and allowed for inhibition, supporting our suggestion that SS and DNIC may vary according to the focus of attention under certain spatial conditions. Although directed attention and distraction may differ in their mechanism, Lautenbacher et al. [20] too have shown that distraction significantly affected DNIC though the effect was small and depended on stimulation modality.

We thus suggest that DNIC is maximal and relatively resistant to attentional influences when conditions are optimal (large distance) and that these influences are considerable under less optimal conditions. The perceptual consequence of directed attention is not clear. It is possible that focusing attention on the test and more so, on the conditioning stimulus increases the division between them and prevents subjects from fully grasp the overall intensity of evoked pain. Furthermore, directing attention towards the conditioning stimulus may strengthen its relative subjective intensity thus reinforcing its inhibitory effect. Quevedo and Coghill [32,33] suggested that directed attention increases inhibition between two stimuli by provoking short-term pseudoplasticity; decreasing excitatory receptive fields or increasing surround inhibition. Regardless of the mechanism of attention, it is yet to be determined whether attention acts additively with DNIC or whether it is one of the uncovered components of DNIC.

It is noteworthy that another cognitive trait-expectation – was able to modulate the amount of DNIC in that expectation of analgesia increased DNIC and expectations of hyperalgesia-blocked DNIC [15], indicating that psychological factors affect the neuronal activity of brain regions involved in descending pain inhibition.

DNIC was attributed to brain-stem loops affecting spinal convergent neurons [3,14,20–22,25,43,45]. Electrophysiological and anatomical data support the involvement of the caudal medulla subnucleus reticularis dorsalis (SRD) in the spino-bulbo-spinal loops that are preferentially or exclusively activated by nociceptive stimuli [21,43]. The response of SRD neurons to noxious stimuli depend on intensity and spatio-temporal features of the noxious stimuli and in rodents, the SRD establish reciprocal connections with the periaquaductal grey and is under the influence of corticofugal modulation via cingulate, somatosensory and insular cortices [44] as well as dorsolateral-prefrontal and orbitofrontal cortex, regions involved in attention [2,24]. fMRI studies indeed show that the activation of these structures during attentional-related task attenuate stimulus induced pain-related activity in the thalamus, somatosensory cortex, insula and caudal cingulate cortex, leading to decreased pain intensity [35,36,41]. Such pain modulation may also occur during DNIC configuration. Interestingly, in animals not all spinal neurons are attenuated by heterotropic stimulation [25] supporting the possibility that additional (cognitive) factors may be involved in their attenuation.

4.4. Sensory–cognitive interactions

In a previous study we showed that SS of pain between two noxious stimuli occurred for separation distance not exceeding 10 cm [although see 33]. In addition, two-point discrimination (2PD) of pain becomes better than chance at 10 cm separation, suggesting that SS and 2PD are antagonistic [9,10]. The present study further suggests that SS and DNIC are antagonistic. It thus appears that DNIC occurs if subjects can distinguish between two discrete noxious stimuli. Most likely, the ability to distinguish between two stimuli grants the ability to direct attention to either one of them. The relations between SS, DNIC, 2PD and attention seem to reflect existing sensory–cognitive interactions.

Interestingly, inverse relations between SS and DNIC were also demonstrated in animals. Bouhassira et al. [4] showed that spinal convergent neurons encode changes in noxious stimulation area in a non-monotonic fashion; they increase their response for stimulation areas up to double their receptive field but exhibit area-dependent decrease in response to further increase in stimulation area. After a series of ablation experiments, these authors concluded that the level of integration of descending inhibitory controls triggered by SS and DNIC is identical and located in the caudal medulla [12]. These findings support our suggestion that noxious stimuli trigger either summation or inhibition of pain depending on their spatial configuration and that both may be mediated by descending medullary feedback loops regulated by higher order, cortical structures involved in attention.

In summary, SS and DNIC are antagonistic processes within the pain system. Both SS and DNIC are predominantly affected by the distance between two noxious stimuli but also by the instructions given to subjects prior to pain measurement. The manner with which instructions and directed attention affect SS and DNIC reflects the importance of sensory–cognitive integration in pain perception.

Conflict of interest

There are no conflicts of interest related with this study.

References

[1] Arendt-Nielsen L, Gotliebsen K. Segmental inhibition of laser-evoked brain potentials by ipsi- and contralaterally applied cold pressure pain. Eur J Appl Physiol 1992;64:56–61.
[2] Bantick SJ, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. Brain 2002;125:310–9.
[3] Bouhassira D, Villanueva L, Bing Z, Le Bars D. Involvement of the subnucleus reticularis dorsalis in diffuse noxious inhibitory controls in the rat. Brain Res 1992;595:353–7.
[4] Bouhassira D, Gall O, Chitour D, Le Bars D. Dorsal horn convergent neurones: negative feed-back triggered by spatial summation of nociceptive afferents. Pain 1995;62:195–200.
[5] Bouhassira D, Danziger N, Attal N, Guirimand F. Comparison of the pain suppressive effects of clinical and experimental painful conditioning stimuli. Brain 2003;126:1068–78.
[6] Calvino B, Grilo RM. Central pain control. Joint Bone Spine 2006;73:10–6.
[7] De Broucker TH, Cesaro P, Willer JC, Le Bars D. Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. Brain 1990;113:1223–34.
[8] Defrin R, Urca G. Spatial summation of heat pain: a reassessment. Pain 1996;66:23–9.
[9] Defrin R, Pope G, Davis KD. Interactions between spatial summation, 2-point discrimination and habituation of heat pain. Eur J Pain 2008;12:900–9.
[10] Defrin R, Givon R, Raz N, Urca G. Spatial summation and spatial discrimination of pain sensation. Pain 2006;126:123–31.
[11] Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiat 1976;39:1071–5.
[12] Gall O, Bouhassira D, Chitour D, Le Bars D. Involvement of the caudal medulla in negative feedback mechanisms triggered by spatial summation of nociceptive inputs. J Neurophysiol 1998;79:304–11.
[13] Gardner ER, Kandel ER. Touch. In: Kadel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. McGraw Hill; 2000. p. 451–71.
[14] Gerhart KD, Yezierski RP, Giesler GJ, Willis WD. Inhibitory receptive fields of primate spinothalamic tract cells. J Neurophysiol 1981;46:1309–25.
[15] Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia – when the spine echoes what the brain expects. Pain 2007;130:137–43.
[16] Granot M, Weissman-Fogel I, Crispel Y, Pud D, Granovsky Y, Sprecher E, Yarnitsky D. Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter? Pain 2008;136:142–9.
[17] Graven-Nielsen T, Babenko V, Svensson P, Arendt-Nielsen L. Experimentally induced muscle pain induces hypoalgesia in heterotopic deep tissues, but not in homotopic deep tissues. Brain Res 1998;787:203–10.
[18] Kakigi R. Diffuse noxious inhibitory control reappraisal by pain-related somatosensory evoked potentials following CO_2 laser stimulation. J Neurological Sci 1994;125:198–205.
[19] Kakigi R, Watanabe S. Pain relief by various kinds of interference stimulation applied to the peripheral skin in humans: pain-related brain potentials following CO_2 laser stimulation. J Peripher Nerv Syst 1996;1:189–98.
[20] Lautenbacher S, Prager M, Rollman GB. Pain additivity, diffuse noxious inhibitory controls, and attention: a functional measurement analysis. Somatosens Mot Res 2007;24:189–201.
[21] Le Bars D. The whole body receptive field of dorsal horn multireceptive neurons. Prog Brain Res 2002;40:29–44.
[22] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent nerurones in the rat. Pain 1979;6:283–301.
[23] Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. Pain 1979;6:305–27.
[24] Luks TL, Simpson GV, Dale CL, Hough MG. Preparatory allocation of attention and adjustments in conflict processing. Neuroimage 2007;35:949–58.
[25] MCgraughty S, Henry JL. Effects of noxious hindpaw immersion on evoked and spontaneous firing of contralateral convergent dorsal horn neurons in both intact and spinalized rats. Brain Res Bull 1997;43:263–7.
[26] Melzack R. Folk medicine and the sensory modulation theory. In: Melzack R, Wall PD, editors. Textbook of pain; 1994. p. 1209–17.
[27] Nielsen J, Arendt-Nielsen L. Spatial summation of heat induced pain within and between dermatomes. Somatosens Mot Res 1997;14:119–25.
[28] Price DD, McHaffie JG. Effects of heterotopic conditioning stimuli on first and second pain: a psychophysical evaluation in humans. Pain 1988;34:245–52.
[29] Price DD, McHaffie JG, Larson MA. Spatial summation of heat-induced pain: influence of stimulus area and spatial separation of stimuli on perceived pain sensation intensity and unpleasantness. J Neurophysiol 1989;62:1270–9.
[30] Pud D, Sprecher E, Yarnitsky D. Homotopic and heterotopic effects of endogenous analgesia in healthy volunteers. Neuroscience Lett 2005;380:209–13.
[31] Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain 2009;144:16–9.
[32] Quevedo AS, Coghill RC. Attentional modulation of spatial integration of pain: evidence for dynamic spatial tuning. J Neurosci 2007;27:11635–40.
[33] Quevedo AS, Coghill RC. Filling-in, spatial summation, and radiation of pain: evidence for a neural population code in the nociceptive system. J Neurophysiol 2009;102:3544–53.
[34] Rollman GB. Signal detection theory pain measures: empirical validation studies and adaptation-level effects. Pain 1979;6:9–21.
[35] Seminowicz DA, Davis KD. Interactions of pain intensity and cognitive load: the brain stays on task. Cerebral Cortex 2007;17:1412–22.
[36] Seminowicz DA, Mikulis DJ, Davis KD. Cognitive modulation of pain-related brain responses depends on behavioral strategy. Pain 2004;112:48–58.
[37] Staud R, Robinson ME, Vierck Jr CJ, Price DD. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. Pain 2003;101:167–74.
[38] Svensson P, Hashikawa CH, Casey KL. Site-and modality-specific modulation of experimental muscle pain in humans. Brain Res 1999;851:32–8.
[39] Talbot JD, Duncan GH, Bushnell MC, Boyer M. Diffuse noxious inhibitory controls (DNIC): psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressure pain. Pain 1987;30:221–32.
[40] Terkelsen AJ, Andersen OK, Hansen PO, Jensen TS. Effects of heterotopic- and segmental counter-stimulation on the nociceptive withdrawal reflex in humans. Acta Physiol Scand 2001;172:211–7.
[41] Valet M, Sprenger T, Boecker H, Willoch F, Rummeny E, Conrad B, Erhard P, Tolle TR. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain – an fMRI analysis. Pain 2004;109:399–408.

[42] Verdugo R, Ochoa JL. Quantitative somatosensory thermotest. A key method for functional evaluation of small calibre afferent channels. Brain 1992;115: 893–913.
[43] Villanueva L, Le Bars D. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. Biol Res 1995;28:113–25.
[44] Villanueva L, Bing Z, Le Bars D. Effects of heterotopic noxious stimuli on activity of neurones in subnucleus reticularis dorsalis in the rat medulla. J Physiol (London) 1994;475:255–66.
[45] Villanueva L, Bouhassira D, Le Bars D. The medullary subnucleus reticularis dorsalis (SRD) as a key link in both the transmission and modulation of pain signals. Pain 1996;67:231–40.
[46] Wattanabe I, Svensson P, Arendt-Nielsen L. Influence of segmental and extra-segmental conditioning stimuli on cortical potentials evoked by painful electrical stimulation. Somatosens Mot Res 1999;16:243–50.
[47] Wilcox GL, Giesler GJ. An instrument using a multiple layer peltier device to change skin temperature rapidly. Brain Res 1984;12:143–6.
[48] Willer JC, Roby A, Le Bars D. Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. Brain 1984;107:1095–112.
[49] Willer JC, De Broucker T, Le Bars D. Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. J Neurophysiol 1989;62: 1028–38.