Are there Gender Differences in Pain and Placebo Analgesia?

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Forord

Ideen til oppgaven ble presentert for meg av stipendiat Sara M. Vambheim, og masteroppgaven er basert på hennes prosjekt. Hypoteser og gjennomføring ble tilpasset min oppgave, i samarbeid med veileder. Rekruttering av deltagere og datainnhenting ble gjort av meg. Det samme gjelder hoveddelen av litteratursøket. Per M. Aslaksen hjalp meg med dataanalysene, da Sara var i fødselspermisjon. Per har også veiledet meg i skriveprosessen, den siste tiden mot innlevering.

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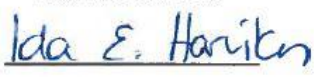
Ida E. Harviken



Per M. Aslaksen

Abstract

Objectives: To examine whether males show higher placebo responses than females, and if this could be explained by gender differences in emotional regulation. High levels of fear of pain were hypothesized to be highest amongst the female participants and thereby related to lower placebo response. Finally, to investigate if experimenter gender would affect participants pain reports. **Method:** 96 healthy volunteers (51 females) were recruited to a 3 condition x 4 intensities x 3trial mixed design. Subjective fear of pain was obtained through a questionnaire of three components; fear of severe pain, medical pain and minor pain. Pain was induced by electrical pulses to the participants lower arms. The stimuli intensity values used in the trials, were obtained from a prior calibration procedure. **Results:** Males reported lower pain intensity compared to females in the pretest and posttest. Conversely, males reported higher pain unpleasantness in the pretest. Fear of pain was not related to gender, but severe pain may predict increased pain intensity, whilst medical pain may predict increased pain unpleasantness. Contrary to the hypothesis, the pain control group reported higher pain intensity to the female experimenter. **Conclusion:** There were no placebo responses detected in this study. Fear of pain may be a mechanism for placebo analgesia, where high levels of fear might reduce the placebo response. It was not possible to conclude if experimenter gender affects placebo analgesia.

Abstrakt

Formål: Å undersøke om menn viser høyere placebo responser enn kvinner, og om dette kan forklares av kjønnsforskjeller i smertefrykt. Høyere grad av smertefrykt ble foreslått å være høyest blant kvinner, noe som antas å redusere deres placebo respons. Videre ble det undersøkt om kjønnet på eksperimentator kunne påvirke deltagernes smerterapport. **Metode:**96 friske deltagere (51 kvinner) ble rekruttert til en 3 betingelses x 4 intensitets x 3 tester mixed design. Smertefrykt ble innhentet ved bruk av et spørreskjema, inneholdende 3 smertekomponenter (alvorlig grad av smerte, medisinsk smerte og mindre grad av smerte). Smerte ble indusert ved elektriske pulser på deltagernes underarm. Stimuli intensitetene brukt i testene, ble innhentet gjennom en foregående kalibreringsprosedyre. **Resultat:** Menn rapporterte lavere smerteintensitet enn kvinner, i pre- og posttest. Smertefrykt var ikke relatert til kjønn. Smertekontrollgruppen rapporterte høyere intensitet og ubehag til den kvinnelige eksperimentatoren. **Konklusjon:** Ingen placeboresponser ble observert i dette studiet. Smertefrykt kan være en mediator for placebo analgesi, hvor høyere grad av frykt kan redusere placebo responsen. Det var ikke mulig å konkludere om påvirkningen av eksperimentatorkjønn.

Placebo and placebo analgesia

A placebo is an initially ineffective drug or treatment, e.g. a cream or a pill (Lyby, Aslaksen & Flaten, 2010). Placebo administered together with an induced expectation of pain relief has proven to give analgesic effects, an effect termed placebo analgesia (Flaten, Aslaksen, Finset, Simonsen, & Johansen, 2006; Lyby, Aslaksen & Flaten, 2010). Several mechanisms for the pain relieving effect of placebo treatment have been suggested, e.g. endogenous pain regulatory systems and hormonal influence (Atlas & Wager, 2012; Zubieta et al, 2002). The present study examined two of the dominant psychological theories in the psychological mechanisms of placebo analgesia, namely the cognitive theory of expectation and the theory of conditioning.

Expectation and conditioning

Previous studies have documented how expectation and conditioning may trigger a placebo response (Klinger, Soost, Flor, & Worm, 2007; Montgomery & Kirsch, 1996; Price, Milling, Kirsch, Duff, Montgomery, & Nicholls, 1999). Expectancy theory suggests that the placebo effect is achieved through information which initiates positive expectation towards the treatment (Klinger et al., 2007) As an example, Flaten et al. (2006) showed how induced expectation can trigger a placebo response, by presenting different drug information to a group of healthy volunteers. One group was informed that the pill they were given was an effective painkiller, whilst another group was told that the pill did not have a significant pain-relieving effect. The individuals were then administered with a submaximum torniquet test, which induce pain through ischemia. The result indicated that the group who received positive information about the administered pill reported higher pain tolerance. Thus, a placebo response was observed. Interestingly, the effect in this study was shown only amongst male participants. In short, positive information may lead to an expectation of a pain relieving effect, and the expectation itself may form a placebo response (Amanzio &

Benedetti, 1999; Kirsch, 1985, Price & Fields, 1997; Vase, Robinson, Verne & Price, 2003)

The conditioning theory suggests how former experience with pain reduction through a specific treatment might make the treatment a conditioned stimulus (Ader, 1997; Tausk, Ader & Duffy, 2013; Wickramasekera, 1980). When conditioning induces a placebo response the individual associates, for example, a pills taste, color or shape with pain relief. Thus, administering a pill that looks like an active drug may have an effect on pain, even though it is inert (Colloca & Benedetti, 2007). To induce a conditioned placebo response experimentally, the stimulus intensity is typically reduced after administering an inactive treatment. This creates an association between the placebo treatment (conditioned stimulus) and the reduced pain intensity (unconditioned stimulus). Experimentally this can be done through three trials: a pretest, a conditioning test and a posttest. To illustrate, the noxious stimuli in the pretest, as an example electric currents or heat, is set to e.g. 7 on a ten-point scale. Then a placebo treatment is presented, e.g. an initially ineffective cream, with an induced expectation of a pain relieving effect. In the conditioning test the painful stimuli is then reduced to 4. Before starting the posttest, the placebo is administered again and the stimuli is then switched back to 7. If the participant reports lower pain in the posttest in comparison with the pretest, a placebo analgesic response is observed. This is called conditioning, since the reduced pain after the treatment creates an association between the treatment and the reduced pain. Nakamura, Donaldson, Kuhn, Bradshaw, Jacobson and Chapman (2012), amongst others, illustrated this procedure by fitting three electrodes on the participant's index, middle and ring finger on the dominant arm, which was followed by trials of pulsed currents to induce pain. Two fingers received an inert placebo cream. The participants were led to believe that the cream contained different strengths of a painkiller. The third finger was applied with a cream that were said to be a control wetting solution. The placebo was presented between the three blocks of pulses. The pulse intensity for the fingers

that received the placebo was reduced, whilst the third finger received the same intensity as in the baseline block. This process conditioned the subjects to believe that the placebo was an active drug and they reported reduced pain. When the stimuli was increased back to the same intensity as in the baseline block, for all three fingers, the subjects still reported reduced pain. This manifests how conditioning may manipulate the expectancy of pain relief, and thereby reduce pain.

An important aspect of expectancy and conditioning is how both mechanisms work together and simultaneously (Klinger et al., 2007). As an example, Montgomery and Kirsch (1996) showed this by informing one group about the reduction in stimuli intensity, whilst the other group did not receive this information. The stimulus intensity was reduced in the conditioning test, then set back to baseline in the posttest. The uninformed group showed placebo analgesic responses in the posttest, as a result of the conditioning procedure. As expected, the informed group did not report pain reduction in the subsequent posttest, since they had no expectation of pain relief. This suggests how conditioning may increase the placebo response. Likewise, how expectancy mediates conditioning.

To summarize, positive information about an initially inert treatment might induce an expectation of pain relief. Furthermore, combining this expectancy with reduced pain intensity has been shown to create an association between the pain relief and the placebo. This combination may enhance the expectation of pain relief in the posttest, which thereby mediates the placebo effect. The present study aimed to examine how these mechanisms are different in males and females, while controlling for emotional modulation and experimenter gender to see how these factors potentially increase or decrease the placebo analgesic response.

Gender differences in placebo analgesia

Psychosocial pain research documents how psychological variables influence pain

modulation (Greenspan et al., 2007; Huyser & Parker, 1999; Meissner, Bingel, Colloca, Wager, Watson & Flaten, 2011; Melzack & Wall, 2008; Rhudy, Williams, McCabe, Russell and Maynard, 2008). Likewise, how this modulation is different in males and females (Fillingim, 2000; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams & Riley, 2009; Frew & Drummond, 2007; Scott, Stohler, Egnatuk, Wang, Koeppe & Zubieta, 2007). Rhudy et al. (2008) suggest that negative emotions increase pain, and positive emotions decrease pain. Furthermore, it has been shown that positive expectations of treatment effects reduce negative emotions and thereby reduce pain symptoms (Flaten, Aslaksen, Lyby & Bjørkedal, 2011). Furthermore, Aslaksen and Flaten (2008) examined whether negative emotions and associated autonomic activity could affect placebo analgesia. The result indicated that the placebo treatment reduced stress, and that reduced stress was a predictor for the placebo analgesic response. This suggests that reduced negative emotional activation is a mechanism in placebo analgesia. Also, Scott et al. (2007) indicate how positive affect increased after placebo administration. This suggests how induced expectation and conditioning affect emotional processes. Additionally, how these mechanisms are mediators of pain and placebo analgesia.

However, expectancy and treatment may not produce the same emotional effect in females. It has been shown that males respond with great pain reduction, after placebo administration (Aslaksen & Flaten, 2008; Aslaksen, Bystad, Vamheim & Flaten, 2011; Bjørkedal & Flaten, 2011; Flaten et al, 2006; Butcher & Carmody, 2012). Reducing negative emotions like feelings of nervousness and anxiety might modulate pain, but the expectation of pain reduction seems to influence male participants more than female participants. Interestingly, Frot and Bushnell (2004) showed how the level of negative emotions in males correlates with pain report. In females this correlation was not as pronounced, which indicates that males seem to respond better to verbally induced expectation than females, and

thereby show a higher placebo analgesic response. This suggests a more effective regulation of negative affect in males compared to females.

In sum, there seems to be a lot of studies on gender difference in pain (Greenspan et al., 2007; Huyser & Parker, 1999; Fillingim, 2000; Fillingim et al., 2009; Frew & Drummond, 2007; Meissner et al., 2011, Scott et al., 2007), whereas research on fear of pain and how it modulates placebo analgesia seems scarce. Therefore, it is of interest to examine this further in the present study, and it is suggested that gender difference in placebo analgesia may be due to variances in emotional regulation after placebo administration. It is important, and a main goal of the present study to further investigate the mechanisms that cause these differences.

Fear of pain. Fear of pain is a dispositional factor which might counteract the mechanisms that increase pain modulation (George, Dannecker & Robinson, 2006; Lyby, Forsberg, Åsli & Flaten, 2012; McNeil & Rainwater, 1998). Likewise, fear of pain might counteract the placebo effect (Lyby, 2012; George, Dannecker & Robinson, 2006). Individual differences in self-reported fear of pain is often measured by The Fear of Pain Questionnaire III (FPQ) (McNeil & Rainwater, 1998), where higher levels of fear of pain have been shown to result in higher self-reported pain (George, Dannecker & Robinson, 2006). Fear of pain refers to how an individual emotionally reacts to situations were pain might be a factor, e.g. breaking an arm, being in a car accident or receiving an injection. Furthermore, the concept of fear of pain is related to the fear-avoidance model (FAM) where elevated fear of pain is hypothesized to induce avoidance behavior. Fear of pain in interaction with disability and avoidance behavior has been suggested to maintain chronic pain (Lethem, Slade, Troup & Bentley, 1983). Additionally, fear of pain might be related to increased negative emotions, which further reduce the placebo analgesic response. As an example, Lyby, Aslaksen and Flaten (2011) hypothesized that fear of pain was related to increased anticipatory stress,

which in turn reduced placebo analgesic responding. The result indicated that fear of medical pain (e.g. fear of injections) was positively related to stress. This suggests that stress is positively related to fear of pain, and that fear of pain is negatively related to placebo analgesia. They also found that individuals with high scores on the FPQ-questionnaire, showed no placebo analgesic response. In addition, individuals with high levels of fear of pain also had a higher autonomic response, before the administration of the placebo treatment. A placebo response was only found in the individuals who reported low fear of pain on the FPQ. Furthermore, Flaten et al. (2011) hypothesized that negative emotions reduce placebo responses, and that factors like nervousness, anxiety and fear of pain would interfere with analgesia. The result suggests that a reduced placebo analgesic response can be predicted by fear of pain, since the fearful participants also in this study did not respond to the placebo treatment. Aslaksen et al. (2011) suggest that higher placebo response in males is related to the information processing regarding the treatment. The study showed that males responded with higher reduction in anticipatory stress after the administration of the placebo, which further had a significant impact on the analgesic response. Additionally, the result showed that females scored higher than males on fear of pain. Thus, the study conveys that males respond more favorably than females to verbally induced expectations in regards to placebo medications. The study also manifested a lack of placebo effect in the study's pain intensity data. Therefore, it was proposed that only the emotional, and not the sensory-discriminative component of pain experience, was affected by the placebo information in male subjects. Conversely, pain unpleasantness was affected by the placebo administration, and only males showed a placebo response on pain unpleasantness.

To summarize, fear of pain has been shown to increase negative emotions, and thereby reduce the placebo response. It is proposed that the modulations of negative emotions, after induced verbal expectancy and reduced stimuli intensity, affect males. This

modulation is not as pronounced in females. Moreover, females seem to be more prone to fear of pain. Since high levels of fear of pain have been shown to abolish the placebo effect, it is suggested that males show a higher placebo response than females.

How experimenter gender may affect pain reports

Experimenter gender, attractiveness, status and authority, amongst others, have also been suggested to modulate pain reports (Aslaksen, Myrbakk, Høifødt & Flaten, 2007; Fillingim et al., 2009; Kàllai, Barke & Voss, 2004; Levine & De Simone, 1991). Furthermore, Kàllai, Barke and Voss (2004) examined experimenter gender and professional status on pain threshold, pain tolerance and pain intensity in males and females. The study found a main effect for professional status of the experimenter on pain tolerance, where the subjects tolerated longer pain when tested by a faculty member compared to a student. The presence of the professional experimenter was therefore suggested to affect the will to endure pain, but it did not affect the perceptual threshold or intensity of the pain (Kàllai, Barke & Voss, 2004). Additionally, there was a main effect for experimenter gender, where males tolerated pain longer when tested by a female experimenter. The result indicated that also female participants reduced their pain reports, when tested by the opposite sex. This suggests that pain report is modulated by social factors. Males do not want to appear weak, and the gender role requirement of being macho and tough emerge when reporting to an attractive woman (Fillingim, 2000; Kàllai, Bare & Voss, 2004). Additionally, Fillingim (2000) points out how previous literature often refer to a psychosocial mechanism, where feminine gender roles is permitted to display a higher pain responsiveness compared to males whos masculine sex role discourages expression of pain. This is supported by Otto and Dougher (1985), who found that masculinity was correlated to stoic response. This was not evident for the female participants. Traditional gender roles were predicted to emerge in this setting, where females would show higher pain responsiveness when tested by a male experimenter, to induce male

protection. Also, male subjects would want to impress the female experimenter, by appearing tough and macho. Gender roles might influence males to under-report levels of pain, to suppress outward signs of pain in certain circumstances (Frot, Feine & Bushnell, 2004; Kàllai, Barke & Voss, 2004). Levine & De Simone (1991) tried to evoke gender-related motives, by selecting experimenters for their attractiveness. After administering cold pressor pain in front of either a female of male experimenter, it was shown that males report significantly less pain to females than males. As shown in the study of Kàllai, Bark & Voss (2004), females in this study also tended to report higher pain to male experimenter in comparison to female, but the difference was not significant.

Aim

The aim of the present study was to examine whether males show higher placebo responses than women. Furthermore, to investigate if a gender difference in placebo responding is a result of higher fear of pain amongst the female participants, since fear has been shown to counteract pain modulation. Positive information given about the placebo treatment is suggested to reduce the negative emotions in the male participants, and result in a higher analgesic response on pain unpleasantness and pain intensity compared to the female participants. This might give insight in which mechanisms cause gender differences in placebo analgesia. It has also been shown in previous studies that males report lower pain to female experimenters compared to male experimenters (Aslaksen et al., 2011; Flaten et al., 2006; Ka'llai et al., 2004; Levine & De Simone, 1991). To further investigate this notion, the female and male experimenters tested an equal amount of male and female participants.

Method

Subjects

96 healthy volunteers between the ages of 18-40 years (51 females) were recruited via information provided through advertisements, at the campus of the University of Tromsø. All participants were informed that the experiment tested psychological differences in pain sensitivity and pain perception, and they gave a written consent which stated they had no medical history of serious disease or injury. Subjects with a history of somatic or psychiatric disorders, e.g. cardiac conditions, diabetes, depression or anxiety, were excluded. Likewise, pregnancy, use of prescription drugs (with the exception of birth control pills) scarred tissue, eczema or tattoos on the lower arm led to exclusion. Furthermore, all participants were asked to abstain from nicotine and caffeine two hours before, and alcohol 24 hours before, the experiment session started.

All participants received either a gift voucher of 200 Norwegian kroner or a completed mandatory assignment. The experiment was conducted at the Department of Psychology, University of Tromsø, Norway, and was approved by the Regional Committee for Medical Research Ethics North Norway.

Experimenters

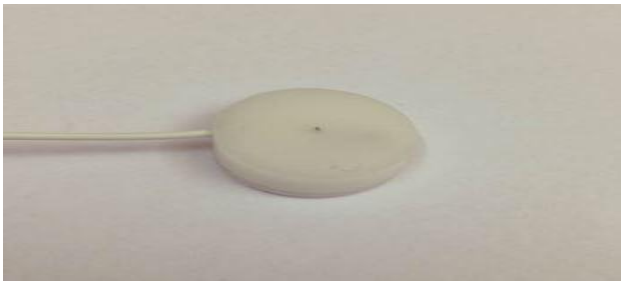
Four experimenters, 1 female and 3 males, conducted the experiment (mean age 30 years). The female experimenter tested 51 participants, 24 males and 27 females. The male experimenters tested 45 participants, 23 males and 22 females.

Pain stimulator

A high voltage stimulator (DS7A, Digitimer Ltd, Hertfordshire, United Kingdom) was used to present IES through an electrode. The electrode had a diameter of 19mm, with a

platina tip of 0,2 mm (picture 1). Stimulation was administered to the lower part of the participants dominant arm. IES from the electrode selectively activates nociceptive Aδ-fibres by concentrating the currents in small sections of the skin (Moureaux, Ianetti & Plaghki, 2002). More precisely, the electrode makes it possible to selectively measure the response from nociceptors, without interference from muscle activation or vibration from using electrodes with a bigger surface. The nociceptors are mainly located in the skins epidermis and respond to noxious stimuli, whilst the non-nociceptive fibers are located in deeper tissue (dermis) (Brodal, 2007).

A study by Mouraux, Ianetti and Plaghki (2010) displayed how IES selectively provide nociceptive input. Their result indicated that when IES are applied at twice the participants perceptual threshold, they elicit behavioral responses which are related exclusively to the activation of epidermal Aδ-fibers selectively. They also showed that when the intensity level was increased beyond this point, the deeper non-nociceptive afferents are activated. This means that the IES loses its selective quality if the intensity is increased to a certain level. The electrode used in the present study is based on the design of Andrè Mouraux, and was made by an engineer at the Faculty of Health Sciences at the University of Tromsø (picture 1). Since the electrode delivers brief electric pulses, it is regarded as safe and the risk of skin damage is small.



Picture 1. The electrode used to induce electric pulses (diameter 19mm, platina tip 0.2 mm)

Placebo medication

The placebo consisted of an E45 cream (Persano Group AS, Norway) packed in a neutral, white tube. The E45 cream is a paraffin- and lanolin based moisturizer. It has initially no known pain relieving effect.

Design

The design was a 3 condition (placebo, pain control, cream control) x 4 intensities (1, 2, 4, 6) x 3 trial (pretest, conditioning, posttest) mixed design. The three conditions were balanced between the participants, so that each condition was represented by an equal amount of males and females. Fear of pain and experimenter gender was also entered in the statistical analyses of the data.

The participants were randomized to one of the three groups. Three pain intensities were used in the pre and posttest. These three intensities equaled 2, 4 and 6 on a visual analogue scale. Between the pre- and post-test a conditioning test was presented. This is where the association between the placebo cream and the reduced pain intensity (1, 2, 4) is created in the placebo group.

Pain measurements

The Fear of Pain Questionaire-III (FPQIII) is a reliable and valid multi-factor self-report instrument consisting of 30 items (McNeil & Rainwater, 1998). These items are further divided into 3 subscales consisting of 10 items, which aim to measure fear of severe pain (e.g. “Breaking your arm”), minor pain (e.g. “Getting a paper-cut in your finger” and medical pain (e.g. “Having a blood sample drawn with a hypodermic needle) (McNeil & Rainwater, 1998). Each item is rated on a five-point Likert scale (1=not at all, 5=extreme). The FPQIII measures the tendency to react with fear and stress in anticipation of and during pain. The

questionnaire was translated into Norwegian by two Ph.D. students at the Department of Psychology, University of Tromsø. In consideration to this study's hypothesis, all subjects with high fear of pain should show reduced placebo analgesic response.

Pain ratings were documented on a psychometric Numerical Rating Scale (NRS). By using the NRS it is possible to record verbal report on pain intensity and pain unpleasantness after presenting the stimuli. The participants were asked to specify the induced pain by ranging it on a scale from 0 to 10, where 0 indicated no perceptual pain, 1 to 3 indicated mild pain, 4 to 6 moderate pain, and finally 7 to 10 for severe pain. A value of 10 on the scale represented worst imaginable pain, the level of pain where the subject could not tolerate a continuation of the pain stimulation. Furthermore, the subjects were informed how pain is a subjective measure and that there is no right or wrong answer. They were told to focus on the stimulation and specify their perception as precise and consistent as possible. Finally, they were asked if they had any questions about how to report the pain they felt.

A visual analogue scale (VAS) was used by the experimenter who administered the electric currents in the initial calibration procedure of the experiment. The VAS was used to document the pain reports from the participants in the foregoing calibration test. The pain ratings documented on the VAS was further used in the following tests. The VAS and calibration procedure is detailed in the following section.

Experimental procedure

The experiment was completed over a total period of 45 days, between 8 a.m. and 7 p.m. The experiment was conducted in a laboratory consisting of a steel cubicle, placed inside a larger room. After signing a written consent, all participants were informed that they might receive a pain-relieving medical treatment depending on which group they were randomly assigned to. If they were randomized to a treatment group, they would either

receive a cream containing a medical drug or an inactive cream with no effect on the pain stimuli. The medical cream was said to be instant-acting and effective on pain signal inhibiting. This corresponds to the information given to the experimenters, whom were told that one effective and one ineffective cream would be used. In reality only one cream was used, a moisturizer with no pain-relieving effect. This was to double blind the experimenters, so that they would not influence the participants response.

The participants were placed in a comfortable chair inside the steel cubicle. Thereafter, a calibration procedure followed to document individual pain thresholds and four pain intensities (1, 2, 4, 6). All mA-values that were equivalent to these intensities, were written on the VAS. The pain threshold was calculated by administering a stimulus intensity of 0.10mA. The intensity was further increased stepwise with 0. 10mA each time, until the participant reported 1 on the pain scale. The mA-values corresponding to the reported 1, was documented on the VAS by the experimenter who controlled the IES. The intensity was then gradually increased until the participant had reported 2, 4 and 6 on the scale. When 6 was reported, the intensity was gradually decreased until the participant reported 1 again. Since participants often reported the same pain intensity for different mA-stimulies in the ascending and descending procedure, an average was calculated. I.e., if a person reported 4 on 0.6mA in the ascending and 4 on 0.5mA in the descending procedure, a stimuli intensity of 0.55mA were given when 4 were presented in the three different tests. The stimulus intensities obtained in the calibration procedure, were further used in the three subsequent tests.

After completing the calibration procedure the participants were given the FPQ-questionnaire. This was followed by three trials of electric stimulation. The participants in the placebo group were administered with the placebo cream before the conditioning test, where the pain intensity of the stimuli was reduced (figure 1). This was done to create an association between the cream treatment and the reduced pain. The pain control group was not given any

cream, but the pain intensity was reduced in the conditioning test just as in the placebo group. This was to control for the pain intensity in the conditioning test, to make sure that it was the intensity decrease and not the placebo cream that caused the pain reduction in the posttest. The cream control group was also administered with a cream, but the stimulus intensity in the conditioning test was not reduced (2, 4 and 6). This was done to control for the cream treatment.

All participants were applied stimuli of varied intensities in all three tests, to avoid a mismatch between expected and experienced pain. When administering the placebo treatment and reducing the stimulus intensity in the conditioning test, the participant will expect pain relief in the posttest. Thus, if the difference in intensity levels between the conditioning test and the posttest is too high, the placebo response might be lost. Stimulus intensities equaling 2, 4 and 6 from the VAS was administered in the pre- and post-test. The placebo group was administered with the intensities 1, 2 and 4 in the conditioning test after the placebo treatment, which was on average lower than in the pretest. This procedure aimed to create an expectation of pain reduction the next time the placebo treatment was administered. In the posttest the pain intensity was gradually increased till the same level as in the pre-test, with an overlap in regards to the intensities in the conditioning test. The cream control group received the same type of cream and information, but the pain intensity was not reduced. The stimulation intensities were set to 2, 4 and 6, as in the pre- and post-test. This was done to control for the cream treatment. If a placebo effect were to be detected in this group, the cream by itself had an effect on pain perception. Every cream application was followed by a ten minute break, which were said to be the amount of time the cream needed to have an effect. The pain control group did not receive any cream treatment, but they still had a 10 min pause between the tests. This was done to ensure that all participants were treated as similar as possible. Furthermore, the pain intensity for the pain control group was reduced to

intensity 1, 2 and 4 in the conditioning test, and then increased to 2, 4 and 6 in the posttest. This was done to control for the pain treatment. Finally, the scores of these three groups were compared. All subjects were asked to report both pain intensity and pain unpleasantness following each stimulus by ranging it on a scale form 0-10.

In short, after calibration and answering the FPQ, all participants were given 54 pain stimulations in the pre- and posttest (Figure 1). In the conditioning test they received 12 pain stimulations (Figure 1). Reported pain intensity and pain unpleasantness were documented on a NRS. The intensity of the stimulations varied after a predefined pattern within the test. 18 stimulations of three different intensities were administered in the pre- and posttest (2, 4 and 6). Four stimulations of three different intensities were administered in the conditioning test, for all three groups (2, 4, 6 or 1, 2, 4). The stimulation intensity pattern is identical for all participants in the pre and posttest. This was done to make it possible to compare the two tests, to investigate eventual placebo responses.

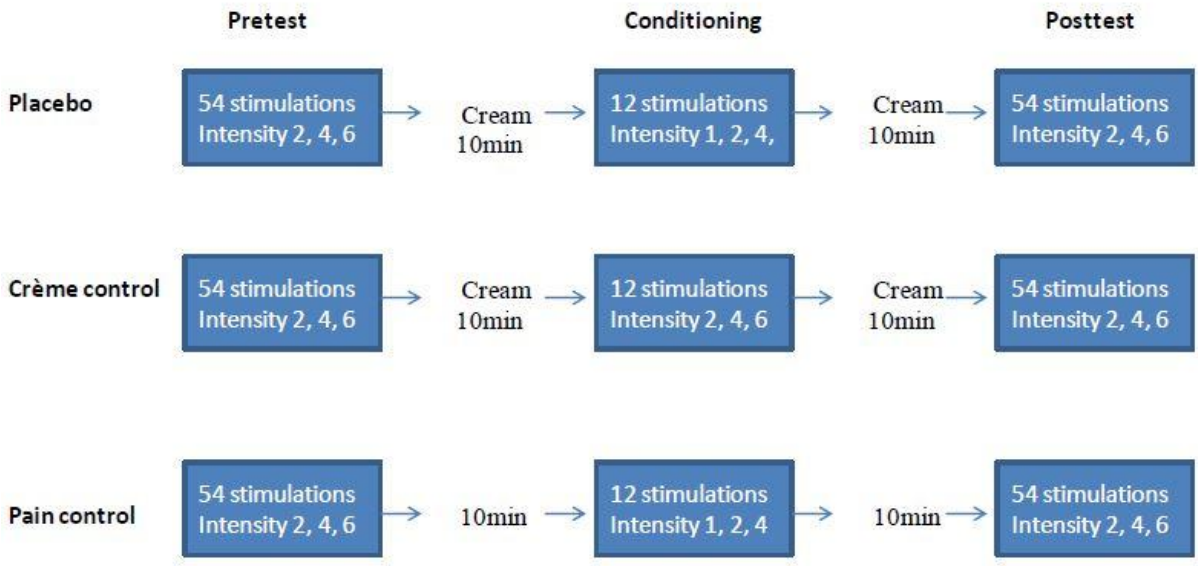


Figure 1. Experimental procedure.

Statistical analysis

Data from the FPQ, experimenter gender and subjective pain reports on the NRS (pain intensity and pain unpleasantness) were entered in a repeated measures analyses of variance (ANOVA) in SPSS 21 (SPSS Inc., Chicago, Illinois). An alpha level of .05 was used for all statistical tests ($p \leq .05$ = significant). Multiple stepwise regression was used to identify whether fear of pain could predict reduced placebo analgesic response. All significant interactions were followed up by post hoc contrast analysis.

Results

Descriptive statistics

The mean and standard deviations for the outcome variables are presented in Table 1. Data in Table 1 shows the change in pain intensity and pain unpleasantness. The change was calculated by subtracting the mean scores of the posttest from the mean scores in the pretest. Thus, a negative value in intensity and unpleasantness indicate a placebo response. These changes are shown for conditions and genders. Furthermore, the mean scores from the three components of the FPQIII are also presented.

Table 1

Mean and standard deviations (SD) for the outcome variables

Variable	Placebo group			Cream control			Pain control		
	Mean	SD	N	Mean	SD	N	Mean	SD	N
Males			15			15			15
Change, pain intensity	-0,3	0,63		-0,13	1,29		0,05	0,75	
Change, pain unpleasantness	-0,56	1,05		0,07	1,61		-0,08	0,59	
Severe pain	25,4	8,82		28,66	8,89		30,4	6,38	
Minor pain	17,13	7,91		17,26	4,97		19,06	5,81	
Medical pain	21,8	6,64		20,46	9,07		23,86	4,53	
Females			17			17			17
Change, pain intensity	-0,47	0,73		-0,53	0,82		-0,52	1,1	
Change, pair unpleasantness	-0,24	0,8		-0,47	0,78		-0,15	1,02	
Severe pain	34,12	6,68		37,17	5,01		37,43	14,76	
Minor pain	19,87	6,11		17,76	4,57		17,5	4,67	
Medical pain	23,62	8,17		23,47	6,08		23,37	9,13	
			32			32			32
Total N									**96**

Pain unpleasantness

There was a main effect of Trial (F (2.168) =55.04. p<.001), with lower pain reports in the conditioning test compared to the pre and posttest. This main effect shows that the participants reported a decrease in pain unpleasantness in the conditioning test (contrast analysis = p<.001), from the conditioning test to the posttest (contrast analysis = p<.001), and a statistical significant difference between the means in the pretest and the posttest (contrast analysis= p=.0.003).

The interaction Trial x Gender reached significance (F (2.168) = 4. 49. P =.01), where males reported higher pain unpleasantness in the pretest in comparison to females, where as there were no significant gender differences in either the conditioning test or the posttest. A contrast analysis showed this difference to be significant (p=.04). Contrary to the hypothesis, the interaction Gender x Group was not significant on pain unpleasantness. However, males tended to report lower intensity compared to females (figure 2), but this difference was not statistically significant. The interaction Trial x Group was significant (F (4. 168) = 2.79, p=.02), with the placebo group reporting significantly lower pain unpleasantness in the conditioning test compared to the control groups. This difference was not sustained in the posttest, where there was no significant difference.

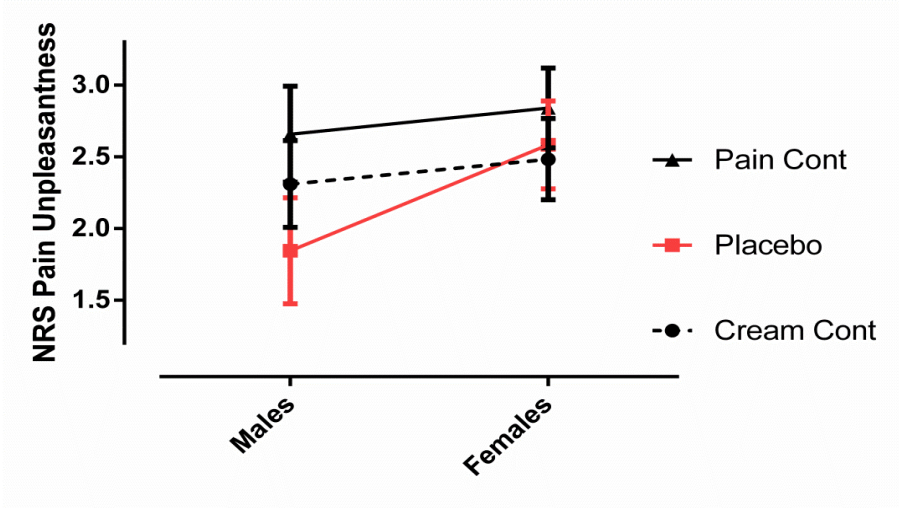


Figure 2: Males reported lower pain unpleasantness in the placebo group. The difference was not statistically significant.

Pain intensity

The main effect of Trial on pain intensity was significant (F (2. 168) =45.93. p < .001). The main effect on gender was significant (F (1, 84) = 5.05. p =.02), where males reported lower pain intensity compared to the female participants in all groups. The interaction Trial x Gender was significant (F (2, 168) =5.90, p =.003), where there was a

gender difference on pain intensity in the pre and the post-test. The contrast analysis showed that males reported lower pain intensity compared to the female participants in the pretest ($p<.001$), and in the posttest ($p =.49$). The interaction Trial x Group was significant ($F(4,168) =3.09$, $p=.01$). The placebo group reported significantly lower pain intensity in the conditioning test compared to the control groups (contrast analysis showed $p =.03$) as shown in figure 3. As the figure indicates, the conditioned placebo response did not persist to the posttest.

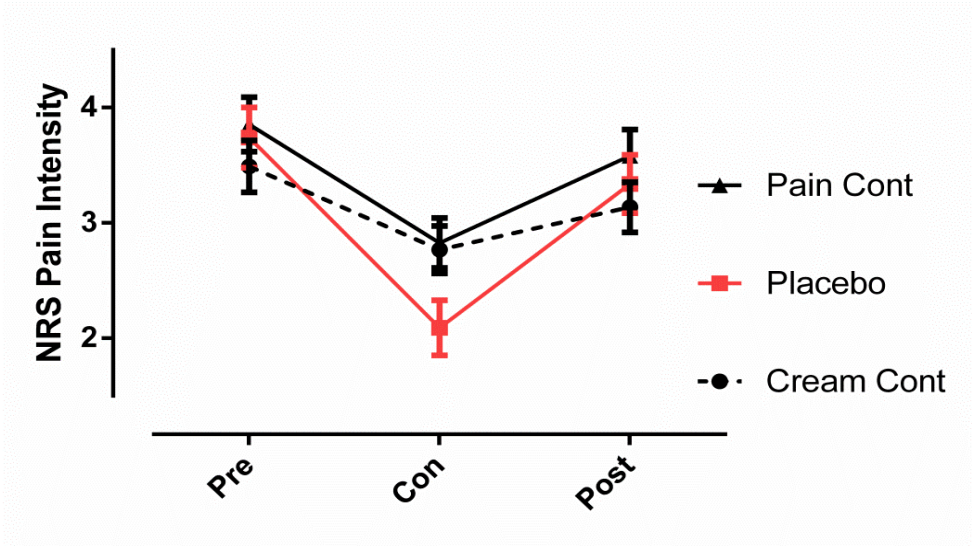


Figure 3. Interaction Trial x Group. Error bars represent standard error of the mean.

The effect of fear of pain on placebo responding

Multiple stepwise regressions were employed, to examine possible predictors of placebo analgesia (table 2). The secondary hypothesis suggested that fear of pain would reduce the placebo response, and the three components of pain from the FPQ were used as predictors on placebo effects on pain unpleasantness and pain intensity. The three components are severe pain, minor pain and medical pain. In addition, groups, participant gender and experimenter gender were included, as predictors for the placebo analgesic response. Severe pain showed to be the only predictor for the placebo effect on pain unpleasantness ($F (1, 90) =5.64$, $p= .20$). 6 participants were excluded from the pain

unpleasantness analysis, due to outlier diagnostics. Observations exceeding two standard deviations from the regression line, was considered outliers and removed. In comparison, medical pain was a predictor for the placebo effect on pain intensity (F (1, 88) =4,90, p=.02). 4 participants were removed from this analysis, as they were considered outliers.

Table 2

Predictors of change in pain unpleasantness and pain intensity from pretest to posttest.

Depedent variable	Predictors	R2	β	*t*	*P*
Pain unpleasantness	Medical pain	.06	-.02	-2,4	.02
Pain intensity	Severe pain	.05	-.01	-2.2	.03

Experimenter gender effect on pain unpleasantness

The interaction Experimenter Gender x Group was significant (F (2. 84) = 5.40. p =.006), with the pain control group reporting higher pain unpleasantness to the female experimenter (contrast analysis = p<.001).

Experimenter gender effect on pain intensity

There was a significant interaction between Experimenter Gender x Group (F (2. 84) = 3.39. p=.03), where the pain control group reported higher pain intensity to the female experimenter compared to the male experimenters.

Discussion and implications

The aim of the present study was to examine whether there is a gender difference in placebo analgesia. It was hypothesized that males show higher placebo analgesic responses than females. Furthermore, that females show higher fear of pain, and that fear of pain is a predictor for reduced placebo analgesic response. Moreover, it was predicted that experimenter gender would affect pain reports.

Gender differences

The result does not support the primary hypothesis of the study, which predicted that males display larger placebo responses than females. There was a tendency of lower pain unpleasantness in males in the placebo group, but this was not statistically significant (Figure 2). This contradicts results from previous studies, which have shown an effect on gender, where males displayed higher placebo analgesic responses compared to females (Aslaksen et al., 2011; Aslaksen & Flaten, 2008; Flaten et al., 2006; Bjørkedal & Flaten, 2011; Butcher & Carmody, 2012). However, the results in the present study will be discussed and compared to previous research as suggestions to what could have been done differently. These suggestions are not put forward as conclusions. Rather implications and ideas for further research.

There was an effect of participant gender on pain intensity in the pre- and posttest, where males reported lower pain intensity compared to females. This was expected, since gender difference in pain has been shown in previous studies (Fillingim, 2000; Fillingim et al., 2009, Flaten et al, 2011; Frew & Drummond, 2007; Frot & Bushnell, 2004; Scott et al., 2007). The result is in line by Aslaksen et al. (2011) who found no placebo effect in their pain intensity data. However, they did find reduced pain unpleasantness in the placebo condition compared to the natural history condition, which was not found in the present study. Since the gender difference in the present study was already evident before treatment, it was probably not a result of the placebo manipulation. It is therefore assumed that the

observed differences in pain intensity report, might indicate that females are more sensitive to painful electrical stimulation compared to males (Fillingim, 2000; Fillingim et al., 2009). This assumption is further supported by studies on gender differences on self-reported electrical pain stimuli perception, which show that pain threshold and tolerance were higher in males than females (al' Absi, France, Harju, France & Wittmers, 2006; Ashina, Bendtsen, Ashina, Magerl & Jensen, 2006; Ayesh, Jensen & Svensson, 2007). Moreover, studies on thermal pain, showed that females discriminated amongst noxious stimuli better than males (Feine, Bushnell, Miron & Duncan, 1991; Fillingim & Maxiner, 1996). The study of Feine et al. (1991) did not directly assess differences in pain reports, but the finding has been suggested to be a result of gender differences in the sensory dimension of pain (Fillingim & Maixner, 1995). Also, Fillingim and Maixner (1996) points out how clinical conditions, e.g. migraine and fibromyalgia, occur more frequently in females.

In comparison, males reported higher pain unpleasantness compared to females in the present study's pretest. This was not found for pain intensity, where males reported lower pain intensity compared to the female participants. This is a contrast to a study on thermal pain, where females reported greater unpleasantness, than the male participants (Wise, Price, Myers, Heft & Robinson, 2002). Moreover, Aslaksen et al. (2011) found that males reported less pain unpleasantness than females. Before the pretest in the present study the participants were instructed how to rate the pain stimuli. They were told to rate pain intensity and pain unpleasantness after the stimuli were presented. To explain the difference between intensity and unpleasantness, a radio analogy was used. The pain intensity was compared to the volume; "How loud is the noise", whilst the pain unpleasantness was compared to which extent you liked what you heard. This suggests a distinction, where the pain intensity is the physical aspect of the pain, and the unpleasantness is the psychological. The result of males reporting higher pain unpleasantness, without the same effect on pain intensity, suggests that

the psychological aspect of pain was affected more than the physiological pain intensity. On the other hand, it may be discussed if the radio analogy was clear enough. Since reports on pain unpleasantness in the present study differ from other studies, it might be that the information provided about how to the rate the stimuli may have been unclear. Since the intensity and unpleasantness data differ for the male participants, which was not expected, the use of IES will be further discussed.

As shown in the pain intensity data of the present study, males might have tolerated the electric pain stimuli better than the female participants. A result of this, was that the experimenters had to increase the stimulus intensity over recommended twice their threshold. Even though all participants who tolerated three times their pain threshold were excluded, we cannot be certain that the non-nociceptive fibers in the dermis were not activated for the remaining participants. Mouraux, Ianetti and Plaghki (2010) indicate that when IES are applied up to twice the participants' perceptual threshold, they elicit behavioral responses which are related exclusively to the activation of epidermal Aδ-fibers selectively. They also showed that when the intensity level was increased beyond this point, the deeper non-nociceptive fibers are activated. If the non-nociceptive fibers were activated, it is assumed that the pain unpleasantness would be higher, than if only the Aδ-fibers were activated. This is because an activation of the non-nociceptive fibres may lead to muscular activation and vibrations, which is assumed to be perceived as more unpleasant than when only the nociceptive Aδ-fibers are activated. Moreover, Mouraux, Ianetti and Plaghki (2010) postulate that IES loses its selective quality if the intensity is increased to a certain level. However, the present study did not measure the activation of Aδ-fibers. It is proposed that without Electroencepholgraphy-observations (EEG) and event-related potentials (ERP) it is difficult to conclude whether or not deeper non-nociceptive fibres were activated. EEG and ERP register electrical activity from cortical areas in the brain. This is done by connecting

electrodes to the participants scalp and observing rhythmical changes in the electrical activity in the cortex. For example, when presenting painful stimuli, e.g. electrical pulses as in the present study, changes in the EEG may be observed. These changes are called event-related potentials. The sensitivity of EEG, refers to the EEG's ability to register pain processing in the brain. The specificity of ERP refers to its ability to separate cortical activity caused by pain as a result of Aδ-fibers from other sensory activity (Granovsky, Granot, Nir & Yarnitsky, 2008). Since the present study did not measure cortical activity, it is not possible to conclude that only the Aδ-fibers were activated.

Finally, the analysis also revealed an effect of the manipulation, displayed by the interaction Trial and Group, where the placebo group reported significantly higher pain reduction than the control groups during conditioning. This was shown in the conditioning trial on both pain intensity and pain unpleasantness. This was expected, since the placebo group received both the cream treatment and reduced pain stimuli. This procedure has been shown to be effective in other studies (Atlas & Wager, 2012; Benedetti & Amanzio, 2013; Stewart-Williams & Podd, 2004; Voudouris, Peck & Coleman, 1990). However, the effect in the present study was not observed in the following posttest. A methodological problem in conditioning-based placebo analgesic research is the mismatch between expected and experienced pain in the conditioning test, compared to the pre- and posttest. When administering the placebo treatment, and reducing the stimulus intensity in the conditioning test, the participant will expect pain relief in the posttest. Thus, if the difference in intensity levels between the conditioning test and the posttest is too high, the placebo response might be lost. The present experiment therefore employed an alternative method to induce and test placebo analgesia. All participants were applied stimuli of varied intensities in all three tests of the experiment, to avoid that a mismatch between expected and experienced pain would reduce the expectations and thereby the placebo analgesic response. This might not have been

effective. On the other hand, the failed continued conditioning might be a result of lowered expectations towards the placebo cream. This assumption is based on previous studies, which indicate how prior positive experience with an analgesic drug enhances the placebo effect (Benedetti, Pollo, Lopiano, Lanotte, Vighetti & Raneiro; 2003; Coloccoa & Benedetti, 2006; Petrovic, Dietrich, Fransson, Andersson, Carlsson & Ingvar, 2005). Previous experience was not taken into account in the present study, which is considered a drawback. For example, if the participants had little experience with pain relieving creams, their expectations towards its effect on pain might have been low. Presenting a pain relieving pill might have triggered an increased placebo response, based on familiarity (e.g. color, taste and shape) and experience. As an example, most people have experience with taking an analgesic pill, for e.g. a headache. If this behavior reduced the headache, the person would probably repeat the behavior next time a headache emerged. As explained earlier, this is termed conditioning. If the participants did not have experience with pain relieving creams, it is assumed that the conditioning in this study would not be as strong in comparison with using a more familiar treatment, e.g. a pill or injection. This is in line with the study of Colloca et al. (2008), who found that an ineffective cream, combined with induced expectation of pain reduction, had no pain relieving effect. Also, a reason for the absent gender difference in the present study, might be due to the ambiguous information given about the cream treatment. However, this was not measured, so a conclusion cannot be drawn. Nevertheless, all participants were told that the cream was either a pain-relieving medical cream or an inactive cream. This information might have failed to trigger a positive expectation of the provided treatment, and thereby not induced a reduction in negative affect towards the pain stimuli. If the participants believed that the cream was non-effective, the gender of the participant might not matter. It has been shown that males are easier affected by positive information towards the treatment compared to females (Flaten et al., 2011, Frot & Bushnell, 2004; Scott et al., 2007).

However, in the present study, the ambiguous information might have failed to trigger such emotional regulation, which in turn might have resulted in equal emotional status amongst the female and male participants. The present study did not take into account if the participants perceived the cream as a real medical cream or not. This is a drawback of the study, since expectancy and conditioning have been shown to work simultaneously on placebo analgesia, where expectancy modulates conditioning (Klinger et al., 2007; Montgomery & Kirsch, 1997). Moreover, the pauses of ten minutes in between each test, might not have been satisfactory. The participants were informed that the cream needed ten minutes to have an effect, and the cream was applied twice for the placebo- and the cream-control group. If the cream were given longer time to have an effect, it might have increased the participants expectations about its effect and possibly abolished their suspicions about the contradicting cream information. By measuring the participants perception of the cream treatment, it might have been possible to separate the response of participants who believed they were applied an active medical drug, compared to the participants who did not believe that the cream was real.

Fear of pain. The secondary hypothesis examined fear of pain as a predictor on placebo responding. Severe pain was shown to predict a reduced placebo effect on pain intensity. Medical pain predicted reduced placebo effect on pain unpleasantness. Contrary to the hypothesis, there were no gender differences in fear of pain on placebo analgesic response. However, it has been suggested that fear of pain might counteract the mechanisms which result in pain modulation (Lyby, 2012). In the study of Lyby, Aslaksen and Flaten (2010), fear of pain was associated with higher levels of stress, before the placebo treatment. It was also shown that the most fearful participants did not respond as well to the placebo treatment, as the non fearful participants. The result showed that fear of severe pain predicted reduced placebo analgesia. Furthermore, that medical pain was a predictor for increased

anticipatory stress, and that this thereby reduced the placebo effect. A drawback of the present study, was that stress was not taken into consideration.

Table 2 displays the predictors of change in pain unpleasantness and pain intensity. The table shows no significant placebo effect. However, the explained variance (R^2) of the FPQ-variables indicate that only six percent of the reduction in pain unpleasantness can be explained by medical pain. Likewise, only five percent of the reduction on pain intensity. This suggests that 94% of the reduction in pain unpleasantness and 95% of the reduction in pain intensity from the pretest to the posttest in the present study remains unexplained. Nevertheless, this is an interesting finding, since it is in line with the study of Lyby, Aslaksen and Flaten (2010). However, since the present study did not measure stress, it is difficult to compare the results to the results of Lyby, Aslaksen and Flaten (2010). It is suggested that more variables should be measured in regards to fear of pain, e.g. stress, valence, arousal and pre existing individual characteristics. For example, Melzack & Wall (2008) suggest how control, meaning of the situation and past experience may affect pain perception. In an experimental setting, the participants may feel a low degree of control, and thereby be more afraid of the pain stimuli compared to if they could control the stimulations themselves. They were not informed when the stimuli would be applied, they just knew that it was coming. This supports the notion of an emotional component of pain modulation. Flaten et al. (2011) describes how valence and arousal is two of the basic dimensions of emotions, and that valence describes if the emotion is good or bad, appetitive or aversive, and different emotions can be classified along this one axis (Flaten et al., 2011). Furthermore, they point out that the continuation of valence and arousal are not independent, since high arousal tends to be associated with very negative or very positive emotions (Flaten et al., 2011). It would have been of interest to measure emotional variables, to see if they potentially affect fear of pain, pain reports and the placebo analgesic response.

Experimenter gender effect

It was predicted that the participants would report lower pain to the female experimenter, in line with previous studies (Aslaksen & Flaten, 2008; Aslaksen et al., 2007; Levine & De Simone, 1991). The pain control group in the present study reported higher pain intensity and pain unpleasantness to the female experimenter. Also, the placebo group showed a tendency of reduced pain unpleasantness, when tested by a male experimenter. The reduced pain unpleasantness in the placebo group was however not statistically significant. Since the findings differ substantially, it is not possible to conclude that experimenter gender alone had an effect. It is suggested that individual differences in the experimenters and the participants should be examined more thoroughly in future research. The present study did not measure individual differences, which complicates the possibility to draw a conclusion on experimenter gender effect. However, it will further be discussed what we could have done differently. Also, what we failed to measure.

Kàllai, Barke & Voss (2004) showed a difference in pain tolerance, when subjects were tested by faculty members compared to students. The study did not find this effect on pain intensity or pain threshold, but they suggest that the difference in reports is a result of the participants feeling safer when a professor handled the pain-inducing situation. The female experimenter in the present study was a fellow student, and therefore might not have been perceived as an authority by the subjects. She might not have been perceived as professional or competent, in comparison to for example a faculty member. Perceived competence and authority has been predicted to modulate pain report, since it underlines the importance of the experiment and gives rise to more effort from the subjects (Kàllai, Barke & Voss, 2004). However, since the present study did not measure how the participants perceived the experimenters, we cannot draw a conclusion based on the authority of the experimenter. Also, Levine and De Simon (1991) showed that males reported lower pain to

attractive female experimenters. If the male participants did not perceive the female experimenter as attractive, they might not have felt the need to maintain an image of being macho, in order to impress the female experimenter. This might have abolished the expected gender difference on the male participants pain reports. Also, the present study did only have one female experimenter, which makes it hard to generalize. The study of Kàllai, Barke and Voss (2004) had four female experimenters. The female experimenters in Levine and De Simone (1999) study were encouraged to dress to accentuate stereotypical gender characteristics, e.g. high heels and skirts. This was not done in the present study. However, since the data in the present study did not establish a gender difference, we cannot conclude that experimenter gender affected the participants pain report.

The missing gender difference might also be a result of emerging equal gender roles, where it is now suggested to be increasingly tolerated for males to express pain compared to the traditional macho male gender role. In this way, both genders would either try to impress the experimenters, or to the contrary none felt the need.

Moreover, since it was the pain control group who reported higher pain, it might be a result of no cream treatment. Since the participants in this group was informed that they would be randomized to either a group who received a medical cream or no cream at all, it might affect their pain reports on both pain intensity and pain unpleasantness. The combination of no authority and no treatment, might have made the participants in the pain control group more negative towards the applied pain stimuli. However, the present study did not measure how the participants perceived the experimenter nor the cream, so we cannot conclude in line with the studies of Levine and De Simone (1991), or Kàllai, Barke and Voss (2004).

Previous studies on emotional factors and placebo analgesia, suggests that males respond more favorably to positive information about the effect of the treatment. A study by

Aslaksen et al. (2007) indicated that this response is not a result of mediation through autonomic parameters, e.g. reduced stress, and thereby concluded that the effect of experimenter gender is probably due to psychosocial factors. A study of Aslaksen & Flaten (2008) predicted that males would display higher placebo analgesia, when tested by a female. Conversely, the result showed that males reported higher pain reduction to the male experimenters. Therefore, it was suggested to focus more on behavior rather than gender of the experimenter. By comparing the present study with previous studies on experimenter gender effects, it is assumed that experimenter gender alone does not affect pain reports. It is suggested that further research should focus on individual differences in participants and experimenters.

Concluding remarks

There were no observed gender differences on placebo analgesic response in the present study. The placebo group did report lower pain in the conditioning test, but this was expected due to reduced stimuli intensity. However, the pain reports amongst males and females differed. Males reported higher pain intensity in the pretest and posttest, but not in the conditioning test. Furthermore, males reported higher pain unpleasantness than females in the pretest, but this difference was not shown for the conditioning or the posttest. Fear of pain was shown to be predictors of higher pain reports, where severe pain was suggested to reduce a placebo effect on pain intensity and medical pain predicted reduced placebo effect on pain unpleasantness. However, since the explained variance only reached 4-5%, more variables should be included when examining fear of pain and placebo analgesic response. Finally, experimenter gender failed to predict gender differences on pain reports. It is not possible to conclude from the results of the present study, since several important factors are missing in the procedure and because the data seem to differ substantially. However, it is suggested that further research on gender differences in placebo analgesia should include measurements of

e.g. EEG, ERP, blood pressure, valence and arousal, individual characteristics of experimenter and participants, and how the participant perceive the placebo treatment.

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