Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Expectations of increased and decreased pain explain the effect of conditioned pain modulation in females

This article was published in the following Dove Press journal:
Journal of Pain Research
16 August 2012
Number of times this article has been viewed

Espen Bjørkedal
Magne Arve Flaten

Department of Psychology,
Faculty of Health Sciences,
University of Tromsø, Tromsø, Norway

Objective: Chronic pain is believed to be related to a dysfunction of descending pain modulatory mechanisms. Functioning of descending pain modulation can be assessed by various methods, including conditioned pain modulation (CPM). CPM refers to the inhibition of one source of pain by a second noxious stimulus, termed the conditioning stimulus. This procedure can activate an endogenous pain inhibitory mechanism that inhibits early nociceptive processing. Chronic pain and anxiety disorders are more prevalent among females and it has been hypothesized that females react with more negative emotions towards unpleasant stimuli and this might be part of the explanation of greater pain sensitivity in females. The present study investigated whether expectations modulate the effect of conditioning stimulation on pain, subjective stress, and heart rate. In addition, we investigated whether the modulation of CPM by expectations differed between males and females.

Methods: Seventy-two subjects (including 36 women) received six noxious heat stimuli to the forearm. During three of these stimuli, a conditioning stimulus (cold-water bath) was applied to the contralateral arm in order to activate CPM. One third of the subjects were told that this would reduce pain (analgesia group), one-third that it would increase pain (hyperalgesia group), and one third received no information about its effect (no info group).

Results: Information that conditioning stimulation decreased or enhanced pain had the corresponding effect in females, but not in males. Conditioning stimulation increased stress, but not heart rate in females in the hyperalgesia group. A higher expectation of analgesia and lower stress during conditioning stimulation was associated with larger inhibitory CPM.

Conclusion: These results suggest that reduced inhibitory CPM can be due to contextually induced cognitive and emotional factors and not necessarily a dysfunction of descending inhibitory pathways.

Keywords: pain, conditioned pain modulation, expectations, placebo analgesia, nocebo hyperalgesia

Introduction

Pain is a subjective experience that not always reflects the intensity of noxious stimulation or activation of nociceptors, but that can be modulated by motivational, emotional, and contextual demands. Top–down modulation of pain is mediated by a descending pain modulatory network that inhibits or facilitates nociceptive processing in the dorsal horn of the spinal cord or at supraspinal sites. Expectations of analgesia have been shown to activate a descending inhibitory network involving the anterior cingulate cortex, periaqueductal grey (PAG), and rostral ventromedial medulla (RVM).[1] RVM, through its connections with neurons in the dorsal horn of the spinal cord, can directly affect nociceptive processing.

Correspondence: Espen Bjørkedal
Department of Psychology,
Faculty of Health Sciences,
University of Tromsø, Tromsø
N-9037, Norway
Tel +47 7764 6779
Fax +47 7764 5291
Email espen.bjorkedal@uit.no

One source of pain can be inhibited by applying a second noxious stimulus, the conditioning stimulus, on a distant body site. This phenomenon is termed conditioned pain modulation (CPM). CPM has a well-documented analgesic effect in both animals and man.[2–8] Evidence from animal studies suggests that conditioning stimulation activates a spinal-bulbo-spinal loop involving the subnucleus reticularis dorsalis (SRD).[9] This mechanism is termed diffuse noxious inhibitory controls (DNIC) and there is evidence that it functions independently of the PAG-RVM pathway.[10]

The hypothesis that chronic pain is maintained by dysfunction of endogenous descending inhibitory mechanisms has received some support. Patients with fibromyalgia, irritable bowel syndrome (IBS) and temporomandibular disorder (TMD) show reduced effect of CPM.[11–17] There is also evidence that CPM can be a predictor of chronic pain. Effectiveness of CPM in pain-free subjects waiting for thoracotomy predicted the development of chronic post-thoracotomy pain 29 weeks after surgery.[18] Thus, assessment of the effectiveness of the descending pain modulatory system by CPM can be a valuable tool in the diagnosis and prediction of chronic pain.

Women are more prone to developing chronic pain and it has been hypothesized that women have a less effective descending pain inhibitory system and thus may be more likely to develop chronic pain.[19] However, studies of sex differences in CPM efficiency have provided ambiguous results. A systematic review found that CPM was larger in males when CPM was measured with subjective reports of suprathreshold pain or pain threshold.[20] However, females showed larger CPM when CPM was measured with neurophysiological measures.

The validity of using CPM to assess dysfunction of endogenous pain modulation is questioned if CPM is under the control of psychological variables that might vary according to the situation. Two functional magnetic resonance imaging studies on humans indicate that the conditioning stimulus triggers a supraspinal endogenous inhibitory network also observed in placebo analgesia, hypnosis, and distraction.[17,21] Recently it was shown that CPM depends on the perceived intensity of the conditioning stimulus, giving support to the notion that cognitive factors are involved in CPM in humans.[22] While CPM activates a descending inhibitory modulating system in a bottom-up fashion, it has been shown to be under the control of expectations.[12,23] Expecting increased pain due to CPM can block the inhibition of pain and nociceptive reflexes triggered by CPM with expectations of decreased pain.[23] To our knowledge, no study has previously investigated how expectations modulate CPM when both positive, negative, and no information is given about the effect of CPM. It is currently not known whether positive expectations increase or negative expectations decrease the effect of CPM when no information is provided. Hence, the aim of the present study was first to investigate whether CPM was modulated by expectations, and second to investigate whether the modulation of CPM by expectations differed between males and females.

Pain is a stressor that increases autonomic sympathetic activity and perceived stress.[24,25] However, there is variability in autonomic and subjective reactivity towards pain. Females show greater reactivity to unpleasant stimuli and less reactivity to pleasant stimuli compared to males.[26] Possibly, females and males show different emotional reactivity towards negative and positive information about pain and this might influence pain and the effect of CPM.[25,27,28] By measuring heart rate (HR) and subjective stress we could investigate whether CPM affected cardiovascular reactivity and perceived stress differently between groups and sex.

Verbal reports of pain, stress, and HR responses to a test stimulus were measured in the presence and absence of a conditioning stimulus. Subjects were randomized to three groups, which differed only with regard to the information about the effect of conditioning stimulation on heat pain. The analgesia group was told that conditioning stimulation would reduce pain; the hyperalgesia group was told that conditioning stimulation would increase pain, and the no information group did not receive any information about the effect of conditioning stimulation. Half the participants in each group were female.

It was predicted that conditioning stimulation would reduce pain, subjective stress, and HR in the analgesia and control groups, but not in the hyperalgesia group. Furthermore, it was predicted that females should respond with more pain, subjective stress, and HR towards negative information about CPM efficacy compared to males, and hence a smaller analgesic and stress dampening effect of conditioning stimulation for females. We predicted that males would respond with less pain, stress, and HR towards positive information towards CPM efficacy compared to females.

Methods

Subjects

Seventy-two healthy volunteers (including 36 females) were recruited via advertisements or verbal information at lectures on campus. All participants were aged between 19 and 33 years

(mean age in the analgesia group 22.8 years [SD = 3.1], hyperalgesia group 25.0 years [4.1], and no info group 24.3 years [3.7]). Sixty-eight of the subjects were students at the University of Tromsø. Individuals were excluded if they reported that they had consumed alcohol, nicotine, or caffeine for the last 3 hours before the experimental session, had less than 4 hours sleep the night before, were hypertensive, were on any medication, had any serious illness, or were pregnant. Females were run on days when they did not have menstruation. Two subjects were excluded. One subject was excluded because he reported pain = 10 on an 11-point numerical rating scale. One subject was identified as an outlier determined on the basis of measures of leverage, standardized difference in fit and standardized difference in beta. Leverage is a measure of how far the observed values for the case are from the mean values of the set of independent variables. Difference in fit and difference in beta are measures of how much the case influences the regression equation, ie, how much the regression equation would change if the case was removed from the data set.[29] Thus, 70 subjects (including 35 females) were included in the analysis. The experiment was run by three female psychology students.

All subjects signed an informed consent form and were paid 200 NOK (about 25 €) for their participation. The experimental protocol was in agreement with the Declaration of Helsinki and was approved by the Regional Committee for Medical Research Ethics North Norway (Project number 31/2008).

Research design

An overview of the experimental design can be seen in Figure 1. A mixed design was used as follows: three-groups (analgesia, hyperalgesia, no information) × two conditioning stimulation (no conditioning stimulation, conditioning stimulation) × three trials × two sex × two order (conditioning stimulation first, test stimulus alone first). The group, sex, and order factors were between subject factors while the rest were within subjects factors. Sex and order was balanced within groups. Order was also balanced within sex. Subjects were randomized to the experimental groups.

Test stimulus

Heat pain was applied to the volar forearm of the nondominant hand using a TSA II Neurosensory Analyzer (Medoc, Ramut Yishai, Israel) with a 30 × 30 mm aluminum thermode and a 10°C/s rise and fall rate. All test stimuli were performed under 46°C for 150 seconds.

Conditioning stimulus

The conditioning stimulus consisted of submerging the dominant hand in a water bath of 8°C for 150 seconds. The water was cooled by a Jeio Tech Lab Companion RW-3025G bath and circulator (Jeio Tech, Gimpo, Republic of Korea). The circulator maintained the water temperature at a constant level. Subjects were instructed to submerge the hand to just above the wrist and keep it in the water for as long as the

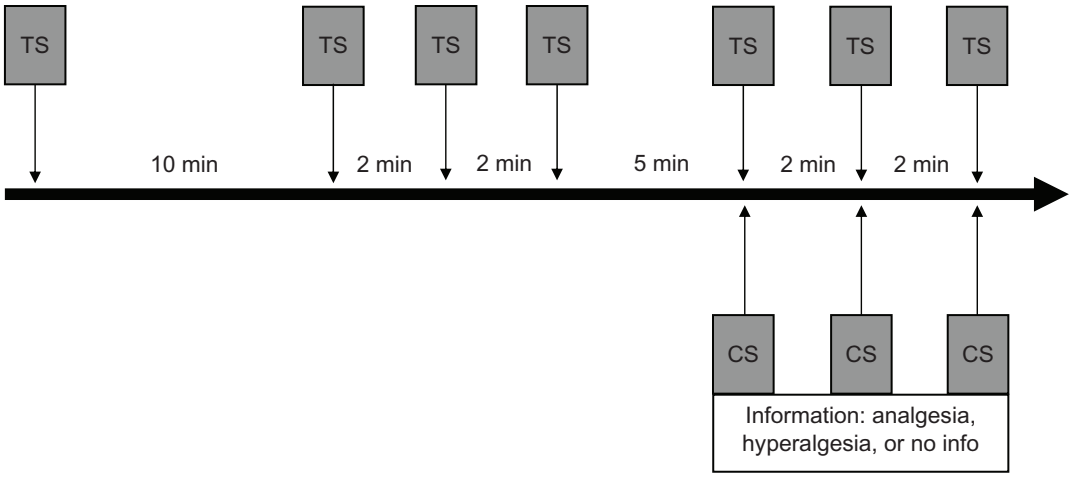

Figure 1 The experimental design.

Notes: All subjects were presented with seven test stimuli (TS), ie, noxious heat stimuli (+46°C) to the nondominant forearm for 150 seconds each. The first TS was administered to familiarize the subjects with the noxious stimulus and the numerical rating scales, and was not included in the analyses. During three of the stimulations the dominant hand was submerged in cold water (+8°C), ie, the conditioning stimulus (CS). For half the subjects the conditioning stimulus was applied during the last three stimuli. For the other half of the subjects the conditioning stimulus was applied during the first three stimuli. Three types of information were given about the effect of the conditioning stimulus on the heat pain: information that the conditioning stimulus would reduce heat pain (analgesia group), information that the conditioning stimulus would increase heat pain (hyperalgesia group), and no information (no info group). Half the participants in each group were females. Measures of pain, stress, and arousal were taken during each test stimulus between 120 and 150 seconds. Heart rate was measured for the entire 150 seconds of each test stimulus. The subjects reported their expected reduction/increase in pain just prior to the application of the conditioning stimulus.

test stimulus lasted. None of the subjects terminated the conditioning stimulation before 150 seconds.

Electrocardiography

Electrocardiography (ECG) was recorded continuously at 1000 Hz from two electrodes attached to the lower ribs and one reference electrode over the right hip-bone by a Biopac MP 150 system with Biopac Acqknowledge 3.7.1 software (Biopac Systems Inc, Goleta, CA) according to the manufacturer guidelines. Raw data were analyzed with MATLAB (The Mathworks Inc, Natick, MA). The signal was first filtered with a 0.5–35 Hz bandpass filter. An automatic QRS detection algorithm was applied to the raw data and R-peaks were identified. The algorithm ('nqrsdetect') is an open source algorithm based on the directions given by Afonso et al[30] and Oppenheim et al.[31] Artifacts were defined as R-R intervals of <1.5 seconds or >0.33 seconds and were removed from the data. Six segments of 150 seconds were created with reference to the test stimulus. Finally, the mean HR (bpm) during each segment was calculated. Due to recording difficulties data from six persons were missing, and the results on HR presents data from 64 participants.

Expectations

Subjects in the analgesia group were asked how much percent decrease in heat pain they expected as a result of putting the hand in cold water. Subjects in the hyperalgesia group were asked how much percent increase in heat pain they expected as a result of putting their hand in cold water.

Questionnaires

Fear of pain might increase pain sensitivity and attenuate placebo responses.[32,33] Optimistic or pessimistic life orientation as assessed by the revised Life Orientation Test (LOT-R) might be related to placebo and nocebo responses.[34] Hence, fear of pain and optimism–pessimism were measured in order to rule out group differences in these variables.

To assess fear of pain related to specific situations the Fear of Pain Questionnaire (FPQ-III) was administrated.[35] The questionnaire consists of 30 items rated on a five-point Likert scale (1 = not at all, to 5 = extreme). The questionnaire was translated into Norwegian and the sum score of all items was used as a dependent variable.[32]

The LOT-R consists of ten self-report items rated on a five-point scale ranging from 0 (strongly disagree) to 4 (strongly agree). Four items are filler items. A sum score on LOT-R was are calculated by reverse coding the three pessimism items and adding them to the three optimism items.[35]

Subjective pain, stress, and arousal measurements

Pain intensity and unpleasantness were recorded by numerical rating scales (NRS) where the subject indicated vocally how intense and unpleasant the pain was on a scale from 0 (no pain) to 10 (unbearable pain or the most unpleasant pain imagined). The difference between pain intensity and pain unpleasantness was explained as in Price et al.[36] Stress and arousal were measured as in O'Neill and Parrott.[37] The subjects indicated vocally, on a scale from 0 to 10, their feelings on the dimensions tense–relaxed and nervous–calm, which indicates stress, and energetic–tired and awake–sleepy, which indicates arousal.

Procedure

Upon arrival the subjects were shown the laboratory and the equipment, and were told that they were part of a project that tested the effect of a pain-modifying procedure, where three consecutive painful stimuli would be applied to the arm for about 150 seconds each, and three identical painful stimuli would be applied as the contralateral hand was submerged in cold water. After giving informed consent, the subjects were seated in a comfortable chair and the electrodes for ECG recordings were attached. Subjective measures of stress and arousal were taken. The test stimulus was presented for 150 seconds, in order to familiarize the subjects with the experimental situation and the subjective ratings. Subjects then spent 10 minutes filling out the FPQ-III and the LOT-R. Thereafter, the subjects were informed that testing would begin. The experimenter attached the thermode within the T1 dermatome of the nondominant arm, left the room and started the program that controlled pain stimulus presentation. Since the behavior of the experimenter might be a distractor and influence pain behavior, the time the experimenter spent in the testing chamber was minimized. The subject was alone in the testing chamber during the first 120 seconds of each trial. After 120 seconds of stimulus presentation, the experimenter entered the room and recorded pain intensity, unpleasantness, stress, and arousal. The test stimulus was presented three times with an interstimulus interval of 2 minutes. After each stimulus, the thermode was moved to an adjacent but not overlapping area within the T1 dermatome in order to avoid sensitization. After the third test stimulus there was a 5-minute break. Towards the end of the break, the experimenter informed participants that three identical

tests were going to be performed, but that this time they were going to submerge the contralateral hand in cold water for the full duration of the test stimulus. Subjects in the no info group were given no further information. The analgesia group was informed that submerging the hand in cold water would reduce the pain experienced to the test stimulus. The hyperalgesia group was informed that submerging the hand in cold water would increase the pain experienced to the test stimulus. Immediately after this information the subjects in the analgesia and hyperalgesia group were asked to rate the expected reduction/increase in heat pain as a consequence of submerging the other hand in cold water. Thereafter, the thermode that delivered the test stimulus was attached to the nondominant hand and subjects were told to submerge the dominant hand in the water bath when they felt the thermode heating up and keep it there for as long as the test stimulus lasted. The experimenter made sure the subject followed the instruction and left the room. Presentation of test stimulus simultaneously with conditioning stimulus was done three times with an inter stimulus interval of 2 minutes. The order of the conditions was balanced such that half of the subjects (half of the males and half of the females in each group) were given the simultaneous presentation of test stimulus and conditioning stimulus in the first three trials while the other half where presented with the test stimulus alone in the first three trials.

Response scoring

There were six trials with the test stimulus. During three of these trials, a conditioning stimulus was presented. The mean of the three test stimulus trials without simultaneous conditioning stimulation was computed. The same was done for the three trials with conditioning stimulation. The effect of conditioning stimulation on pain intensity, pain unpleasantness, subjective stress, and HR was defined as the difference between the mean of the trials with test stimulus alone compared to the mean of the conditioning stimulus trials. Negative scores indicate less pain, stress or HR during conditioning stimulation compared to test stimulus alone.

Statistics

Differences in the effect of CPM between the groups, and interaction effects with group and sex were tested with a three-group (analgesia, hyperalgesia, no info) × two conditioning stimulation (no conditioning stimulation, conditioning stimulation) × two sex × two order (conditioning stimulation first, test stimulus alone first) repeated measures analyses of variance (ANOVA). The conditioning stimulation factor was within-subjects factor while the rest were between-subjects factors. Significant interactions involving groups were followed up with planned comparisons. Other interactions were followed up with Tukey's Honestly Significant Difference test for unplanned comparisons. A sign test of the effect of conditioning stimulation in the groups was performed.

Correlations were performed with Pearson's r (two-tailed). The significance level was set to $P < 0.05$.

Results

Baseline

Descriptive data of the main outcome measures are displayed in Table 1. There were no group or sex differences in pain intensity ratings to test stimulus alone, in pain unpleasantness, in LOT-R sum score, in FPQ sum score, or in reported stress upon arrival. The groups did not differ in age (all F's < 2, all $P > 0.15$). However, there was a sex difference in participants, age ($F(1,68) = 4.37$, $P = 0.04$). The average age of females was 23.27 (SD = 3.31) and males 25.01 (SD = 3.98). As the results from the ANOVA and regression analysis showed the same main effects and interactions for pain intensity and unpleasantness the latter data were omitted from the analysis.

Manipulation check

The mean expected pain reduction in the analgesia group was 16.1% (SD 13.2) (19.2% for females and 12.5% for males). Four subjects in the analgesia group (three males) did not expect any reduction in pain and hence did not believe the verbal information provided by the experimenter. They were, nevertheless, included in the analysis. Subjects in the hyperalgesia group reported a mean expected increase of 23.6% (SD 12.5) (24.1% for females and 23.1% for males). All subjects in the hyperalgesia group believed that pain would increase during conditioning stimulation. The difference in expectations between the analgesia and hyperalgesia groups was significant ($F(1,42) = 106.82$, $P < 0.01$, partial $\eta^2 = 0.72$). There was no interaction between group and sex.

Effect of conditioning stimulation on pain

The repeated measures ANOVA showed no main effect of conditioning stimulation ($P = 0.16$) nor any difference in effect of conditioning stimulation between the groups ($P = 0.36$) or sex ($P = 0.44$) (Figure 2A).

There was a significant three-way interaction between conditioning stimulation, groups, and sex ($F(2,58) = 4.81$, $P = 0.01$, partial $\eta^2 = 0.14$). Contrast analyses showed that for females the conditioning stimulation increased pain in the hyperalgesia group compared to the analgesia group

Table 1 Descriptive data for the main outcome measures for males and females in the experimental groups

Outcome	Analgesia group			Hyperalgesia group			No info group		
	TS	TS + CS	Mean % change	TS	TS + CS	Mean % change	TS	TS + CS	Mean % change
Males									
Pain intensity	4.97 ± 1.94	4.63 ± 2.35	−10.60 ± 6.02	4.89 ± 1.80	4.06 ± 1.60	−12.76 ± 7.68	4.94 ± 1.65	5.00 ± 1.56	8.10 ± 13.43
Pain unpleasantness	4.60 ± 1.70	4.70 ± 2.08	1.8 ± 8.47	5.08 ± 1.82	4.28 ± 1.89	−11.38 ± 12.06	4.79 ± 2.00	5.00 ± 1.73	9.94 ± 11.30
Subjective stress	3.08 ± 1.95	4.05 ± 2.05	35.53 ± 9.82	3.75 ± 1.54	3.97 ± 1.42	10.72 ± 8.52	3.98 ± 1.30	4.76 ± 1.36	23.09 ± 7.40
Heart rate	72.94 ± 8.71	72.69 ± 8.45	−0.23 ± 1.11	65.09 ± 8.05	69.06 ± 10.34	7.29 ± 2.87	61.87 ± 8.76	68.96 ± 15.67	4.76 ± 3.15
Females									
Pain intensity	5.94 ± 2.50	4.94 ± 2.25	−15.75 ± 5.80	4.58 ± 1.36	5.42 ± 2.04	21.33 ± 13.91	4.64 ± 2.09	4.56 ± 1.77	11.09 ± 16.00
Pain unpleasantness	6.36 ± 2.17	5.83 ± 1.73	−3.65 ± 6.95	4.97 ± 1.83	6.08 ± 1.81	35.08 ± 19.27	5.18 ± 2.09	5.28 ± 2.19	14.54 ± 16.07
Subjective stress	4.43 ± 1.90	4.90 ± 1.69	40.94 ± 28.90	2.89 ± 1.37	4.68 ± 2.14	71.71 ± 21.60	2.87 ± 1.88	3.96 ± 1.82	64.59 ± 18.17
Heart rate	68.47 ± 8.22	70.48 ± 7.51	3.25 ± 1.88	74.35 ± 10.86	76.78 ± 9.01	3.75 ± 1.39	69.43 ± 10.22	70.43 ± 9.84	1.66 ± 1.45

Note: Mean percentage of change was computed by calculating the percentage of change in pain due to conditioning stimulation for each subject and computing the mean of all subjects.
Abbreviations: TS, test stimulus; CS, conditioning stimulus.

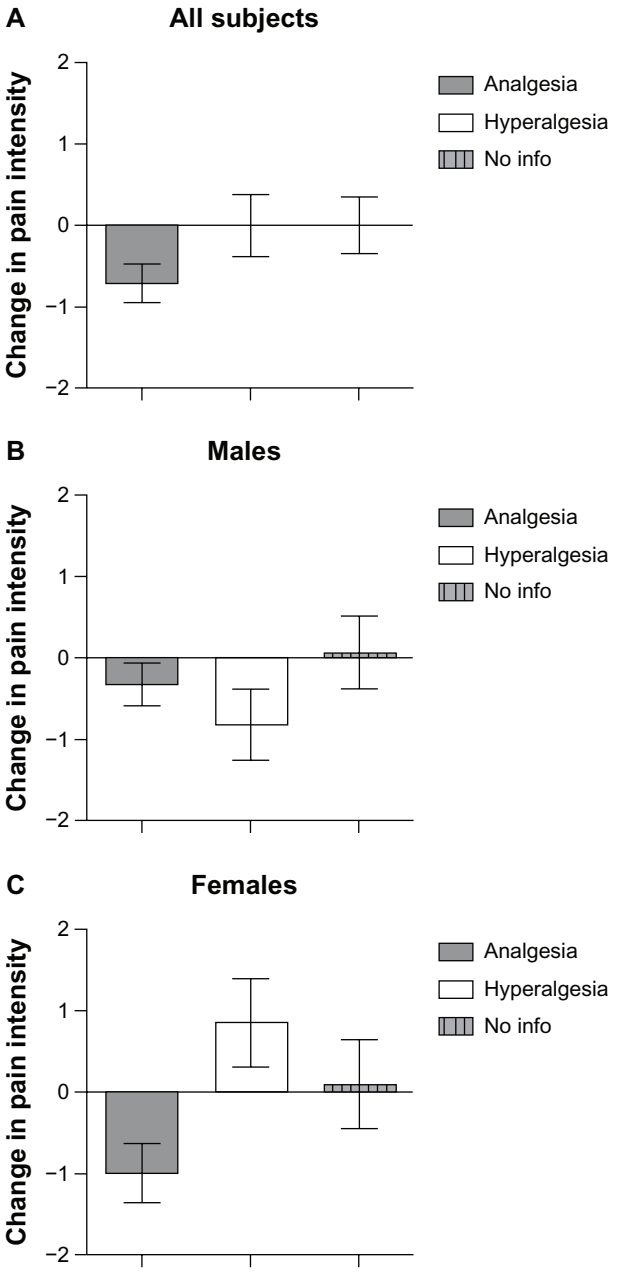

Figure 2 Change in pain intensity from test stimulus alone to conditioning stimulation. Negative scores indicate a reduction in pain during conditioning stimulation. Error bars depict standard error of the mean. (**A**) Change in pain intensity across the experimental groups including both males and females. (**B**) Change in pain intensity across the experimental groups in males. (**C**) Change in pain intensity across the experimental groups in females.

(F(1,58) = 9.36, $P < 0.01$) (Figure 2C). The decrease in pain in the analgesia group was significant ($P = 0.02$) and the increase in pain in the hyperalgesia group almost reached significance ($P = 0.05$). However, there was no difference between the effect of conditioning stimulation in the analgesia and no info group or the hyperalgesia and no info group. For males, there were no group differences in the effect of conditioning stimulation (Figure 2B).

There was an interaction between order and conditioning stimulation (F(1,64) = 6.06, $P = 0.02$, partial $\eta^2 = 0.10$) (Figure 3). Conditioning stimulation reduced pain when it was presented after the test stimulus alone ($P < 0.05$), but not when applied before the test stimulus alone.

There was no main effect of conditioning stimulation. However, a sign test showed that more subjects in the analgesia group reported reduced pain than not reduced pain (hypothesized proportion 0.50, observed proportion 0.83, $P = 0.002$). This was not the case in the hyperalgesia (hypothesized proportion 0.50, observed proportion 0.46, $P = 0.84$) or no info group (hypothesized proportion 0.50, observed proportion 0.54, $P = 0.84$).

Effect of conditioning stimulation on subjective stress

There was a main effect of conditioning stimulation due to increased subjective stress during conditioning stimulation compared to the test stimulus alone (F(1,58) = 38.82, $P < 0.01$, partial $\eta^2 = 0.40$) (Figure 4A). There was no difference in effect of conditioning stimulation between the groups or orders of presentation. The interaction of conditioning stimulation × group × sex was significant (F(2,58) = 4.46, $P = 0.02$, partial $\eta^2 = 0.13$). This was due to a significant increase in stress during conditioning stimulation compared to during test stimulus alone in females in the hyperalgesia group, ($P < 0.01$) (Figure 4B and C).

Effect of conditioning stimulation on heart rate

A main effect of conditioning stimulation showed that HR increased during conditioning stimulation compared to test stimulus alone (F(1,52) = 21.47, $P < 0.01$, partial $\eta^2 = 0.29$). There were no group differences in the effect of conditioning stimulation. The interaction of conditioning stimulation by order was significant (F(1,52) = 21.19, $P < 0.01$, partial $\eta^2 = 0.29$). Post-hoc tests showed that the HR was lower during test stimulus alone when presented after conditioning stimulation compared to during test stimulus alone when conditioning stimulation was presented first ($P = 0.02$) and compared to during conditioning stimulation irrespective of

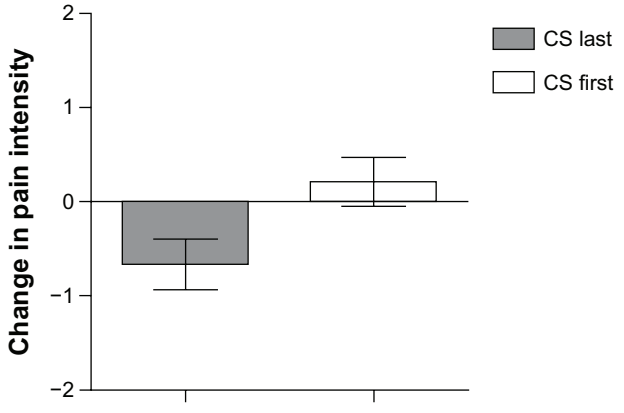

Figure 3 Change in pain intensity from test stimulus alone to conditioning stimulation as a function of order of presentation of conditioning stimulation.
Notes: Error bars depict standard error of the mean. Conditioning stimulation reduced pain when presented after test stimulus alone, but not when presented first.
Abbreviation: cs, conditioning stimulation

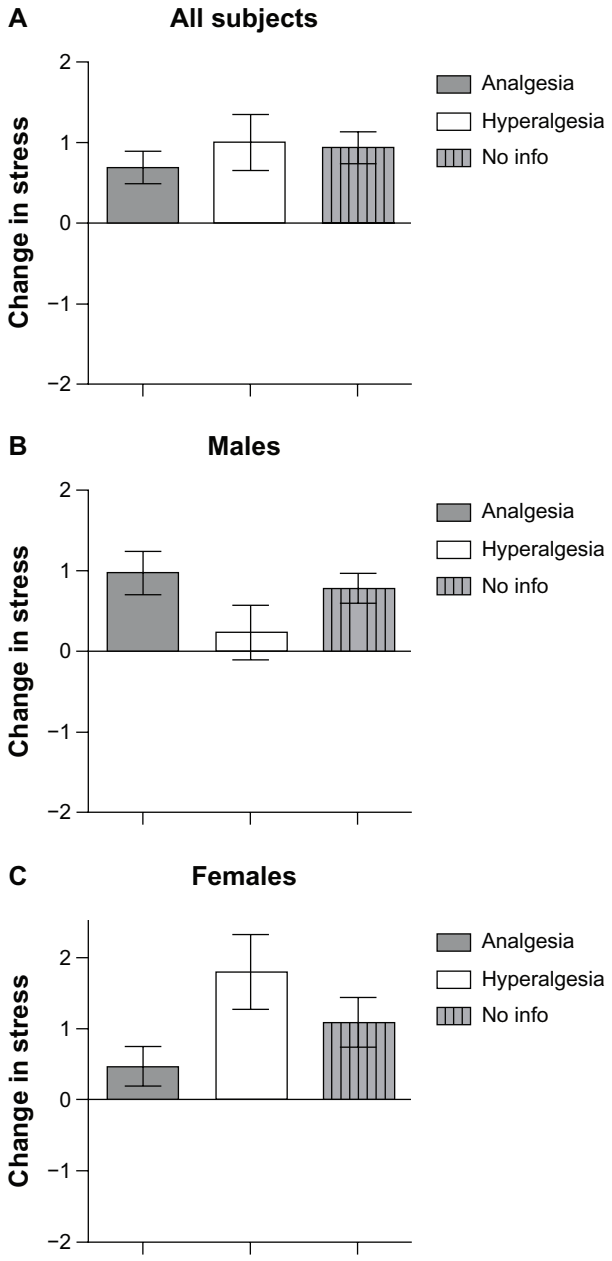

Figure 4 Change in stress from test stimulus alone to conditioning stimulation. Positive scores indicate an increase in stress. Error bars depict standard error of the mean. (**A**) Change in stress across the experimental groups including both males and females. (**B**) Change in stress across the experimental groups in males. (**C**) Change in stress across the experimental groups in females.

order of presentation (both $P \leq 0.05$). No other comparisons were significant. There was a main effect of sex showing that females had higher HR than males ($F(1,52) = 4.10$, $P = 0.05$, partial $\eta^2 = 0.07$).

Correlations between pain, expectations, heart rate, and stress

Change in pain intensity (conditioning stimulation – test stimulus alone) correlated positively with expectations ($r(46) = 0.33$, $P = 0.03$) (Figure 5A), ie, higher expectations of decreased pain were associated with more pain reduction during conditioning stimulation. The correlation between change in pain intensity and change in HR approached significance ($r(64) = 0.24$, $P = 0.06$). Change in pain intensity correlated with change in perceived stress ($r(70) = 0.52$, $P > 0.01$) (Figure 5B). There was a tendency towards a significant positive correlation between change in HR and change in stress ($r(64) = 0.21$, $P = 0.09$).

Discussion

The present study investigated whether expectations modulated the effect of conditioning stimulation on tonic pain and whether the modulation of CPM by expectations differed between males and females. A conditioning stimulus (water at 8°C) was applied in the presence of tonic heat pain with information that the cold water would increase or decrease pain in the hyperalgesia and analgesia groups, respectively, or no information about the effect of the cold water was provided in the no information group. Mean pain levels were about 5 on an 11-point NRS, allowing for the observation of both increases and decreases in pain. The main finding was that information that conditioning stimulation decreased or enhanced pain had the corresponding effect in females, not in males.

Effect of conditioning stimulation

A main effect of conditioning stimulation on pain was not observed which seems to be in contrast to previous research. However, the experiment included two factors that modified the effect of conditioning stimulation: order and information. A sign test revealed that 83% of the subjects in the analgesia group reported reduced pain after conditioning stimulation compared to the test stimulus alone. This is within the normal range of studies reporting significant effects of conditioning stimulation, as response rates of 100%,[23] 80%,[38] and 78.8%[3] have been reported. Furthermore, 46% of the subjects in the hyperalgesia group reported lower pain during conditioning stimulation compared to test stimulus alone, which is similar to the 50% observed in Goffaux et al.[23] Additionally, using a tonic test stimulus could have attenuated the magnitude of CPM in the present study. Most studies have investigated the effect of conditioning stimulation on phasic test stimuli. The conditioning stimulus has often induced stronger pain than the test stimulus, thus introducing distraction as a confounding factor.[12,21,23,38–40] In the present study the duration of the conditioning and test stimuli were identical. Thus, one explanation of the weak effect of conditioning stimulation in the present study could be that the duration and intensity of the test and conditioning stimuli were similar and, hence, that distraction played less of a role.

The conditioning stimulus decreased pain only when it was applied after the test stimulus alone. The effect of

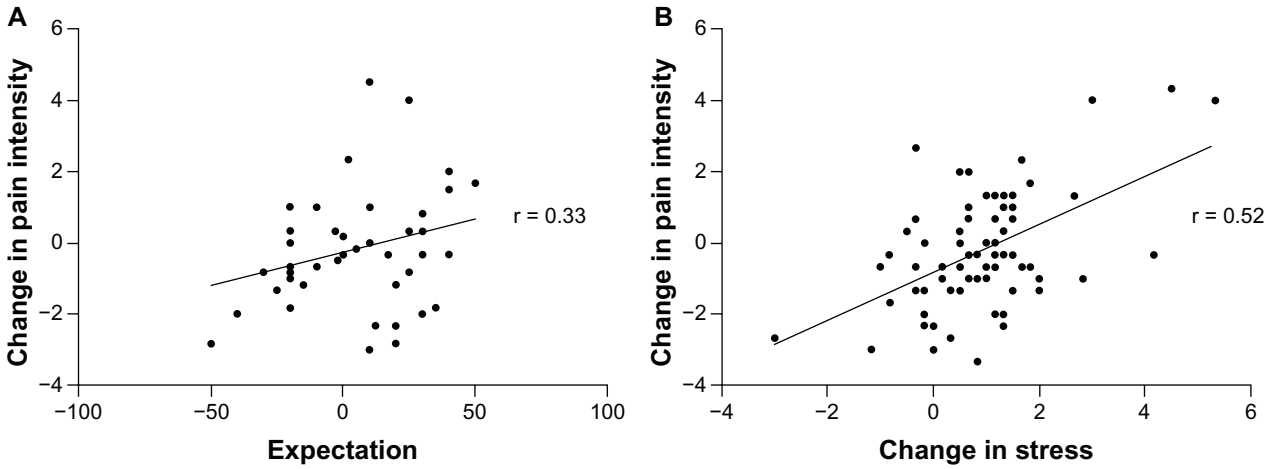

Figure 5 (**A**) Relationship of expectation to the effect of conditioning stimulation on pain intensity. Only subjects in the analgesia and hyperalgesia groups were asked about expectations (n = 46). (**B**) Relationship of change in stress to the effect of conditioning stimulation on pain intensity (n = 70).

Notes: Negative scores on the y-axis indicate a reduction in pain during conditioning stimulation compared to during test stimulus alone. Negative scores on the x-axis indicate expectations of reduced pain or reduction in stress during conditioning stimulation compared to during test stimulus alone.

order was possibly due to an after-effect of conditioning stimulation. Previous research reported decreased pain and somatosensory evoked potentials 5 minutes after termination of the conditioning stimulation compared to a control condition.[41] There was a 5-minute interval between the end of the last conditioning stimulation trial, and the onset of the first test stimulus alone trial. Thus, the effect of conditioning stimulation may have lasted into the trials with test stimulus alone when conditioning stimulation was presented first. Interestingly, HR was lower during test stimulus alone when presented after conditioning stimulation compared to during test stimulus alone when conditioning stimulation was presented last and compared to during conditioning stimulation. Hence, the observed difference in HR due to conditioning stimulation is best explained by a decreased HR response to test stimulus alone after conditioning stimulation. Since there was no effect of order on subjective stress this suggests that conditioning stimulation resulted in inhibition of cardiovascular reactivity to the test stimulus 5–16.5 minutes after termination of the cold pressor test. Roy and Steptoe found that 20 minutes of high intensity exercise reduced cardiovascular reactivity to a mental stressor presented after 20 minutes of recovery, compared to low intensity exercise and no exercise.[42] Morris et al found that naloxone increased HR during the Stroop task compared to saline, thus implicating opioid mechanisms in the inhibition of cardiovascular reactivity to a stressor.[43] Thus, lower pain and HR during test stimulus alone when presented last compared to when presented first could be related to an after effect of conditioning stimulation implicating endogenous opioids. The order effect could also be explained according to the adaptation level theory of perception.[44] According to this theory the current experience of pain will be interpreted relative to a previous reference point. Rollman found that subjects reported the same noxious stimulus as more painful when it was preceded by a low-intensity stimulus compared to when preceded by a high-intensity stimulus.[44] In the present experiment the subjects who were presented with the test stimulus alone first had a reference point against which the combined stimulation could be compared. This reference point was lacking when the combined stimulation was presented first. Since most designs investigating CPM present the test stimulus alone first, this adaptation effect could be a possible confounder in some studies. The problem is best avoided by including a condition where the conditioning stimulus is not applied.

Expectations and CPM

Informing participants that conditioning stimulation would increase or decrease pain induced opposite expectations in the groups. Interestingly, only females showed antagonistic responses to positive and negative expectations. Previous studies have observed placebo analgesia in males and not in females.[25,27,45,46] In the previous studies placebo analgesia was induced by verbal information that a powerful painkilling medication had been administered, although placebo capsules were administered that had no subjective effects. In the present study, the purported analgesic or hyperalgesic treatment had subjective effects that could have strengthened expectations. It has been shown that pairing information about the effect of medication with treatment that induces an internal stimulus, may modulate the effect of the treatment in the direction suggested by the information.[45,47,48] This so called "active placebo effect" has been shown to be larger in magnitude compared to placebo effects induced by verbal information alone.[47,48] The point here is that females have been reported to show larger nocebo effects than males when the nocebo effect has been induced by experience (ie, classical conditioning) and not by verbal report.[49] Thus, the larger effect of expectations in females in the present study could be due to the internal stimulus induced by the conditioning stimulus.

Expecting an increase in pain might induce more negative emotions in subjects high in fear of pain or pain catastrophizing, and this might influence pain. Although we observed no differences between males and females in reported fear of pain, females in the hyperalgesia group reported increased stress during conditioning stimulation compared to during test stimulus alone. No change was observed in the other groups. However, there were no group differences or group by sex interaction in cardiovascular reactivity to conditioning stimulation. Previous research shows that females have greater pain sensitivity and report more negative emotions to unpleasant stimuli[26] while males show larger cardiovascular reactivity to stressors.[50] For example, Kelly et al[51] found that while females reported more negative emotions after the Trier Social Stress Test, there were no differences between males and females in cortisol or HR reactivity. Tousignant-Laflamme et al[50] observed a strong correlation between HR and pain in males but no correlation in females. Hence, the relation between negative emotions and pain might not be mediated by the same cardiovascular responses in males and females.

The results of the present study suggest that the sex difference in modulation of CPM by expectations could be due to cognitive evaluation/appraisal mechanisms. One possibility is that males and females differ in primary appraisal of threat or secondary appraisal of their coping resources for pain. Through social learning males and females adapt to gender roles in the expression of pain.[52]

Males might consider experimentally induced pain as a possibility to display toughness and thereby show less appraisal of threat while females might perceive greater threat in the face of pain.[52] Previous research shows that there is more pain catastrophizing in females compared to males, and higher pain catastrophizing reduce the effect of conditioning stimulation.[53] One previous study found that increased stress during conditioning stimulation was associated with decreased CPM in females and increased CPM in males.[54] Hence, a possible explanation of the present results is that expectations of increased pain are appraised as more threatening by females and that this affected pain and emotional reactivity. Although we observed no sex difference in the scores on FPQ, a proper investigation of this hypothesis would have to include a state measure of fear and anxiety, for instance the startle response, measured immediately prior to pain.

However, there is also evidence that males report more pain-related anxiety and a stronger association between anxiety and pain.[55] Hence, the relationship between sex, expectations, emotions, and pain is complex and further research is needed.

It has been suggested that females have a less efficient CPM and that this might be an explanation for why females are more prone to develop chronic pain.[19] The results of the present study suggest that less efficient CPM in females might also be the result of expectations and how females react towards information about upcoming pain. Thus, rather than reflecting physiological dysfunction, sex differences in CPM could also be the result of differences in contextual effects on psychological state. Thus, when assessing CPM, one should take great care to control for expectations and negative emotions.

Expectations of analgesia had a graded influence on pain since stronger expectations were related to more pain relief, which replicates earlier findings.[12,23,45] Thus, the effect of expectations seems to vary according to the magnitude of expected relief. Expectations of reduced pain have been shown to trigger a descending pain inhibitory network that modulates ascending nociceptive processing in the dorsal horn.[45] By virtue of its inhibitory influence on the RIII nociceptive flexion reflex (a spinal withdrawal reflex evoked by activation of nociceptive A-delta fibers), it can be inferred that CPM also has an inhibitory effect at the spinal level. Since both expectations and CPM have been shown to modulate nociceptive processing at the spinal level, a possible explanation of the present results is that the influence of expectations on conditioning stimulation reflects an additive effect on spinal pain modulatory neurons. This explanation is supported by the observation that expectations of analgesia and hyperalgesia towards conditioning stimulation had opposite effects on the dorsal horn mediated RIII reflex.[23] However, in another study from the same group, expectations had no influence on the RIII reflex in fibromyalgia patients, but produced opposite effects on pain report and somatosensory evoked potentials.[12] Thus, expectations could also modulate CPM without affecting early nociceptive processing.

Limitations

It has recently been shown that the effect of CPM depends on the perceived painfulness of the conditioning stimulus.[22] Perceived pain to the conditioning stimulus was not measured, but Granot et al[3] showed that water at 12°C was reported as painful, suggesting that the conditioning stimulus in the present study was painful. As a result of this limitation the painfulness of the conditioning stimulus could not be correlated with any changes in the effect of conditioning stimulation.

Stress was not measured in the absence of pain and, due to technical difficulties, neither was HR. In order to investigate whether stress and cardiovascular reactivity during pain are antecedent to or consequent upon pain one should also take these measures immediately before the painful stimulation.

Conclusion

In conclusion, the present study demonstrated that the inhibitory effect of conditioning stimulation can be enhanced by positive expectations, attenuated in females by negative information and increased stress levels, and affected by the order in which conditioning stimulation and test stimulus are presented. Thus, the results suggest that reduced inhibitory CPM can be due to contextually induced cognitive and emotional factors and not necessarily a dysfunction of descending inhibitory pathways. These results are relevant for understanding sex differences in endogenous pain modulating systems and using CPM as a tool for assessing deficiencies in descending pain modulation.

Acknowledgments

This study was funded by the University of Tromsø, the Bial Foundation (grant 161/06), and the Norwegian Research Council.

Disclosure

The authors have no conflicts of interest to declare.

References

1. Eippert F, Bingel U, Schoell ED, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron*. 2009;63(4):533–543.

2. Debroucker T, Cesaro P, Willer JC, Lebars D. Diffuse noxious inhibitory controls in man – involvement of the spinoreticular tract. *Brain*. 1990;113:1223–1234.
3. Granot M, Weissman-Fogel I, Crispel Y, et al. 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(1–2):142–149.
4. Le Bars D. Diffuse noxious inhibitory controls (DNIC). 1. Effects on dorsal horn convergent neurons in the rat. *Pain*. 1979;6(3):283–304.
5. Le Bars D. Diffuse noxious inhibitory controls (DNIC). 2. Lack of effect on non-convergent neurons, supraspinal involvement and theoretical implications. *Pain*. 1979;6(3):305–327.
6. Willer JC. Diffuse noxious inhibitory controls in man – involvement of an opioidergic link. *Eur J Pharmacol*. 1990;182(2):347–355.
7. Willer JC, Debroucker T, Le Bars D. Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. *J Neurophysiol*. 1989;62(5):1028–1038.
8. Willer JC, Roby A, Le Bars D. Psychophysical and electrophysiological approaches to the pain-relieving effects of heterotopic nociceptive stimuli. *Brain*. 1984;107(Pt 4):1095–1112.
9. 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(2):353–357.
10. Bouhassira D, Bing Z, Le Bars D. Studies of brain structures involved in diffuse noxious inhibitory controls in the rat: The rostral ventromedial medulla. *J Physiol*. 1993;463:667–687.
11. Lautenbacher S. Possible deficiencies of pain modulation in fibromyalgia. *Clin J Pain*. 1997;13(3):189.
12. Goffaux P, de Souza JB, Potvin S, Marchand S. Pain relief through expectation supersedes descending inhibitory deficits in fibromyalgia patients. *Pain*. 2009;145(1–2):18–23.
13. Potvin S, Larouche A, Normand E, et al. DRD3 Ser9Gly polymorphism is related to thermal pain perception and modulation in chronic widespread pain patients and healthy controls. *J Pain*. 2009;10(9):969–975.
14. Potvin S, Larouche A, Normand E, et al. No relationship between the ins del polymorphism of the serotonin transporter promoter and pain perception in fibromyalgia patients and healthy controls. *Eur J Pain*. 2010;14(7):742–746.
15. Normand EE, Potvin SS, Gaumond II, Cloutier GG, Corbin JJ-F, Marchand SS. Pain inhibition is deficient in chronic widespread pain but normal in major depressive disorder. *J Clin Psychiatry*. 2011;72(2):219–224.
16. King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. *Pain*. 2009;143(3):172–178.
17. Wilder-Smith CH, Schindler D, Lovblad K, Redmond SM, Nirkko A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut*. 2004;53(11):1595–1601.
18. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138(1):22–28.
19. Staud R, Robinson ME, Vierck 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(1–2):167–174.
20. Popescu A, LeResche L, Truelove EL, Drangsholt MT. Gender differences in pain modulation by diffuse noxious inhibitory controls: A systematic review. *Pain*. 2010;150(2):309–318.
21. Sprenger C, Bingel U, Buchel C. Treating pain with pain: Supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. *Pain*. 2011;152(2):428–439.
22. Nir RR, Yarnitsky D, Honigman L, Granot M. Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. *Pain*. 2012;153(1):170–176.
23. Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia – When the spine echoes what the brain expects. *Pain*. 2007;130(1–2):137–143.
24. Loggia ML, Juneau M, Bushnell MC. Autonomic responses to heat pain: Heart rate, skin conductance, and their relation to verbal ratings and stimulus intensity. *Pain*. 2011;152(3):592–598.
25. Aslaksen PM, Flaten MA. The roles of physiological and subjective stress in the effectiveness of a placebo on experimentally induced pain. *Psychosom Med*. 2008;70(7):811–818.
26. Rhudy JL, Bartley EJ, Williams AE, et al. Are there sex differences in affective modulation of spinal nociception and pain? *J Pain*. 2010;11(12):1429–1441.
27. Aslaksen PM, Bystad M, Vambheim SM, Flaten MA. Gender differences in placebo analgesia: Event-related potentials and emotional modulation. *Psychosom Med*. 2011;73(2):193–199.
28. Flaten MA, Aslaksen PM, Lyby PS, Bjorkedal E. The relation of emotions to placebo responses. *Philos Trans R Soc B-Biol Sci*. 2011;366(1572):1818–1827.
29. Cohen J, Cohen P, West SG, Aiken LS. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. 3rd ed. Mahwah, NJ: Lawrence Erlbaum Associates; 2003.
30. Afonso VX, Tompkins WJ, Nguyen TQ, Luo S. ECG beat detection using filter banks. *IEEE Trans Biomed Eng*. 1999;46(2):192–202.
31. Oppenheim AV, Schafer RW, Buck JR. *Discrete-Time Signal Processing*. 2nd ed. Prentice Hall: Pearson Education; Upper Saddle River, NJ. 1999.
32. Lyby PS, Aslaksen PM, Flaten MA. Is fear of pain related to placebo analgesia? *J Psychosomat Res*. 2010;68(4):369–377.
33. Meulders A, Vansteenwegen D, Vlaeyen JWS. Women, but not men, report increasingly more pain during repeated (un)predictable painful electrocutaneous stimulation: Evidence for mediation by fear of pain. *Pain*. 2012;153(5):1030–1041.
34. Morton DL, Watson A, El-Deredy W, Jones AKP. Reproducibility of placebo analgesia: Effect of dispositional optimism. *Pain*. 2009;146(1–2):194–198.
35. McNeil DW, Rainwater AJ. Development of the Fear of Pain Questionnaire-III. *J Behav Med*. 1998;21(4):389–410.
36. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*. 1983;17(1):45–56.
37. O'Neill S, Parrott A. Stress and arousal in sedative and stimulant cigarette smokers. *Psychopharmacology*. 1992;107(2):442–446.
38. Defrin R, Tsedek I, Lugasi I, Moriles I, Urca G. The interactions between spatial summation and DNIC: Effect of the distance between two painful stimuli and attentional factors on pain perception. *Pain*. 2010;151(2):489–495.
39. Treister R, Eisenberg E, Gershon E, Haddad M, Pud D. Factors affecting – And relationships between – Different modes of endogenous pain modulation in healthy volunteers. *Eur J Pain*. 2010;14(6):608–614.
40. Moont R, Pud D, Sprecher E, Sharvit G, Yarnitsky D. 'Pain inhibits pain' mechanisms: Is pain modulation simply due to distraction? *Pain*. 2010;150(1):113–120.
41. Fujii K, Motohashi K, Umino M. Heterotopic ischemic pain attenuates somatosensory evoked potentials induced by electrical tooth stimulation: Diffuse noxious inhibitory controls in the trigeminal nerve territory. *Eur J Pain*. 2006;10(6):495–504.
42. Roy M, Steptoe A. The inhibition of cardiovascular responses to mental stress following aerobic exercise. *Psychophysiology*. 1991;28(6):689–700.
43. Morris M, Salmon P, Steinberg H, et al. Endogenous opioids modulate the cardiovascular response to mental stress. *Psychoneuroendocrinology*. 1990;15(3):185–192.
44. Rollman GB. Signal-detection theory pain measures – empirical validation studies and adaptation-level effects. *Pain*. 1979;6(1):9–21.
45. Bjorkedal E, Flaten MA. Interaction between expectancies and drug effects: an experimental investigation of placebo analgesia with caffeine as an active placebo. *Psychopharmacology*. 2011;215(3):537–548.

46. Flaten MA, Aslaksen PM, Finset A, Simonsen T, Johansen O. Cognitive and emotional factors in placebo analgesia. *J Psychosomat Res*. 2006; 61(1):81–89.
47. Flaten MA, Simonsen T, Olsen H. Drug-related information generates placebo and nocebo responses that modify the drug response. *Psychosom Med*. 1999;61(2):250–255.
48. Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. *Lancet*. 1995;346(8984):1231.
49. Klosterhalfen S, Kellermann S, Braun S, et al. Gender and the nocebo response following conditioning and expectancy. *J Psychosomat Res*. 2009;66(4):323–328.
50. Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a link between heart rate and pain in healthy subjects: A gender effect. *J Pain*. 2005;6(6):341–347.
51. Kelly MM, Tyrka AR, Anderson GM, Price LH, Carpenter LL. Sex differences in emotional and physiological responses to the Trier Social Stress Test. *J Behav Ther Exp Psychiatry*. 2008;39(1):87–98.
52. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain*. 2000;87(3): 325–334.
53. Goodin BR, McGuire L, Allshouse M, et al. Associations between catastrophizing and endogenous pain-inhibitory processes: Sex differences. *J Pain*. 2009;10(2):180–190.
54. Quiton RL, Greenspan JD. Sex differences in endogenous pain modulation by distracting and painful conditioning stimulation. *Pain*. 2007;132:S134–S149.
55. Frot M, Feine JS, Bushnell MC. Sex differences in pain perception and anxiety. A psychophysical study with topical capsaicin. *Pain*. 2004; 108(3):230–236.