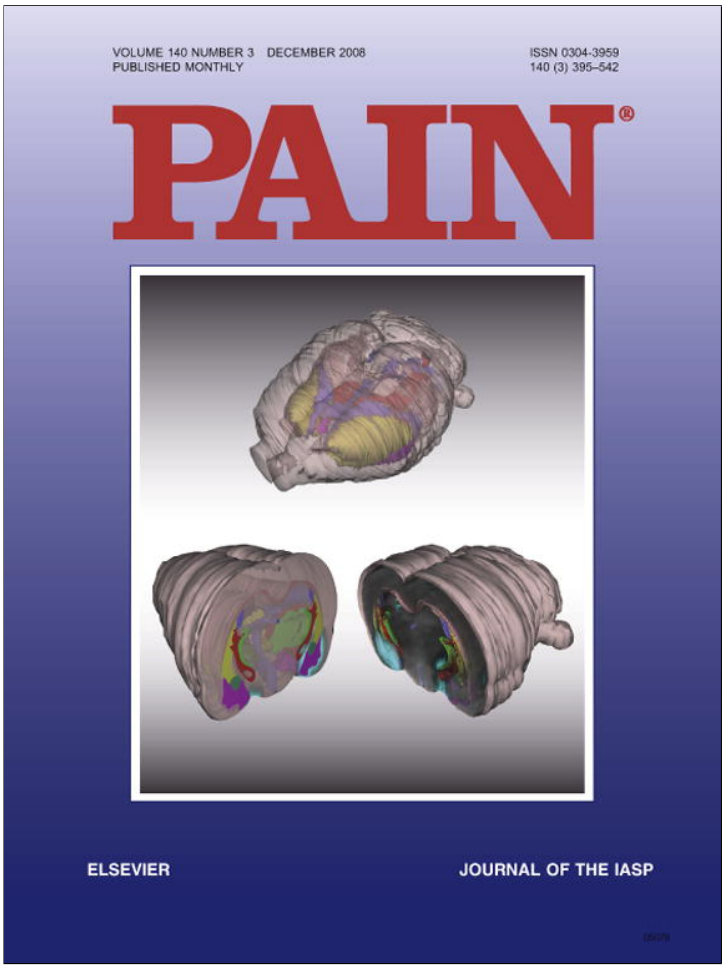

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The effects of DNIC-type inhibition on temporal summation compared to single pulse processing: Does sex matter?

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Abstract

A few experimental observations have suggested that diffuse noxious inhibitory control (DNIC)-type inhibition acts preferentially on the pain system if this is in a sensitised state, e.g. after slow temporal summation (wind-up). However, firm evidence is still missing. Furthermore, sex-related factors, which seem to affect temporal summation as well as DNIC effects, might thus also modulate the interaction of these two processes. To answer these questions, we investigated 40 young and pain-free subjects (20 female and 20 male). The conditioning stimulus in our DNIC paradigm was realized by immersion of the hand into a water tub containing either 42 °C (non-painful heat) or 46 °C (painful heat) hot water. The test stimuli were either single pulses or series of five pulses (0.5 Hz repetition frequency) produced by a pressure algometer. The VAS ratings for the last stimulus in the series were significantly higher than for the single pulse (temporal summation). The ratings were significantly reduced by the 42 °C conditioning stimulus and even more by the 46 °C conditioning stimulus, suggesting DNIC-like inhibition. This was equally true both for the single pulse and for the series of pulses. Sex differences were not observed for temporal summation, DNIC inhibition or for the interaction of the two processes, although women exhibited significantly lower pressure pain thresholds and higher ratings for the tonic heat stimuli. In conclusion, DNIC-type inhibition apparently does not preferentially act on a sensitised pain system after slow temporal summation. Considering the sex of the subjects does not change this insight.

Keywords: DNIC; Temporal summation; Wind-up; Sex differences

1. Introduction

Slow temporal summation of pain is characterized by an increase in pain during application of repetitive noxious stimuli (critical repetition frequency around 0.5 Hz). The basis is an increase of C-fibre-mediated responses in multi-receptive dorsal horn neurons, which is called "wind-up" and thought to be NMDA-mediated. Exaggerated temporal summation of pain has been regarded a potential patho-mechanism in the development of chronic pain. Meanwhile, experimental methods have become available to study temporal summation in humans [1,3,22].

It has been hypothesized that descending inhibitory pathways control this form of central sensitisation [33]. A mechanism, which has attracted particular interest in this respect, is the diffuse noxious inhibitory controls (DNICs). A reason for this interest might be that the DNICs are easily accessible by psychophysical and electrophysiological methods in humans [37]. But even besides this methodological convenience, it is definitely worth studying the DNIC because of its proven inhibitory potency.

Since there are many comprehensive descriptions of DNIC e.g. [36], a few words shall suffice. Le Bars and

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associates [18,19] demonstrated that pain occurring in one part of the body reduces pain in the rest of the body by activating DNICs, which are spinal and supra-spinal (i.e. subnucleus reticularis dorsalis in the brainstem) neural mechanisms that modulate the transmission of nociceptive signals via multi-receptive neurons. Neurotransmitters and modulators involved in DNIC are serotonin and endogenous opioids. In studies on DNIC-like mechanisms in humans, a reduction of sensitivity to phasic pain was repeatedly observed while a tonic pain stimulus was applied concurrently to another site of the body [17,35]. A deficiency of DNIC has been reported for several chronic pain conditions [21,33].

Given that multi-receptive neurons in the spinal cord have been shown to be involved both in DNIC and in wind-up, it seems feasible that these neurons are physiological links between DNIC and wind-up. Accordingly, the assumption of the DNIC regulating the intensity of temporal summation is not too far-fetched.

Sex has been found to be a modulating factor for both temporal summation and DNIC [14]. Whereas for temporal summation there is almost no doubt that women have the higher excitatory drive [5,9,12,26,29–31], findings are less clear with regard to DNIC because a lack of inhibitory power in women has been observed in some [7,8,11,32,33] but not in all studies [2,6,23,24,28]. Nevertheless, given that there is some evidence that sex modulates the two mechanisms separately, it appears likely that sex does also affect the interaction of these two mechanisms.

This study was set-up to investigate whether DNIC counter-regulates temporal summation and whether this interaction depends on the sex of the subject studied.

2. Materials and methods

2.1. Subjects

Forty young subjects (female: $N = 20$, male: $N = 20$), mostly students of psychology between the ages of 20 and 39 years (mean age for women: 22.8 years ($SD = 3.7$), mean age for men: 24.8 years ($SD = 3.9$); $t = 2.813$, $p = 0.102$ for sex differences) were recruited via advertisements posted in the university buildings. None had taken any analgesic medication or alcohol for at least 24 h prior to the test session. Exclusion criteria were all kinds of acute or chronic diseases. Seven women took oral contraceptives. Those who did not take contraceptives were asked for the time of their last menstruation and for the usual length of their menstrual cycles. 46% of these women were in the first third, 31% were in the second third and 23% in the third phase of their menstrual cycle while studied. All subjects were either paid for participation or received course credits. The study protocol was approved by the local ethics committee. All subjects gave written informed consent.

2.2. Materials and procedures

During the whole session, which lasted for approximately 2 h, subjects sat upright in a comfortable chair at a table. Subjects were carefully familiarized with all the methods to be used before the start of the experiment. The testing procedure included the assessment of pressure pain thresholds and the assessment of temporal summation of pressure pain as well as the assessment of DNIC-like effects using pressure pain as test stimuli and non-painful and painful levels of heat as the conditioning stimuli. The subjects were instructed that we were interested in the perception of pressure and heat applied concurrently and in potential perceptual interactions, carefully avoiding any clue to the expected type of interaction.

2.2.1. Apparatus

Pressure stimuli (also test stimuli) were delivered with a computer-controlled pressure algometer (Mermaid Institute, Aalborg, Denmark; see [20] for a detailed description). A rounded aluminum foot plate with a padded probe area of 1.00 cm^2 was fixed to the tip of a piston, which was moved by an electric motor. The pressure stimulation was controlled by feedback via a built-in force transducer. Pressure stimuli were applied to the inner fingertip of the ring, middle and index fingers of the right and left hands (six stimulation sites). The pressure algometer was positioned on a table in front of the subject in such a way that the subject could place her/his fingertip comfortably below the probe.

Heat stimuli (conditioning stimuli) were applied using a water tub, containing either 42 °C (non-painful heat) or 46 °C (painful heat) hot water. The subject immersed her/his hand up to 10 cm above the wrist in this hot water bath. The water temperature was controlled with a thermostat (Variostat, Huber), and the water was stirred with a force and suction pump to avoid regional temperature difference within the water bath. Tonic heat stimuli were applied to the right and left hand (always contralateral to the application of the pressure stimuli).

2.2.2. Assessment of pressure pain thresholds

Pressure pain thresholds were assessed using the method of limits. The piston was lowered till the probe touched the skin of the fingertip. Then the pressure increased at a rate of 80 kPa/s until the subjects felt the stimulus to be slightly painful and responded by pressing a stop button. Each time they pressed the button, the probe lifted and returned the pressure to zero. Five trials were presented at each finger (ring, middle and index fingers) with an inter-stimulus interval (ISI) of > 8 s. These 5 trials were averaged to deliver estimates of pressure pain thresholds for each finger. The assessment of pressure pain thresholds always preceded the DNIC parts of the study for both body sides. We always

started on the left hand. Pain thresholds for the right body side were assessed only after the first DNIC part of the study was finished - with pressure stimuli applied to the left body side (see Section 2.2.4 for assessment of DNIC-like inhibition and Table 1).

2.2.3. Assessment of temporal summation

Temporal summation was tested by comparing the sensations evoked by single pulses of pressure stimulation to sensations evoked by a series of five pulses (only the last pulse was rated), which were applied with a repetition frequency of 0.5 Hz. The series of five pulses was always delivered 60 seconds after the single pulse. The stimuli were presented relative to the individual pain thresholds (50% above the individual pain threshold) and increased with a rate of rise of 75% of the target intensity. The stimuli had a saw-tooth shape with stimulus duration at maximum of only 0.1 s. Three single pulses and three series of five pulses were presented in each block of experimental conditions (see Section 2.2.4 for assessment of DNIC-like inhibition). The stimulation site differed between experimental blocks (see Table 1). The three runs of single pulses and pulse series were separated by intervals of 60 s.

2.2.4. Assessment of DNIC-like inhibition

The effects of DNIC-type inhibition on temporal summation of pressure pain compared to single pulse processing were tested using non-painful heat (42 °C) and painful heat (46 °C) as conditioning stimuli; these conditioning stimuli were compared to baseline (application of pressure stimuli without immersion of the other hand into the water bath). The two temperatures were selected as non-painful and painful intensities, respectively, based on previous studies [17,37]. The immersion time of the hand into the water bath was as long as necessary to apply all pressure stimuli (three single pulses and three series of five pulses), which took around 6 min. The three conditions were first applied to the right hand and after this to the left hand (inverse sequence of conditions for the right hand compared to that for the left hand) to control for order effects), resulting in six experimental blocks (see Table 1). The sequence of the stimulation sites of the test stimuli is also listed in Table 1. The interval between the experimental conditions (blocks) was always >7 min. Body sides were selected for the conditioning and the test stimuli in a way that the two types of stimuli were always applied contralaterally to minimize segmental effects of inhibition.

Table 1
Description of the experimental protocol and stimulation sites

Experimental blocks	Heat stimuli (conditioning stimuli)	Pressure stimuli (test stimuli)
	Assessment of pressure pain thresholds on the left body side	
1	Baseline	Ring finger (left hand)
	7 Min pause	
2	Non-painful heat (42 °C, right hand)	Middle finger (left hand)
	7 Min pause	
3	Painful heat (46 °C, right hand)	Index finger (left hand)
	7 Min pause & Assessment of pressure pain thresholds on the right body side	
4	Painful heat (46 °C, left hand)	Middle finger (right hand)
	7 Min pause	
5	Non-painful heat (42 °C, left hand)	Index finger (right hand)
	7 Min pause	
6	Baseline	Ring finger (right hand)

2.2.5. Rating scale

After the application of each single pulse of pressure and each series of five pulses, subjects were asked to rate the perceived intensity. For this purpose a horizontal visual analogue scale (VAS) of 100 mm was used with an anchor of "faintly painful" in the center so that all non-painful sensations should be rated below 50 and all painful ones above 50. In addition, subjects also rated the perceived intensity of the heat stimuli (blocks 2, 3, 4, 5) using the same scale. Ratings of the heat stimuli always followed the rating of the pressure stimuli, resulting into six ratings for pressure stimulation (three single pulses and three series of five pulses) for each experimental block and six ratings for heat stimulation in blocks 2, 3, 4 and 5. For further analyses, the ratings for pressure stimulation were averaged in each experimental block (separately for ratings of single pulses and ratings of last pulses in the series of five pulses).

2.3. Statistic

Since we were not interested in side effects we averaged all pain parameters (pain thresholds, ratings for test and conditioning stimuli) over the two body sides within a given condition. We did this with reasonably good cause because neither "body side" had a significant effect on pain threshold and pain ratings, nor did "body side" significantly interact with the factors "temporal summation and "sex". Only the DNIC effect varied slightly between body sides and appeared slightly stronger for the combination, "test stimulus left – conditioning stimulus right" than for the reverse combination ($F(1,39) = 4.60$; $p = 0.041$). Alternatively, this might have been a pure order effect because we always started with the first combination. However, although the DNIC effect was stronger for the first combination, we did find significant DNIC effects for both side combinations of stimuli used ((1) test stimulus left – conditioning

stimulus right: $F(2,78) = 43.80$; $p < 0.001$; (2) test stimulus right – conditioning stimulus left: $F(2,78) = 3.93$; $p = 0.046$). Therefore, the existence of DNIC effects in both combinations let us cleave to our protocol of averaging sides.

The effects of DNIC-type inhibition on temporal summation of pressure pain compared to single pulse processing were evaluated by computing a multiple analysis of variance with repeated measurement with one between-subject factor (sex) and two within subject factors (temporal summation$_{\text{single pulses, series of five pulses}}$, condition$_{\text{baseline, non-painful heat, painful heat}}$). In case of significant results, post hoc tests were computed for single comparisons as well as effect size calculations.

Further multiple analyses of variance with repeated measurements were conducted to investigate the effect of sex on pressure pain thresholds (within-subject factor: finger$_{\text{ring finger, middle finger, index finger}}$) as well as on ratings of thermal heat stimulation (within-subject factors: temperature$_{\text{non-painful heat, painful heat}}$ and minute$_{1–6}$).

The value of α was set to 0.05 throughout.

3. Results

3.1. Temporal summation and DNIC effects

We found a significant main effect for temporal summation ($F(1,38) = 93.627$; $p < 0.001$). As can be seen in Fig. 1, the last pulse in a series of five pulses was rated as more painful compared to single pulses of pressure stimulation. There was also a significant main effect for the factor "condition" ($F(2,76) = 31.213$; $p < 0.001$). As can be seen in Fig. 1, immersing one hand into the hot water bath significantly decreased the perceived intensity of concurrently applied pressure stimuli compared to baseline condition. More precisely, ratings of the pressure stimuli decreased significantly during non-painful heat condition compared to baseline ($F(1,39) = 5.921$; $p = 0.020$) and again decreased significantly during painful heat stimulation compared to non-painful heat ($F(1,39) = 29.884$; $p < 0.001$), thus suggesting DNIC-type inhibition. Considering the effect sizes of these comparisons (Cohen's d for repeated measures), it becomes obvious that the decrease in pressure pain perception was less pronounced when comparing baseline with non-painful heat conditions (small to medium effect sizes; single pulse: $d = 0.50$, series of five pulses: $d = 0.39$) as when comparing non-painful heat to painful heat conditions (strong effect sizes; single pulse: $d = 1.02$, series of five pulses: $d = 1.15$). There were no significant correlations between the ratings of the hot water and the size of the DNIC effect (difference between the pressure ratings at baseline and during conditioning stimulation) for both intensities of the conditioning stimulus: non-painfully hot water, $r = 1.181$ ($p = 0.265$) and painfully hot water, $r = 0.070$ ($p = 0.669$).

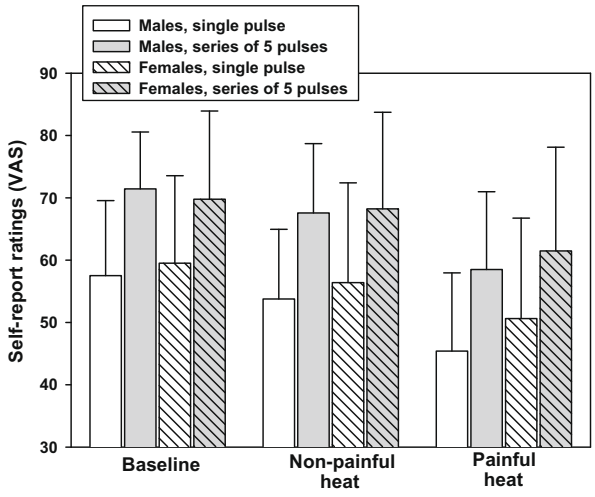

Fig. 1. Self-report ratings (mean values (±SD)) for single pulses and series of five pulses of pressure stimulation during baseline, non-painful heat and painful heat conditions; separately for males and females.

3.2. DNIC effects on temporal summation

However, there was no significant interaction between the factors "temporal summation" and "condition" ($F(2,76) = 0.180$; $p = 0.836$). This finding suggests that the effect of DNIC-type inhibition on the sensitivity for single painful pulses of pressure did not differ from the DNIC effect on the sensitivity after temporal summation.

3.3. Sex differences

With regard to sex differences in temporal summation and in DNIC-type inhibition, there neither was a main effect for sex ($F(1,38) = 0.287$; $p = 0.595$) nor did sex interact significantly with "temporal summation" ($F(1, 38) = 1.068$; $p = 0.308$) or "condition" ($F(2.76) = 1.037$; $p = 0.359$). Therefore, males and females seem to have experienced comparable magnitudes of temporal summation and DNIC-type inhibition. Moreover, sex did not modulate the interaction between DNIC and temporal summation, as indicated by a non-significant three-way interaction effect ($F(2,76) = 0.175$; $p = 0.840$). This finding is of critical relevance for this study, which aimed at assessing the effect of DNIC on temporal summation and its presumed modulation by the sex of the subject studied.

However, we found significant sex differences in pressure pain thresholds ($F(1,38) = 12.481$; $p = 0.001$) as well as in the perception of the tonic heat stimulation ($F(1,38) = 4.935$; $p = 0.032$). As can be seen in Fig. 2a, females had significantly lower pressure pain thresholds compared to males. Moreover, females rated the thermal heat stimulation as more intense compared to males

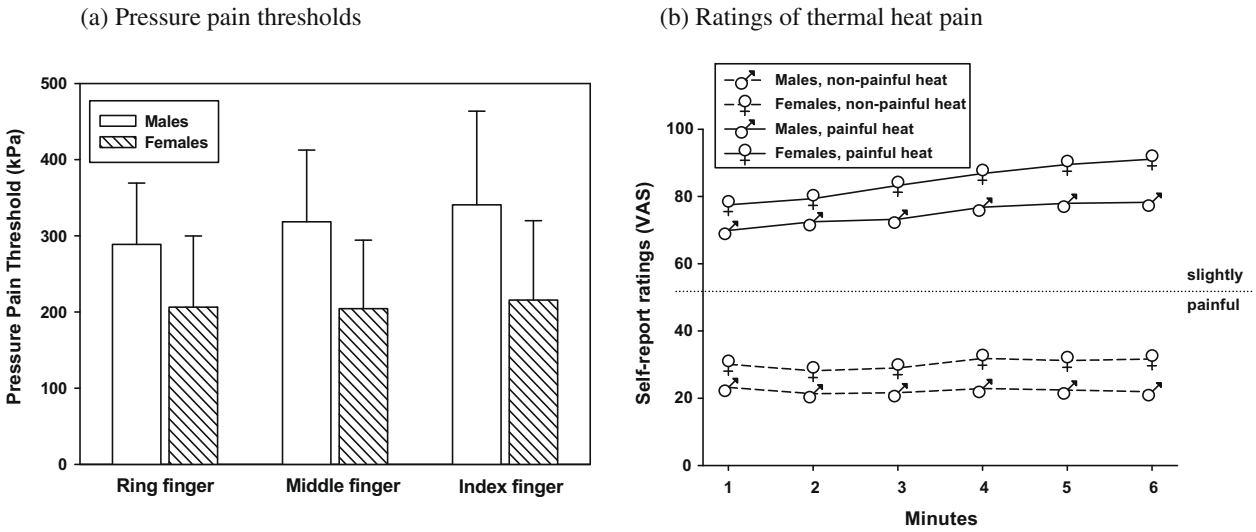

Fig. 2. Pressure pain thresholds (mean values (±SD)) and self-report ratings of tonic non-painful and painful heat (mean values) in males and females.

(see Fig. 2b). As can also be seen in Fig. 2b, the water temperature of 46 °C was rated as significantly more intense compared to the temperature of 42 °C ($F(1,38) = 396.618$; $p < 0.001$), with the first having been perceived painful (VAS scores > 50) and the latter having been perceived non-painful (VAS scores < 50). This finding proves our conditioning stimuli to be effective for a DNIC paradigm in the intended way.

4. Discussion

This study was set-up to assess the counter-regulatory interaction between the inhibitory mechanism "diffuse noxious inhibitory controls" (DNICs) and the excitatory mechanism "temporal summation" as well as the dependency of this interaction on the sex of the subject studied. We obtained the following major findings: (i) Our experimental set-up was suitable to allow observing critical degrees of temporal summation of pressure pain as well as of DNIC effects produced by hot water. (ii) However, the DNIC effects on the sensitivity for single painful pulses of pressure did not differ from the DNIC effects on the sensitivity after temporal summation. In other words, the inhibition was not stronger in the state of summation than in the state of non-summation. (iii) We observed some well-known sex differences for phasic pressure pain (test stimulus) and tonic heat pain (conditioning stimulus), with women showing the lower pain thresholds and the higher pain ratings, respectively. In contrast to our expectations, the females in this study did exhibit neither greater temporal summation nor reduced DNIC effects compared to males. Furthermore, the lack of evidence for a counter-regulatory interaction between DNIC and temporal summation (see ii) was evident in both sexes, and thus, was not a specific contribution of one of the two sexes.

The induced DNIC-type inhibition did not appear to affect the pain ratings at the end of a series of pulses to a stronger degree than the ratings for single pulses, thus suggesting no preferential modulation of the pain system after slow temporal summation (wind-up) by DNIC. This also implies that DNIC-type inhibition apparently does not act as functional counterbalance to temporal summation (wind-up).

Since only a few attempts have been made so far to study this interaction, our findings contradict only a few pieces of evidence. Staud et al. [33] found that the immersion of one hand into painfully hot water reduced the pain ratings for the last pulse in a series of heat pain pulses (0.5 Hz repetition frequency) applied to the other hand to a relatively stronger degree than it reduced the pain ratings for the first pulse. This suggests more inhibitory action for temporal summation than for single pulse processing. However, this was only true for male subjects because this phenomenon was absent in females. Whereas Staud et al. [33] used – as we did – painfully hot water as conditioning stimulus, their and our studies differed with respect to the test stimulus (Staud et al.: heat taps; present study: pressure pain pulses) and the exact method of pain assessment. Given that Staud et al. [33] found an interaction between DNIC and temporal summation only in males and we did not find an interaction at all, there is still not much evidence pointing to a modulation of temporal summation by the DNIC. Furthermore, in a study by Serrao et al. [32] the effects of DNIC (cold-pressor pain) did not appear to differ when the temporal summation threshold of the RIII reflex (5 electrical trains applied with a repetition frequency of 2 Hz) and the RIII reflex area after application of single trains were compared as dependent variables. The evaluation of the pain ratings told a similar story. Again, there was no convincing evidence for a preferential modulation

of the pain system in a state of summation by the DNIC.

The discussion so far relates to slow temporal summation (repetition frequencies roughly between 0.5 and 2 Hz). Giffin el al. [10] showed convincingly that the DNICs reduce the amount of temporal summation of the nociceptive blink reflex induced by much higher repetition frequencies (around 180 Hz).

In this study, the sex of the subject neither affected the interaction between DNIC and temporal summation nor did we find sex differences in temporal summation or in DNIC effects when considering them separately. This might suggest that we sampled subjects who are not representative for their respective sex. Two findings contradict this argument. As observed in numerous studies before, the women in this study exhibited lower pressure pain thresholds compared to males [15,25]. Furthermore, in this study we found higher pain ratings in the female subjects for the 46 °C hot water, which is in line with previous findings of increased pain perception for tonic pain in females compared to males. [4,13]. Given the sex differences found in this study, it seems unlikely that we drew samples with hypo-responsive women or hyper-responsive men. Therefore, a sampling bias cannot be assumed to be responsible for the lack of sex differences in DNIC action and slow temporal summation.

Our failure to find sex differences in DNIC action added a piece of evidence to the perspective that this inhibitory system is not related to factors associated with the sex of the individual studied. There have been some reports of this kind before [2,6,23,24,28], which counterbalance roughly in number the studies in which women were found to have less efficient DNIC [7,8,11,32,33]. In two earlier studies in our laboratory, published only in book chapters [15,27], we also did not observe sex differences in DNIC. In the first one we tested the effects of tonic contact heat on the ratings for electrocutaneous noxious stimuli, in the second one, the same conditioning stimulus was applied to induce inhibitory action on the ratings for pressure pain stimuli. Therefore, sex differences in DNIC are presumably that small that their manifestation seems to depend on many parameters.

The lack of sex differences in slow temporal summation of experimental pain is more atypical. In a series of studies women have appeared to show stronger temporal summation, seemingly not dependent on the physical type of stressor. In all studies available, in which heat pain pulses were used to trigger temporal summation, females showed significantly higher pain ratings after a few pulses than males [5,9,12,26]. There have also been a couple of studies, in which repeated mechanical stimuli were used to induce temporal summation, with a similar outcome [29–31]. However, interestingly, Nie et al. [20], who used the same computer-controlled pressure algometer as we did, also reported no sex differences in temporal summation for a variety of repetition rates (1 Hz to 0.03 Hz) and application sites (m. tibialis anterior, tibia, first web of the hand). The most striking difference between the investigations of Nie et al. [20] and of this authors on the one hand and the experiments of Sarlani and associates [29–31] on the other hand was the area of stimulation, with stimulation areas of 1 cm^2 in the first group of studies compared to 0.245 mm^2 in the second group. This suggests that increasing degrees of spatial summation might hide sex differences in slow temporal summation for mechanical stimuli. Alternatively, differences in the pools of targeted nociceptors, with more deep tissue stimulation associated with larger pressure probes, may account for discrepancy between studies. However, these hypotheses yet require verification.

Our DNIC findings require a further comment. The sub-threshold and non-painful water temperature of 42 °C already lowered the pain ratings for the pressure stimuli. It is not the first time that non-painful conditioning stimuli have been shown to do this [16,17,34]. Whether these inhibitory effects are mediated by the same mechanism or by additional mechanisms, which are also activated in experimental paradigms for assessment of DNIC effects in humans, is a still an unanswered question. For note, the decrease in pain rating was less pronounced when comparing non-painful heat to baseline as when comparing painful heat to non-painful heat conditions, suggesting more inhibitory power in the genuine range of action of DNIC.

In sum, our study contributed to the small volume of evidence stemming from a few preceding studies, which let it appear unlikely that the DNICs are preferentially acting on slow temporal summation of pain (wind-up). Their action appeared similar in the state of summation as in that of non-summation. Although we found some sex differences, with lower pressure pain thresholds and higher pain ratings for tonic heat pain in women, we did not observe such differences in DNIC effects or in slow temporal summation. Whereas the lack of such sex differences is not unusual for DNIC, it is more surprising for temporal summation. It might be the case that in experimental paradigms for temporal summation of pressure pain, the size of the stimulated area is critical because the application of larger probes has appeared to prevent sex differences.

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