
# Can Drug-Related Information Reverse the Effects of a Local Anesthetic Cream? An Investigation into the Nocebo Hyperalgesic Response

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## Foreword

In this study, we were both engaged as experimenters with the task to recruit participants and conduct the experiment. Based on this we decided to write our main thesis on the subject, and asked the project leader, associate professor Per Matti Aslaksen to be our supervisor. Statistical analyses were executed in collaboration with him. We wish to thank our supervisor sincerely for aiding us in analyzing the statistical data and for his advice and guidance in shaping the thesis. We would also like to thank our co-experimenters Marta Maria Gorecka and Martin Schevik Lindberg for their contribution. Likewise, we would like to thank Andrea Pretscher at the University hospital pharmacy for her contribution in making sure the Emla cream would not inflict harm when heated within the temperatures used in the study. We also would like to thank our participants for volunteering to take part in the experiment. Last, but not least, thanks to Leah Éowyn and Liam for having patience with their parents.

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## Abstract

Objective: Verbal information accompanying administration of a drug has been shown to modulate treatment outcome, in both positive and negative directions. If drug effects alter as a function of verbal suggestions, negative information may potentially abolish or even reverse treatment effects. To test whether nocebo information can reverse the effect of a drug, we investigated how such information modified the effect of a local anesthetic cream (Emla) on heat pain. Based on previous research, we further hypothesized that there would be an increase in negative emotions in the form of elevated levels of sympathetic arousal and stress in the groups receiving nocebo information. Method: Onehundredandfifty healthy volunteers (76 females) participated in a Six-Condition X Six-Trial between-subjects design, whereby heat pain was induced to the right volar forearm. Pain intensity was rated on a 10-mm visual analogue scale (COVAS), and negative emotional activation was assessed by skin conductance level (SCL), subjective stress ratings and systolic blood pressure measurements. Results: Nocebo information about the effect of Emla reversed its analgesic properties into hyperalgesia. The nocebo hyperalgesic response was accompanied by increased SCL and subjective stress, which indicates that the negative information about the effect of the cream led to increased psychological and sympathetic arousal. Conclusions: Negative information produced the opposite response of the intended effect of an anesthetic cream. The notion that mental processes overrode the biological effects of a pharmacologically based analgesic treatment may have important implications for clinical practice.


*Keywords*: *Drug Information, Nocebo hyperalgesia, Expectations, Pain, Sympathetic arousal, Stress, Emla.*

# Can Drug-Related Information Reverse the Effects of a Local Anesthetic Cream? An Investigation into the Nocebo Hyperalgesic Response

Several studies have shown that verbal information given prior to administration of a medical procedure or drug can significantly modulate treatment outcome in both positive and negative directions (Bingel et al., 2011; Flaten, Simonsen & Olsen, 1999). Since a drug`s pharmacodynamic profile is modulated by drug-related information, the possibility exists that negatively charged information may abolish or even reverse the effect of the treatment (Dworkin, Chen, LeResche & Clark, 1983). As pain and emotions are closely interlinked at the neuronal level, information suggesting pain intensification may be accompanied by an expectancy-induced increase in negative emotions such as anxiety and stress (Pollo & Benedetti, 2012; Flaten, Aslaksen, Lyby & Bjørkedal, 2011). The fact that adverse information about the effect of a drug may produce an opposite response of the intended drug effect has important relevance for clinical practice and the conveying of information regarding side effects or treatment-related risks (Colloca & Miller, 2011).

A placebo or nocebo may be defined as an inert compound or procedure that is intended to create a positive or negative expectation, respectively. The placebo response is the positive expectancy or conditioning-induced change in a person's brain-body unit (e.g. symptom amelioration), and the nocebo response is the adverse one (e.g. symptom deterioration) (Colloca & Miller, 2011). When a reduction in pain occurs based on positive information regarding an inactive substance, this is termed placebo analgesia. Conversely, when negative information regarding an inert substance leads to an increase in pain, a nocebo hyperalgesic response has occurred (Flaten et al., 2006; Benedetti, Amanzio, Vighetti & Asteggiano, 2006).

Previous research has suggested that positive emotions reduce pain, whereas negative emotions increase pain. In a study by Rhudy, Williams, McCabe, Russell and Maynard (2007) positive and negative emotional valence was evoked by displaying photos from the Internal Affective Picture System. While the photo slides were presented, painful electric stimulations were delivered to the sural nerve of the ancle. Emotional activation was assessed by means of physiological recordings such as nociceptive flexion reflex magnitude (NFR), skin conductance level (SCL) and

heart rate (HR). In addition, subjective pain ratings were obtained. The NFR, SCL and HR are modulated by emotional processing (Rhudy et al., 2007), and the SCL is a reliable physiological measurement of psychological and autonomic arousal (Armel & Ramachandran, 2003). The results suggested that the induction of positive emotions led to a reduction in both pain reports and physiological measurements, and that negative emotions led to pain increase (Rhudy et al., 2007).

Based on these findings it may be ventured that the placebo analgesic and nocebo hyperalgesic responses are mediated by emotional modulation. As for placebo analgesia, the logic is that the placebo manipulation or treatment reduces negative emotions (or induces positive emotions) which in turn leads to a decrease in pain perception (Aslaksen & Flaten, 2008). However, in order to assess causality between emotions and placebo responses, one must establish whether reduced emotional activation, i.e. in the form of decreased levels of stress is a cause of, or consequence of reduced pain. This can be done by recording emotions in the absence of pain. In a recent study by Aslaksen, Bystad, Vambheim and Flaten (2011) using experimental pain in a placebo procedure, subjective stress levels were obtained in the anticipatory periods when pain stimulation was absent. The results showed that administration of a placebo reduced stress, and that the reduction in stress levels could explain 17 and 26 per cent of placebo analgesia. The findings suggest that reduced stress and hence reduced negative emotional activation may be a mechanism for placebo responses in pain.

A logical extension of this hypothesis is that expectations of impending pain increase negative emotions like nervousness and fear, which in turn increase pain perception. Interestingly, at the molecular level the neurotransmission of the neuropeptide cholecystokinin (CCK) may play a pivotal role in the transformation of anxiety and stress into pain (Benedetti, Lanotte, Lopiano & Colloca, 2007). Experimental work by Rhudy and Meagher (2000) further illustrates the association between negative emotions and pain. In that study, healthy volunteers were assigned to either a fear condition, an anxiety condition or a neutral condition. Before and after the emotional inductions pain thresholds to radiant heat pain were tested. The findings revealed that anxiety led to increased pain reactivity, but that fear led to a decrease in pain reactivity. The results are in agreement with findings from animal studies, whereby anxiety has been shown to enhance pain and fear has been found to inhibit pain (stress-induced analgesia). A confirmation that the different conditions

produced the targeted emotional states was obtained by measuring skin conductance level and heart rate. Findings from this study lend further support to the view that negative emotional states modulate pain reactivity.

In sum, it seems that a reduction in stress and negative emotions reduces pain and could therefore be mechanisms mediating placebo analgesia. It may also be deducted that an increase in negative emotions such as anxiety and stress leads to enhanced pain perception, a possible mechanism behind nocebo hyperalgesia. To our knowledge, no previous studies have directly examined whether negative emotions increase as a result of nocebo-related negative information. This hypothesis was investigated in the present study.

Neurobiological correlates to the emotional modulation of pain are reflected in findings from brain imaging research. Imaging studies of the nocebo response show that nocebo hyperalgesia is accompanied by increased activity in the bilateral dorsal anterior cingulate cortex (dACC), insula, left frontal and parietal operculum, orbitofrontal cortex and hippocampus. Of particular interest is the involvement of the hippocampus, which is associated with anticipatory anxiety (Kong et al, 2008). Additionally, the entorhinal cortex of the left hippocampal formation has shown increased activity when painful stimulations followed the induction of negative emotions (Ploghaus et al., 2001). Overall, the findings are consistent with the hypothesis that the nocebo hyperalgesic response is predominantly produced through the (medial) affective-cognitive pain pathway, projecting through the thalamic nuclei to the ACC, insula and prefrontal cortices. Further support for this notion is that the lateral orbitofrontal cortex and dACC are areas associated with cognitive modulating of the emotional components of pain and the processing of affective aspects of pain (Kong et al., 2008), such as pain unpleasantness. The ACC, prefrontal cortex (PFC) and the insula are also activated during the anticipation of pain (Benedetti et al., 2007).

Several studies have demonstrated that placebo analgesia is mediated by the activation of the opioidergic endogenous pain modulatory system (Pollo & Benedetti, 2012; Benedetti et al., 2007). This top-down regulatory system consists of descending antinoceptive pathways extending from cognitive and affective cortical brain regions to the brain stem and spinal cord dorsal horns. Such findings have been confirmed in many experimental studies, including those employing brain imaging (Meissner et al., 2011). These studies establish that placebo analgesia involves the

activation of cingulo-frontal regions (rostral anterior cingulate cortex (rACC), insula, nucleus accumbens, dorsolateral prefrontal cortex (DLPFC), subcortical structures such as the periaqueductal gray (PAG), hypothalamus and amygdala (Meissner et al., 2011) and the ipsilateral dorsal horn of the spinal cord.

Taken together, imaging and pharmacological studies indicate that placebo analgesia and nocebo hyperalgesia directly affect pain-related cognitive-affective neural activity in approximately the same areas of the brain, with opposite activation (Pollo & Benedetti, 2012). Accordingly, they illustrate that pain and emotions are closely interlinked at the neuronal level.

Apart from emotional modulation mediating the placebo analgesic and nocebo hyperalgesic responses, the most widely employed explanatory theory centers on cognitive top-down mechanisms such as expectations (Pollo & Benedetti, 2012). Other commonly mentioned theories are conditioning and social observation (Meissner et al, 2011).

The open-hidden paradigm is an experimental approach which clearly demonstrates the importance of expectations in shaping the placebo and nocebo responses. In the open condition of a placebo procedure the patient is informed by a clinician that his or her symptoms will improve, inducing expectations of clinical benefit. In a nocebo procedure, the clinician informs the patient that the treatment has been discontinued, inducing expectations of symptom deterioration. A hidden administration in a placebo procedure consists of a continuation of treatment by a computer, whereby the participant is unaware of the fact that the treatment is being carried out. In this manner, no expectations are induced. In a nocebo intervention, a hidden administration means that the treatment has been interrupted without the patient`s knowledge of the discontinuation (Benedetti et al., 2007). The difference between the open and hidden treatment is thought to represent the placebo or nocebo component of the treatment, even though no inert substance has been administered. The reduced effectiveness of hidden treatments illustrates how knowledge about a treatment influence the therapeutic outcome. In a study by Colloca, Lopiano, Lanotte and Benedetti (2004) an open versus hidden nocebo procedure was performed in post-operative pain patients who underwent a treatment with morphine for 48 hours. In the open condition, the patients were informed that morphine infusion had been discontinued, and in the hidden condition, morphine was terminated without informing the patients. The results showed that more patients requested further

painkillers at 10 hours from the morphine interruption in the open group than in the hidden group, indicating that fear and negative expectations of pain relapse increased subjective sensations of pain in the open condition.

Experimental work by Dworkin et al. (1983) further illustrates the power of negative expectations on pain perception. In that study, the effect of 33% nitrous oxide on dental pulp pain was reversed from analgesia to hyperalgesia in healthy participants who expected an increase in pain level. In a more recent study by Bingel et al. (2011) similar findings emerged. Using functional magnetic resonance imaging (fMRI) in a within-subject design on healthy volunteers, they investigated how different expectancies were capable of altering the efficacy of the potent analgesic opioid agonist Remifentanil. The results showed that while expectations induced by positive verbal suggestions doubled the analgesic benefit of Remifentanil, negatively induced expectations abolished Remifentanil analgesia. To further support these findings, fMRI imaging showed that positive expectations were associated with activity in the endogenous pain modulatory system and negative expectations with modulated activity in the hippocampus. According to the authors, the results suggested that an individual's expectations of the effects of a given drug can strongly influence its therapeutic efficacy and that these expectations are paralleled by significant changes in neural activity of core regions of the pain neuromatrix.

A study by Flaten et al. (1999) investigated whether positive and negative information regarding the muscle relaxant carisoprodol was able to induce physiological and psychological responses, and whether the information could modify the drug response. In order to test this either a placebo or carisoprodol was administered to half of the participants in three different groups. Drug administration was accompanied by verbal information stating it was either a muscle relaxant, a stimulant or with no information. When analyzing the results, the authors found that carisoprodol administered along with relaxant and with no information decreased subjective tension. Placebo administration along with information that it was as a stimulant increased tension. However, when carisoprodol was administered together with information suggesting it was a stimulant, subjective tension increased more compared to when the placebo was administered along with the same information. In fact, serum concentrations of carisoprodol increased in a parallel manner with reported tension. The findings indicate that the effects of the relaxing properties of carisoprodol was reversed by information suggesting it was a stimulant.

Overall, these studies show that information accompanying drug administration might induce expectations that are able to override the pharmacological agents of the drug (Dworkin et al., 1983; Bingel et al., 2011).

In the present study, we investigated whether nocebo information could reverse the effect of 3 ml of the topical anesthetic EMLA cream© (AstraZeneca) on experimental heat pain in healthy volunteers. We studied the effects of drug information on EMLA and placebo cream under five different conditions: Nocebo/negative information before application of EMLA (nocebo EMLA condition), positive information before application of EMLA (EMLA standard info condition), positive information before application of an inert cream (placebo condition), nocebo/negative information before application of an inert cream (nocebo condition), and finally reduced information before application of EMLA (EMLA reduced info condition). A no information (natural history) condition was conducted as a control condition. The effects of these conditions were assessed on pain recordings and emotions.

Based on findings from previous research (Dworkin, 1983; Flaten et al., 1999) we expected that nocebo information would override the analgesic effect of Emla, and turn analgesia into hyperalgesia in the nocebo EMLA group.

Furthermore, we hypothesized that there would be an increase in negative emotions after nocebo information, as assessed by self-reports and biological measurements (subjective stress, skin conductance response and blood pressure).

In the EMLA standard info condition and the placebo condition, we expected a significant reduction in pain level and negative emotions.

# METHOD

## Subjects

Onehundredandfifty (N=150) healthy volunteers (76 females) between the ages of 19 and 40 years (Mean = 23,4, SD = 4,1) completed the experiment. Participants were recruited through announcements at campus of the University of Tromsø. Pregnant woman were not allowed to participate in the experiment. Participants who presently suffer from or had experienced any severe disease (including chronic pain), had cutaneous injuries on arms and hands or took prescribed medication (except birth control pills) were also excluded. All volunteers who were allowed to participate received a gift certificate worth 250 Norwegian kroner as compensation. The study was approved by the Regional Committee for Medical Research Ethics North Norway (Project 402/2012).

## Design

A Six-Condition (nocebo EMLA condition, EMLA standard info condition, placebo condition, nocebo condition, EMLA reduced info condition) X Six-Trial (two pretests + four posttests) between-subjects design with repeated measures (ANOVA) was employed. The order of the conditions was balanced across participants, and the participants were randomized to the different conditions according to their participant number (n=25 per condition). All experimenters (2 males, 2 females) were clinical psychology students with experience from experimental laboratory testing. The experiment was executed according to a double-blind procedure in the five conditions where application of a placebo or EMLA was required. Since there was no application of placebo or EMLA cream in the natural history condition, this group was not included in the blinding.

**Pain Stimuli**

Pain was induced by contact-heat stimuli (30 x 30 mm aluminum contact thermode, Pathway System, Medoc, Israel) applied to the right volar forearm. The thermode had a baseline temperature of +32$^{o}$ C when applied to the arm, increasing to +48$^{o}$ C during the pain stimulations. The duration of pain stimuli was 15 seconds. The temperature rise-and-fall rate of the thermode was 10$^{o}$C/s.

**Physiological Recordings**

The electrodes for the SCL were attached to the medial phalanges of the first and second finger of the left hand. SCL were recorded using two EL258 electrodes (Biopac Systems, Inc., USA). GEL101 (Biopac Systems, Inc.) electrode gel was used. The signal was recorded at 15 Hz with the Biopac Acqknowledge software (Biopac Systems Inc., USA) and analysed off-line with the Biopac Acqknowledge 3.1 software. The SCL data was visually inspected offline to exclude artefacts. Blood pressure was measured by a standard electronic blood pressure device (MicroLife, Switzerland).

**Placebo cream and EMLA**

EMLA cream is the most widely used topical anesthetic, and is a 5% eutectic mixture of 25 mg/ml lidocaine and 25 mg/ml prilocaine in an oil-water emulsion cream. The application period of EMLA varies depending on the location of treatment, but multiple studies have shown that EMLA can produce dermal anesthesia 10-15 minutes after application, with a peak analgesic effect after a minimum of 60 minutes (Friedman, Mafong, Friedman & Geronemus, 2001).

The University hospital pharmacy at the University Hospital of Northern Norway produced tubes of EMLA© cream (AstraZeneca) and placebo cream (E45 Cream; Crookes HealthCare, UK). The tubes were numbered according to a list of codes. The code list was created by the University hospital pharmacy, and was kept

by the supervisor of the study that did not participate directly in the experimental work. We chose the E45 placebo cream based on its similarity with EMLA both in color and consistency. In order to be certain that heating of the creams would be harmless, the pharmaceutical properties of EMLA and the E45 cream were assessed by a pharmacist at the University hospital pharmacy. The pharmacist concluded that a heating within the limits of the temperatures used in the present study would not inflict any kind of harm.

**Pain and Stress Measurements**

During each pain stimulus the participants reported pain intensity on a Visual Analogue Scale (0-10 (VAS) where 0 represented "no pain" and 10 represented "most intense pain imaginable". The VAS was connected to the pathway system (COVAS, Medoc, Israel) and therefore reported pain intensity was electronically recorded after each pain stimulus. Subjective stress was measured by two adjective pairs from the Short Adjective Check List (SACL) (Mackay, Cox, Burrows & Lazzarini, 1978) in Norwegian translation (Appendix A). The adjective pairs were tensed-relaxed and nervous-calm. The SACL items were chosen for their high factor loadings on stress factors similar to previous studies (Aslaksen & Flaten, 2008; Lyby, Aslaksen & Flaten, 2010).

**Procedure**

The order of conditions was randomized across participants. The experiment took place inside a steel cubicle (2.8 x 2.8 m) where the thermode, electrodes and blood pressure apparatus were positioned. The steel cubicle was placed inside a larger room containing the apparatus for control of experimental events and response recordings. The cubicle was shielded for sound and electricity, holding a constant temperature of 20$^{o}$ C. All instructions were given verbally to the participants.

Upon arrival at the laboratory the participants signed the informed consent form (Appendix B). They then filled in personal information and the Norwegian translations of the Fear of Pain Questionnaire (FPQ-III) (McNeil & Rainwater, 1998)

(Appendix C) and the Positive and Negative Affect Scale (PANAS) (Watson, Clark, Tellegen, 1988) (Appendix D). The FPQ-III and the PANAS were recorded for use in another study, and the data from these questionnaires are therefore not included in the analysis in the present study. After completing the pen-and-paper measurements, the experimenters delivered the necessary information about the experimental procedure. They were then seated in a comfortable chair inside the cubicle. Subsequently blood pressure and subjective stress were measured and skin conductance electrodes attached to the medial phalanges of the first and second finger of the left hand. Thereafter, the experimenters instructed the participants in how to use the COVAS and attached the thermode to the volar right forearm, at dermatome corresponding to C8. The participants were then informed that the experiment would commence shortly.

Next, the experimenter stepped out of the steel cubicle and into the lager area of the laboratory and started the first two pain stimulations by activating the Pathway system (pretests). The time interval between pain stimulations was 60 seconds. Just before onset of the Pathway, skin conductance recordings were initiated. After the pretests, the experimenter delivered information regarding the cream, followed by application of the cream to a 5×5 cm location to the right volar forearm. Both the cream and information were selected according to instructions. The instructions were either: “The cream that will be applied to your arm reduces pain. The substance in the cream is used as a local anesthetic in many pain-reducing remedies, and is effective against heat pain” (the EMLA standard info condition and placebo condition) or “The cream that will be applied to your arm increases the effect of the heat pain and you will feel more pain. The substance in this cream is used in many medical remedies. Even though the pain feels more intense, the cream will not inflict any burn wounds” (the nocebo EMLA condition and nocebo condition) or “You will now receive a treatment with a medical cream. Because of the fact that we are interested in the pharmacological effect of this cream, we cannot provide information about which kind of medical properties it contains” (the EMLA reduced info condition). In the natural history condition no cream was applied and no information given.

Next, subjective stress and blood pressure were measured. Following a 16 minutes application period the thermode was again attached to the forearm and the experimenter initiated the last four pain stimulations via the Pathway (posttests).

After the posttests, the final subjective stress and blood pressure measurements were obtained. The experimental procedure had a total duration of approximately one hour. See Figure 1 for an overview of the procedure.

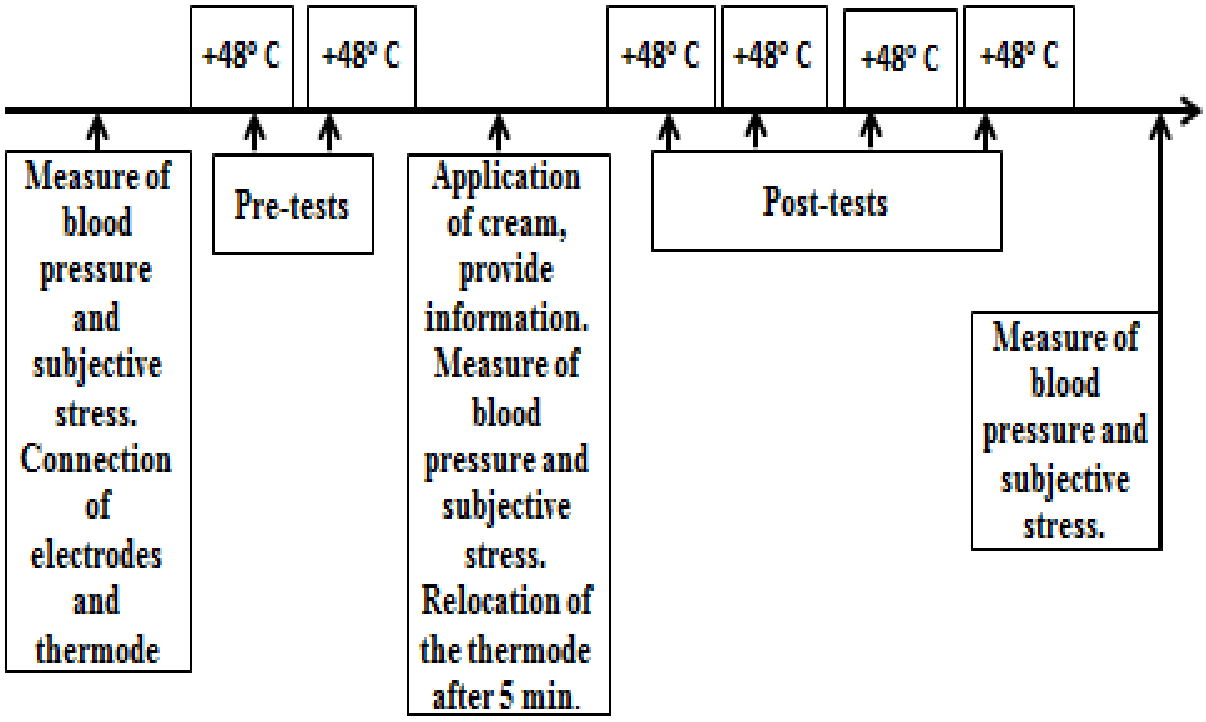


*Figure 1*. Overview of the procedure.

**Statistical Analysis**

The statistical procedures were performed in SPSS 19.0 (SPSS, Chicago, IL, USA). Group differences and interactions were analyzed by general linear models (GLM), repeated measures ANOVA. In cases where Mauchly`s test indicated that the assumption of sphericity was violated, degrees of freedom were corrected using Greenhouse-Geisser corrections. Treatment effects for dependent variables were determined by subtracting the posttest score from the pretest score, and were analyzed by univariate GLMs. A significance level of .05 was employed. Significant

interactions in the GLM were contrasted by Fisher LSD post-hoc tests.

## Results

### Descriptive statistics

Descriptive statistics are presented in Table 1. None of the participants terminated any of the pain stimulations or the experiment as a whole.

Table 1

*Means and Standard Error of the Mean for Response Variables in the Study*

| Measure | EMLA standard info condition | | Nocebo EMLA condition | | Placebo condition | | Nocebo condition | | Natural history condition | | EMLA reduced info condition | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| Pain intensity | 38.11 | 3.19 | 53.86 | 5.12 | 50.32 | 4.39 | 46.57 | 3.35 | 46.80 | 5.03 | 41.38 | 3.74 |
| Subjective stress | 2.24 | 0.25 | 2.85 | 0.30 | 2.36 | 0.31 | 2.70 | 0.36 | 2.58 | 0.35 | 1.71 | 0.20 |
| Blood pressure | 124.62 | 2.30 | 126.83 | 3.03 | 125.41 | 2.30 | 132.49 | 42.73 | 128.73 | 2.36 | 124.39 | 1.69 |
| Skin condutance | 29.34 | 1.34 | 31.46 | 2.23 | 26.54 | 2.33 | 32.88 | 1.69 | 27.05 | 1.82 | 26.11 | 0.87 |

### Pain intensity

There was a significant main effect of trial on pain intensity, as pain changed from the first pre-test to the last post-test ($F(3.41, 469.83) = 5.10$, $p < .001$, $\eta^2 = .036$). The interaction trial by group was significant ($F(17.02, 469.83) = 8.89$, $p < .001$, $\eta^2 = .24$). Post hoc analyses using Fisher LSD revealed significantly lower pain

intensity in the EMLA condition compared the placebo condition ($p$ = .025) , and a significantly higher pain intensity for the nocebo EMLA condition compared to the EMLA reduced info condition ($p$ = .022) and the EMLA standard info condition ($p$ = .004). There was a significant main effect of Gender ($F(1, 138) = 33.82$, $p < .001$, $\eta^2$ = .20), with an average of higher pain intensity for females compared to males, independent of conditions. Additionally, there was a significant main effect of group on VAS change scores ($F(5, 144) = 11.38$, $p < .001$, $\eta 2 = .28$) (Figure 2). No other main effects or interactions were significant in the pain intensity data.

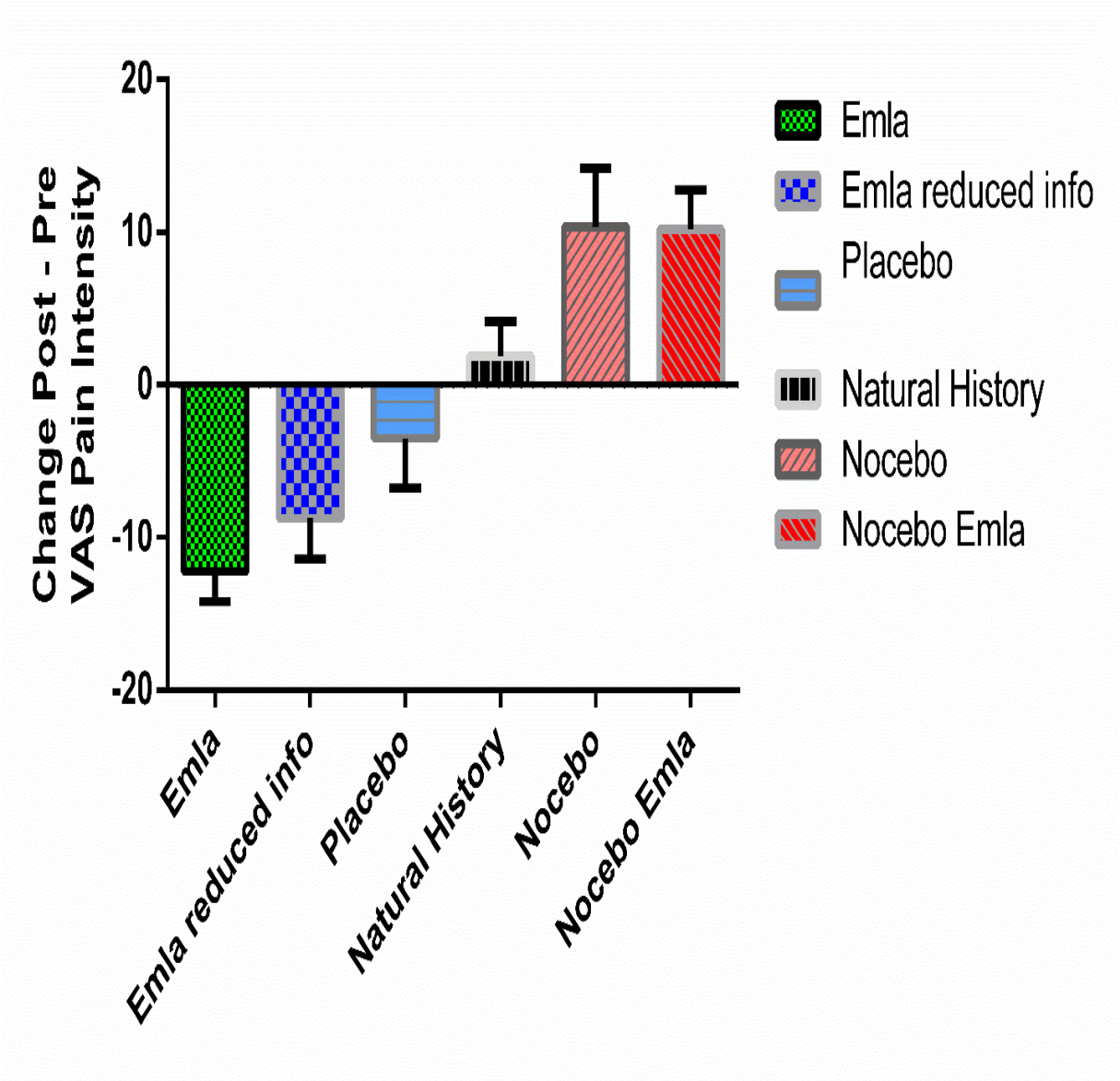


*Figure 2*. Pain intensity: Pain intensity was reported on a 10-mm VAS (COVAS). The figure shows treatment effect in each group (posttest - pretests). VAS pain

intensity values below zero indicates pain decrease, whereas VAS pain intensity values above zero shows pain increase. Standard errors are represented in the figure by the error bars attached to each column.

**Subjective stress**

There was a significant main effect of trial on stress ($F(1.81, 224.20) = 61.06$, $p < .001$, $\eta^2 = .33$) as stress changed from the first pretest to the last posttest. Post hoc analyses using Fisher LSD showed significantly higher levels of subjective stress in the nocebo EMLA condition compared to the EMLA reduced info condition ($p = .006$) and significantly higher levels of subjective stress in the nocebo condition compared to the EMLA reduced info condition ($p = .014$). There was a significant main effect of Gender ($F(1, 124) = 6.17$, $p = .014$, $\eta^2 = .047$), with an average of higher levels of subjective stress for females compared to males, independent of conditions. There was no significant main effect of group on stress change scores ($F(5, 138) = .78$, $p = .57$, $\eta2 = .08$) (Figure 3), as stress decreased in all groups independent of treatment. No other main effects or interactions were significant in the subjective stress data.

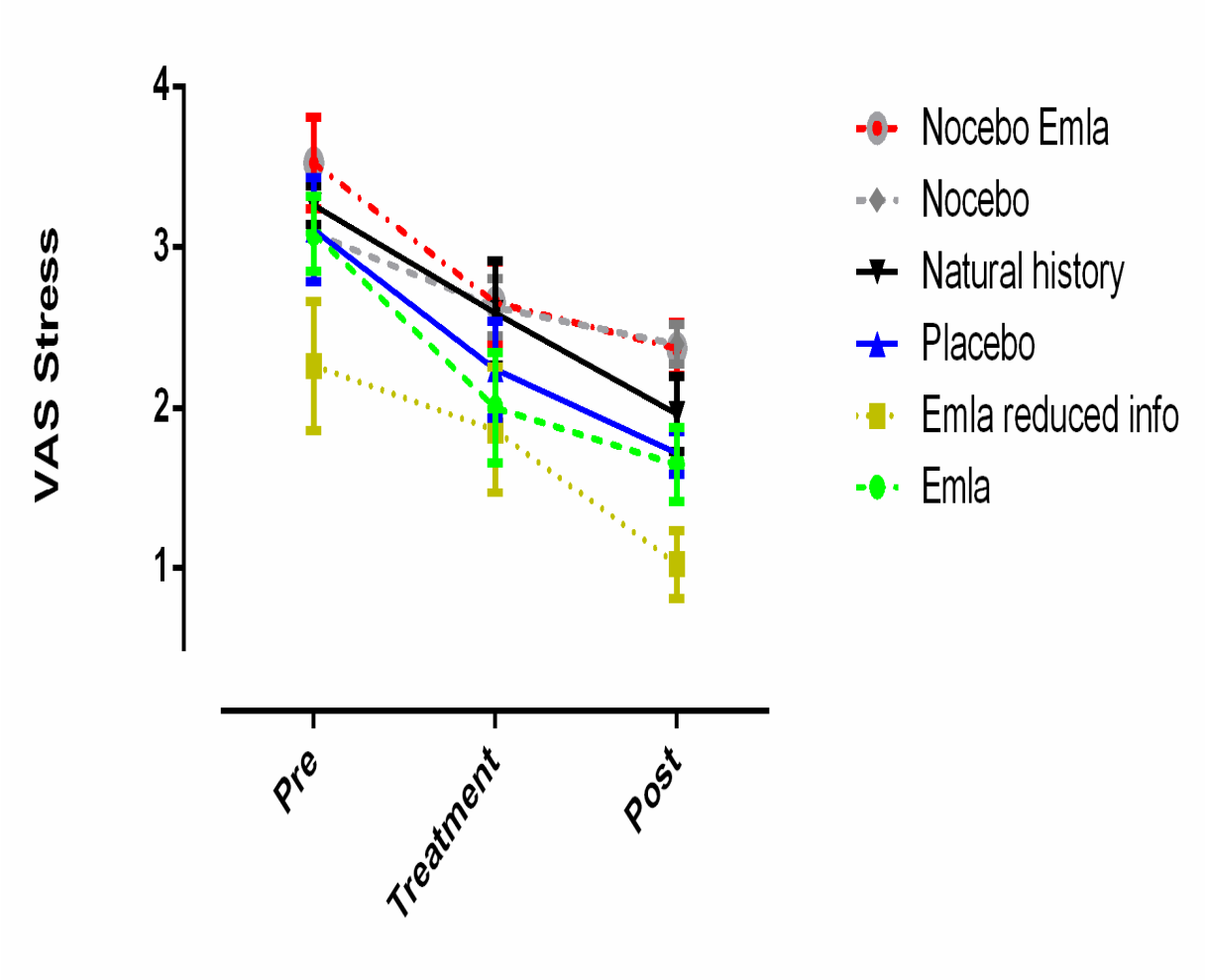


*Figure 3*. Subjective stress: The figure shows the effect of treatment in each group (posttests – pretests). Standard errors are represented in the figure by the error bars attached to each column.

**Systolic blood pressure**

There was a significant main effect of trial on systolic blood pressure ($F(1.79, 216.04) = 15.44$, $p < .001$, $\eta^2 = .11$) as blood pressure changed from the first pre-test to the last post-test. The interaction systolic blood pressure and group was significant ($F(8.93, 216.04) = 2.30$, $p = .022$, $\eta^2 = .084$). Post hoc analyses using Fisher LSD showed significantly higher systolic blood pressure in the nocebo condition compared to the EMLA reduced info condition ($p = .005$), the EMLA standard info condition ($p = .008$) and the placebo condition ($p = .016$). Additionally, there was a significant main effect of Gender ($F(1, 121) = 37.37$, $p < .001$, $\eta^2 = .24$), with an average of higher systolic blood pressure for males compared to females,

independent of conditions. There was also a significant main effect of group on systolic blood pressure change scores ($F(5, 138) = 2.78$, $p < .05$, $\eta^2 = .09$) (Figure 4). No other main effects or interactions were significant in the systolic blood pressure data.

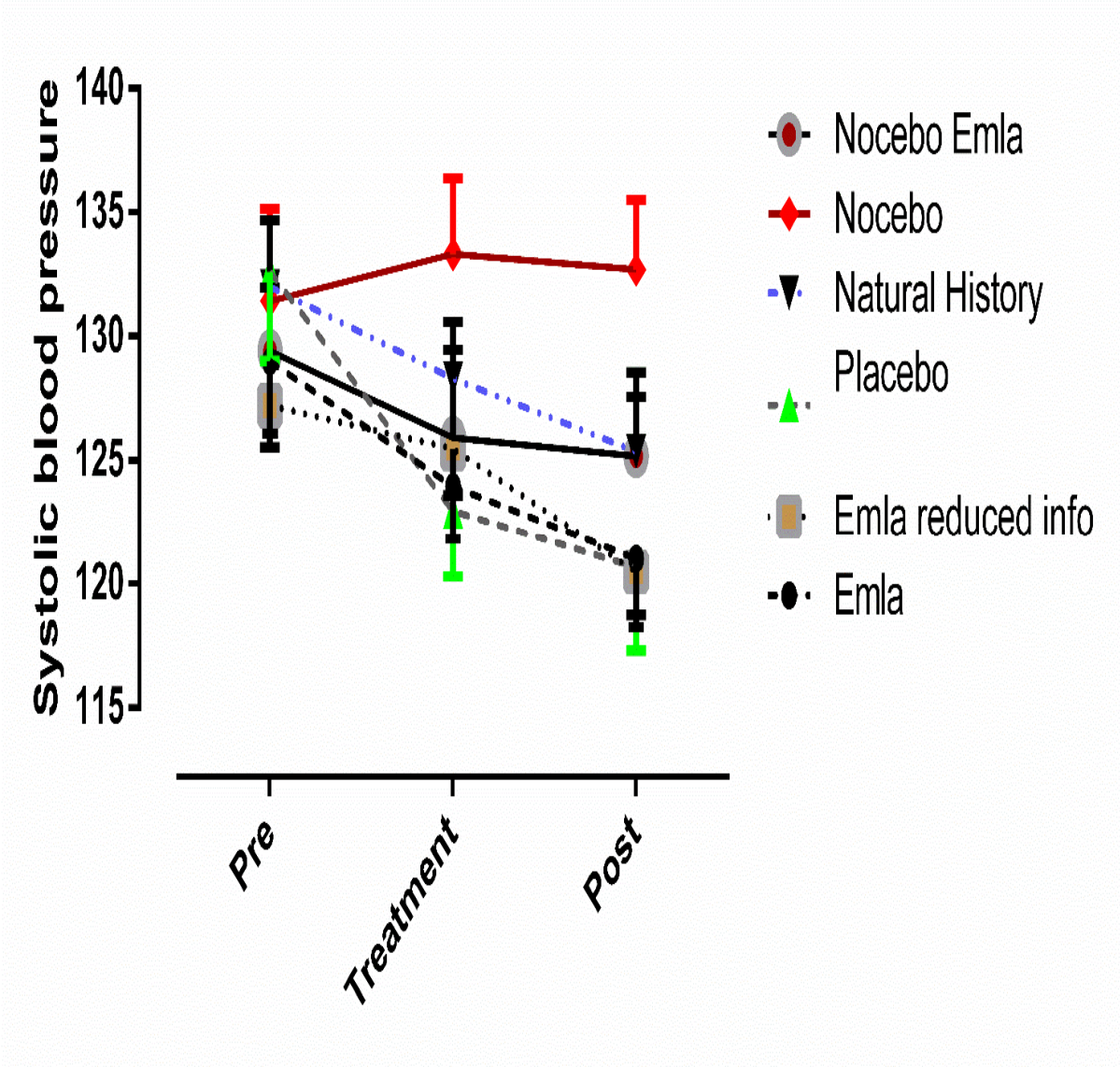


*Figure 4*. Systolic blood pressure: The figure shows the effect of treatment in each group (posttests – pretests). Standard errors are represented in the figure by the error bars attached to each column.

**Skin Conductance Level (SCL)**

There were no significant effects in the repeated measures data on Skin conductance levels during pain (all F's < 2,4), however, there was a significant main effect of group on SCL change scores ($F(5, 134) = 21.87$, $p < .001$, $\eta^2 = .45$) (Figure 5). Post hoc analyses using Fisher LSD revealed significantly higher SCL in the nocebo EMLA condition compared to the EMLA standard info condition ($p < .001$), the placebo condition ($p < .001$), the natural history condition ($p < .001$) and the EMLA reduced info condition ($p < .001$), and significantly higher SCL in the nocebo condition compared to the EMLA standard info condition ($p < .001$), the placebo condition ($p < .001$), natural history condition ($p < .001$) and EMLA reduced info condition ($p < .001$). There was significantly lower SCL in the EMLA standard info condition compared to the natural history condition ($p = .026$) and the EMLA reduced info condition ($p < .001$) and lower SCL in the placebo condition compared to the EMLA reduced info condition ($p = .028$).

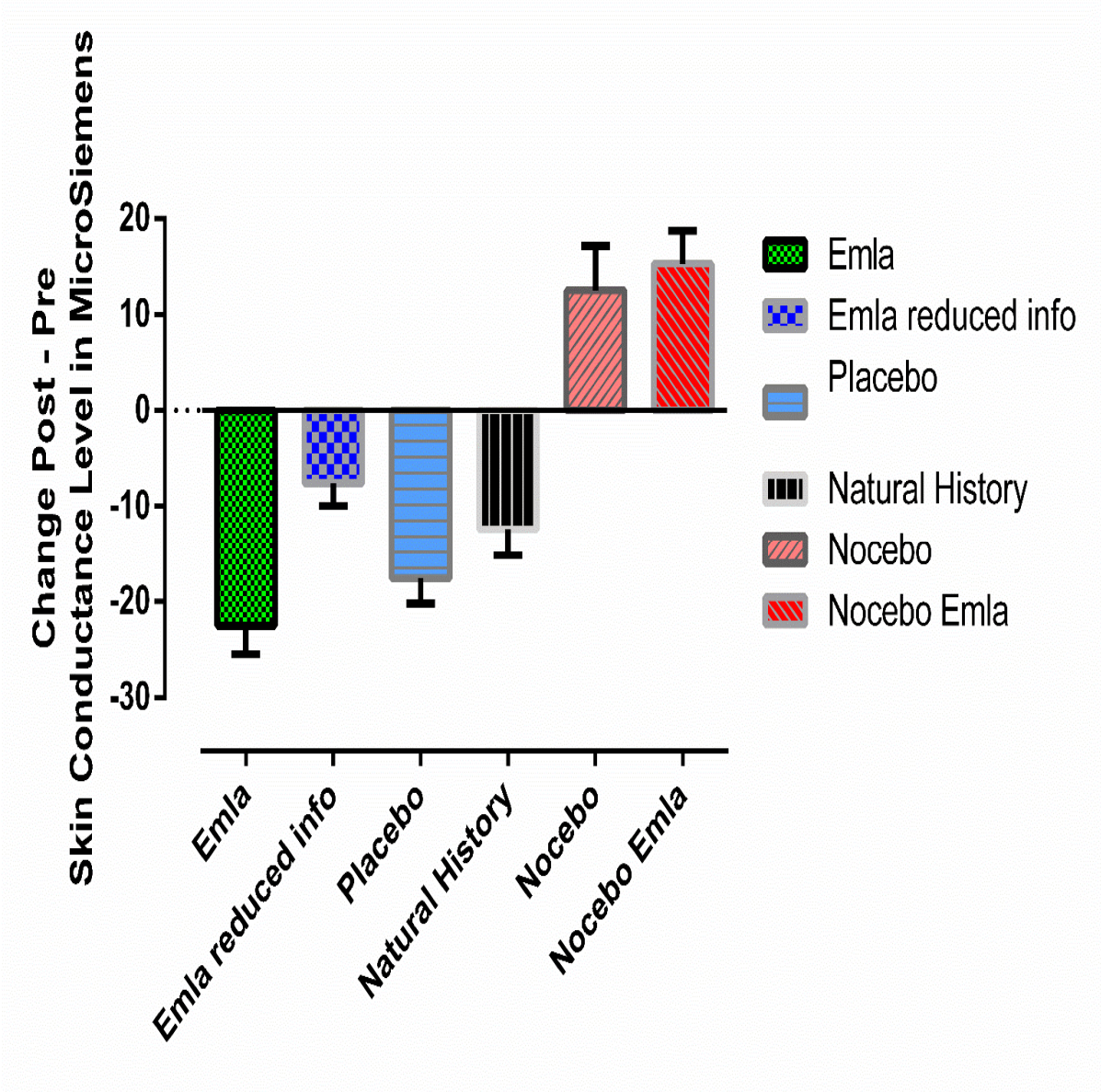


*Figure 5*. Skin conductance level. The figure displays treatment effect in each group (posttest - pretests). Values below zero indicate a decrease in skin conductance levels, while values above zero show an increase in skin conductance levels. Standard errors are represented in the figure by the error bars attached to each column.

## DISCUSSION

The present study examined whether nocebo information could reverse the effect of 3 ml of the topical anesthetic Emla cream on experimental heat pain in healthy volunteers. We found that pain intensity reports in the nocebo EMLA condition were significantly higher compared to the EMLA reduced info condition and the EMLA standard info condition. The finding suggests that nocebo information about the effect of Emla reversed its analgesic properties into hyperalgesia. Hence, these data indicate that mental processes overrode the biological effect of a pharmacologically based treatment.

We further expected a decrease in levels of pain and negative emotions in the EMLA standard info condition and the placebo condition. We found significantly lower pain intensity reports in the EMLA standard info condition compared to the placebo condition. We also found a significant reduction in SCL in the EMLA standard info condition compared to the natural history condition and the EMLA reduced info condition. These results suggest that Emla had an analgesic effect, accompanied by a reduction in sympathetic arousal.

Finally, we hypothesized that there would be an increase in negative emotions after nocebo information, as assessed by self-reports and biological measurements. We found significantly higher levels of subjective stress and increased SCL in the groups receiving nocebo information, and increased systolic blood pressure in the nocebo condition compared to the EMLA reduced info condition, the EMLA standard info condition and the placebo condition. Increased SCL, systolic blood pressure and levels of subjective stress in the groups receiving nocebo information indicate increased psychological and sympathetic arousal, possibly due to the adverse information about the effect of Emla. Thus, nocebo information may have led to an expectancy-induced increase in negative emotions. The results also show that the hyperalgesic response exhibited in the nocebo EMLA condition was accompanied by increased SCL and subjective stress.

The findings from the present study are consistent with previous research on the nocebo response, which suggests that the information given to patients may influence the therapeutic outcome negatively. For instance, Varelmann, Pancaro, Capiello and Camann (2011) tested whether the use of gentler words prior to administration of a local anesthetic affected pain reports and patient comfort in

women at term gestation requesting neuraxial analgesia. The women were randomized to either a placebo or a nocebo condition, whereby positive or negative information accompanied the local anesthetic skin injections, respectively. Following the injections, pain was assessed using a visual analogue scale. The results showed that whereas the use of gentler, more encouraging words led to a reduction in subjective pain reports, the use of harsher, nocebo-related words induced hyperalgesia.

Although clinically relevant pain such as injecting neuraxial analgesia is different from the experimental heat pain induced in the present study, our results extend the research by Varelmann et al. (2011) by showing that negative information was able to produce opposite responses of the intended effect of an analgesic treatment by turning analgesia into hyperalgesia. Accordingly, results from the present study are comparable with findings from experimental work by Dworkin et al. (1983) and Flaten et al. (1999), which demonstrate how mental processes can modify drug effect paradoxically. Moreover, our results resemble those obtained in a nocebo procedure by Colloca, Sigaudo and Benedetti (2008). In their study, verbal information of pain increase was provided to healthy volunteers before the administration of either tactile or low-intensity painful electrical stimulations. Pain intensity was reported on a Numerical Rating Scale ranging from 0 to 10, where 0 represented no pain and 10 represented maximum imaginable pain. The results showed that the negative information was capable of turning tactile stimuli into pain and low-intensity painful stimulations into high-intensity pain. In a double-blind experiment by Luparello, Leist, Lourie and Sweet (1970) related findings emerged. Here, asthmatic patients were randomized to four conditions. In two groups, the participants were told that they received a bronchoconstrictor, when in reality they were administered a bronchodilator. Conversely, the other two groups were informed that they received a bronchodilator, but were provided with a bronchoconstrictor. The results showed that expectations induced by misinforming the participants about the medication reduced its biological effectiveness by 43% (bronchoconstrictor) and 49% (bronchodilator).

Overall, it seems that in Dworkin et al. (1983) a reversal of the biological action of 33% of nitrous oxide was induced by negative information about drug effect, and in Flaten et al. (1999) the pharmacological agents of the muscle relaxant carisoprodol were overridden by contradicting information. Likewise, Luparello et

al. (1970) demonstrated how the biological properties of asthma medication were reversed by almost 50% after misinforming about its effect. Similarly, the effect of the opioid agonist Remifentanil was abolished by nocebo-related information (Bingel et al., 2011). In the present study, however, negative drug information regarding the effect of a local anesthetic cream reversed its analgesic agents into a nocebo hyperalgesic response. The fact that nocebo information produced antagonistic responses of the intended effects of a medical cream, has, to the best of our knowledge, not been previously demonstrated.

The finding that negative information reversed the analgesic effects of Emla into hyperalgesia could have implications for clinical practice, where similar nocebo effects may occur after disclosure of drug related side effects. Some experiments have been explicitly designed to investigate the relation between informing patients about side effects, and the occurrence of such effects. In a study by Mondaini et al. (2007) patients with benign prostatic hyperplasia (BPH) were randomized to two different conditions; in one condition participants received information about possible sexually related side effects of 5 mg of Finasteride, an anti-BPH medication, and in the other condition no such information was disclosed. All patients were sexually active. Results showed that the group who was informed about sexually related dysfunctions reported a significantly higher number of side effects compared to the group with no information at a 6 to 12 months follow-up. In a study by Lang et al. (2005), warning patients about possible side effects or undesirable treatment outcomes led to significantly higher levels of reported pain and anxiety.

A similar question is how the results can be translated to clinical pain states. In the present study, nocebo-related information induced negative treatment expectancies within a matter of minutes. This is a short time-frame compared to the sometimes year-long experience of failure of analgesic treatments experienced by for instance chronic pain patients, whereby such adverse encounters may result in more robust negative expectations regarding future treatment outcomes. As such, our experimental data probably underestimate rather than overestimate similar effects in clinical practice. In addition, it is reasonable to assume that the experimental heat pain induced in our conditions is less susceptible to modulation by psychological factors than clinically relevant pain in which emotional and cognitive influences may be greater and the psychosocial context more complex (Bingel et al., 2011).

In the present study, we further found that nocebo-related information about the effects of Emla led to an increase in negative emotions. Similar results were obtained in experimental work by Johansen, Brox and Flaten (2003), which tested whether placebo and nocebo responses were mediated through a modulation of stress. In that study, participants were randomized to a placebo condition, nocebo condition or a natural history condition. In the placebo and nocebo conditions, the subjects were injected with a saline solution, and in the natural history condition, no injections were administered. When pain intensity reports reached "7" on a 10-point scale, information was delivered stating that the injection consisted of either a pain increasing (nocebo) or a pain reducing (placebo) substance. Subsequently, pain ratings and serum concentrations of cortisol and beta-endorphin were obtained. The results showed that cortisol secretions increased most in the nocebo condition, indicating elevated stress responses. However, pain levels were already at seven when the stress-inducing information was given, and an additional increase in pain could not be observed. This indicates that stress levels may have been increased prior to the provision of the negative information. As such, one can only speculate an assumption of a causal relation between nocebo information and negative emotions in the study.

In a different experiment by Schweiger and Parducci (1981) nocebo information that a (nonexistent) electrical current was being passed through the heads of healthy participants led to an increase in subjective pain reports. According to the authors, verbally induced psychological stress played a key role in mediating pain perception. In this particular study, on the other hand, the notion that the nocebo-related information generated corresponding stress responses was based on subjective ratings of anxiety, in the absent of actually recording biological stress i.e. in the form of increased autonomic arousal or elevated blood pressure levels.

Moreover, the literature indicating a causal association between nocebo information and negative emotional activation seems sparse. Thus, to our knowledge, it appears that the present study`s finding that nocebo-related information induced negative emotions as assessed by elevated levels of skin conductance responses, subjective stress and blood pressure has not been demonstrated in previous studies.

Results from the present study additionally showed that the hyperalgesic response exhibited in the nocebo EMLA condition was accompanied by increased SCL and subjective stress. Based on these findings it may be hypothesized that a

possible course of mechanisms producing the results may have been that information regarding impending pain increased negative emotions like nervousness and fear, which in turn increased pain perception. As the anticipation of impending pain or pain increase can be highly stressful and anxiolytic, this process may have been mediated by the neurotransmission of cholecystokinin (CCK). CCK is a neuropeptide found in key structures of the descending pain modulatory system. It is involved in numerous physiological functions, but is especially central in the induction and persistence of anxiety and major depression and the induction of subjective and physiological stress (Hebb et al., 2005). In previous research by Benedetti et al. (2006), negative verbal suggestions accompanying the administration of an inert substance led to nocebo-induced hyperalgesia. The hyperalgesic response resulted in hyperactivity of the hypothalamic-pituary-adrenal (HPA) axis, as assessed by means of adrenocorticotropic hormone (ACTH) and cortisol plasma concentrations. Both HPA hyperactivity and nocebo hyperalgesia were antagonized by the benzodiazepine Diazepam, indicating that anxiety plays an important role in the nocebo response. By contrast, the administration of the CCK receptor antagonist Proglumide blocked nocebo hyperalgesia entirely, but seemed to have no effect on the HPA hyperactivity, suggesting an involvement of CCK in the hyperalgesic but not in the anxiety component of the nocebo response. Importantly, both Proglumide and Diazepam showed no analgesic properties on baseline pain, but acted only on the pain increase induced by the nocebo intervention.

In sum, these data suggest a close link between anxiety and nocebo hyperalgesia, in which CCK turns anxiety into pain. Interestingly, individuals with an elevated level of fear of pain could have a tendency for increased neurotransmission of CCK in situations where impending pain is anticipated. In a study by Lyby et al. (2009) the hypothesis was tested that fear of pain would be related to both higher pain intensity and stress and to a reduced placebo analgesic response. In that study, healthy volunteers were randomized to either a placebo or a natural history condition. In both conditions, heat pain was induced while measuring stress, arousal, pain intensity and pain unpleasantness, but in the placebo condition two capsules containing lactose was administered accompanied by information stating that it was a potent painkiller. Fear of pain was assessed by means of the Fear of Pain Questionnaire (FPQ-III). The results showed that higher scores in fear of pain were positively related to higher stress during the anticipation of pain and during

pain stimulations, and negatively related to placebo analgesia. Accordingly, findings from Lyby et al. (2009) may indicate that individuals high in fear of pain who respond with elevated levels of stress in painful situations exhibit stronger nocebo responses, mediated by increased CCK-ergic activity. In relation to the present study, such mechanisms may possibly have facilitated responding in the nocebo EMLA condition.

The present study`s result that nocebo information led to hyperalgesia accompanied by increased sympathetic arousal in the nocebo EMLA condition may paradoxically have been mediated by the pharmacological properties of the Emla cream. In some cases, expectations of drug effects can be modulated if subjective sensations of the drug inform the individual that active medication has been administered. In placebo procedures this means that interoceptive or peripheral cues from the active agent may be interpreted in the direction of the positive information, thereby enhancing expectancies of pain relief and hence placebo responding. In experimental work by Bjørkedal and Flaten (2011), caffeine was used as an active substance to test whether side effects of drugs were able to increase both expectancies and placebo responses. In that study, healthy volunteers underwent painful laser stimulation before and after they received a drink with 0 or 4 mg/kg caffeine. Administration of the drink was crossed with verbal suggestions that it was either a painkiller or a placebo. The results showed that information that a painkiller had been administered increased the analgesic effects of caffeine compared to caffeine administration without drug information. This occurred on the bases of the interaction between the pharmacological properties of the caffeine combined with expectations. In relation to the present study, it may therefore be hypothesized that dermatological sensations produced by the Emla cream were interpreted in the direction of the negative information regarding its effect, thus leading to enhanced nocebo responding in the nocebo EMLA condition. Albeit plausible, further studies should be performed to unravel how negative expectations interact with the biological effects of pharmacologically based treatments.

In the present study, we found no significant reduction in pain intensity report in the placebo condition compared to the natural history condition, nor did we find a significant decrease in SCL, systolic blood pressure or subjective stress in the placebo condition compared to the natural history condition. A calibration of pain levels would potentially have induced a significant placebo response, and as such,

lack of calibration may represent a limitation of the present study. On the other hand, not calibrating can also be regarded a strength because it makes the findings more relevant for clinical settings.

Since the possibility exists that the biological effects of the Emla cream was detectable, a potential extension of this hypothesis is that such effects may have led to an anticipation of pain reduction in participant who had previous experiences with similar analgesics. Hence, biological effects of Emla may have acted as a cue associated with the experience of treatment effects induced by resembling anesthetic creams in the past, thereby eliciting a conditioned response. According to such an interpretation, conditioning mechanisms may at least partly account for a significantly lower pain intensity report in the EMLA standard info condition compared to the placebo condition, and thus to some extent explain the lack of a placebo analgesic response in the present study. Based on such considerations, future studies investigating the effect of drug-related information on analgesic treatments should perhaps account for previous experience with analgesics.

In conclusion, results from the present study suggest that a consideration of the effects of negatively charged information regarding treatment effect is necessary especially in clinical situations, where nocebo-related responses represent a point of vulnerability. Providing the appropriate information about treatment outcome, potential side effects and the expected drug effect should therefore be considered an important feature of the patient-physician interaction.

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Appendix A

# Stressmål
(dere nevner **ikke** eksplisitt for deltakeren at dette er en måling av stress)
Spørsmålene stille ihht prosedyre 3 ganger ila forsøket

**PRETEST**

På en skal fra 0 til 10 der 0 indikerer ”rolig” og 10 indikerer ”nervøs”, hvordan føler du deg?

**Verdi =**

På en skal fra 0 til 10 der 0 indikerer ”avslappet” og 10 indikerer ”anspent”, hvordan føler du deg?

**Verdi =**

**FØR 2. BLODTRYKKSMÅLING:**

På en skal fra 0 til 10 der 0 indikerer ”rolig” og 10 indikerer ”nervøs”, hvordan føler du deg?

**Verdi =**

På en skal fra 0 til 10 der 0 indikerer ”avslappet” og 10 indikerer ”anspent”, hvordan føler du deg?

**Verdi =**

**POST-TEST**

På en skal fra 0 til 10 der 0 indikerer ”rolig” og 10 indikerer ”nervøs”, hvordan føler du deg?

**Verdi =**

På en skal fra 0 til 10 der 0 indikerer ”avslappet” og 10 indikerer ”anspent”, hvordan føler du deg?

**Verdi =**

Appendix B

# Forespørsel om deltakelse i forskningsprosjektet

## *Informasjon og effekten av legemiddel*

**Bakgrunn og hensikt**

Formålet med denne studien er å teste hvordan informasjon om effekten av legemiddel påvirker smerteopplevelse ved behandling med smertedempende og smertesensitiverende krem.

Vi ønsker å spørre friske personer mellom 18 og 40 år om å delta. Denne studien utføres ved Institutt for psykologi, UIT.

## Hva innebærer studien?

Eksperimentet gjennomføres ved Institutt for psykologi, UIT. Eksperimentet innebærer at forsøkspersonene blir påført smerte ved hjelp av en datastyrt varmetermode som festes til armen. Kremene som benyttes er enten smertedempende krem med god smertedempende effekt mot varmesmerte, placebokrem, eller en krem som gjør huden mer sensitiv for smerte. Enkelte deltakere vil ikke få behandling med krem, og de vil inngå i kontrollgruppen i studien. Verken du som deltaker eller personen som gjennomfører eksperimentet vil ha eksakt kunnskap om kremen inneholder legemiddel eller er en placebokrem.

Gjennom forsøket blir det målt subjektive og fysiologiske reaksjoner. Smertestimuleringene er relativt smertefulle, men ufarlige. Fysiologiske reaksjoner måles ved hjelp av skin conductance respons som måles ved hjelp av overflateelektroder. Varigheten på eksperimentet er ca 45 minutter.

**Mulige fordeler og ulemper**

Smertestimulus kan føre til at huden blir sensitiv og rød noen minutter etter forsøket. Dersom du får smertedempende krem, kan huden på armen oppleves som nummen i opptil 4 timer etter at forsøket er ferdig.

Det er ingen personlige fordeler knyttet til eksperimentet, utover erfaring med hvordan eksperimentell forskning på mennesker kan utføres, samt hva som kan være med på å

forklare personlighetsmessige og emosjonelle forskjeller i smerte fra et psykologisk perspektiv.

**Hva skjer med prøvene og informasjonen om deg?**
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

**Frivillig deltakelse**

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte prosjektleder Per M. Aslaksen på tlf **776 49234 /** epost **per.aslaksen@uit.no.**

# Kapittel A- utdypende forklaring av hva studien innebærer

**Kriterier for deltakelse**
Vi søker etter friske studenter i alderen 18 – 50 år. De som deltar må ha god helse, ikke være gravid, ikke ha eller ha hatt alvorlige sykdommer eller bruke reseptbelagte legemiddel, med unntak av p-piller. Man kan heller ikke ha skader i huden på armene/hendene eller ha kronisk smertelidelse.
**Tidsskjema – hva skjer og når skjer det?**
Dersom du samtykker i å delta kontakter du Lab386@hotmail.no for å gjøre avtale om dato og tidspunkt for oppmøte på IPS, teorifagbygget, hus 5, plan 3. Ved ankomst vil du få prøve smertestimulus før du starter eksperimentet og eventuelt avgjøre om du vil delta eller ikke. Dersom du ønsker å delta vil du gjennomgå den eksperimentelle prosedyren som varer i ca 45 minutter.

**Studiedeltakerens ansvar**
Som deltaker i denne studien er det ditt ansvar å lese informasjonen vedrørende deltakelse.

**Eventuell kompensasjon til dekning av utgifter for deltakere**
Etter gjennomføring av eksperimentet vil du få et gavekort på 200 kr som kompensasjon for deltakelse i eksperimentet.

# Kapittel B - Personvern, økonomi og forsikring

***Personvern***
Opplysninger som registreres om deg er navn, alder, fødselsdato og kjønn. Navn vil bli lagret separat fra resultatene som framkommer i eksperimentet og vil bare bli brukt for å sende deg rapport på funnene for hele studien etter at studien er fullført for alle deltakerne. Navnelister vil bli slettet så snart studien er fullført for alle deltakerne. Informasjonen om deg skal kun brukes som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og resultater gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Universitetet i Tromsø ved administrerende direktør er databehandlingsansvarlig.

**Rett til innsyn og sletting av opplysninger om deg**
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.
**Økonomi og Universitetet i Tromsøs rolle**
Studier er finansiert utelukkende gjennom forskningsmidler fra Universitetet i Tromsø. Det er ingen økonomiske interessekonflikter som kan påvirke gjennomføringen av studien, eller publiseringen av resultatene.

**Forsikring**
Alle deltakere i denne studien er dekket av Produktansvarsloven og av særskilt forsikring for laboratorier ved Institutt for psykologi, UIT.
**Informasjon om utfallet av studien**
Dersom du ønsker det, vil du få tilsendt en skriftlig rapport om resultatene fra denne studien så snart alle deltakerne har gjennomført. Dersom du ønsker dette, ber vi deg føre opp kontaktadresse på samtykkeerklæringen som vi beholder.

# Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

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(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

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(Signert, rolle i studien, dato)

Appendix C

## Fear of pain questionnaire – III

**Instruksjon: Setningene under beskriver smertefulle opplevelser. Les hvert spørsmål og tenk på hvor redd du er for å oppleve SMERTEN som er forbundet med hver opplevelse. Hvis du aldri har opplevd smerte knyttet til en av situasjonene, svar slik du forventer at FRYKTEN ville vært dersom du hadde en slik opplevelse. Sett en sirkel rundt tallverdien for å rangere din FRYKT FOR SMERTE i forhold til hver opplevelse.**

## *GRAD AV FRYKT*

| ***Ikke*** **i det hele tatt** | **Litt** | ***En*** **god del** | **Veldig mye** | **Ekstrem** | |
|---|---|---|---|---|---|
| **1** | **2** | **3** | **4** | **5** | 1. Være med i en bilulykke. |
| **1** | **2** | **3** | **4** | **5** | 2. Bite deg i tungen mens du spiser. |
| **1** | **2** | **3** | **4** | **5** | 3. Brekke armen. |
| **1** | **2** | **3** | **4** | **5** | 4. Skjære deg i tungen på en konvolutt. |
| **1** | **2** | **3** | **4** | **5** | 5. Noe tungt treffer deg i hodet. |
| **1** | **2** | **3** | **4** | **5** | 6. Brekke en fot. |
| **1** | **2** | **3** | **4** | **5** | 7. Slå deg på et følsomt sted på albuen. |
| **1** | **2** | **3** | **4** | **5** | 8. Ta en blodprøve med en sprøyte. |
| **1** | **2** | **3** | **4** | **5** | 9. Noen slenger en tung bildør over hånden din. |
| **1** | **2** | **3** | **4** | **5** | 10. Ramle ned en betongtrapp. |
| **1** | **2** | **3** | **4** | **5** | 11. Få en injeksjon med en sprøyte i armen. |
| **1** | **2** | **3** | **4** | **5** | 12. Brenne fingrene på en fyrstikk. |
| **1** | **2** | **3** | **4** | **5** | 13. Brekke nakken. |
| **1** | **2** | **3** | **4** | **5** | 14. Få en injeksjon med en sprøyte i hoften. |
| **1** | **2** | **3** | **4** | **5** | 15. Få en flis i fotsålen og deretter få den fjernet med pinsett. |

Fortsetter på neste side.

## *GRAD AV FRYKT*

| ***Ikke* i det hele tatt** | **Litt** | ***En* god del** | **Veldig mye** | **Ekstrem** | |
|---|---|---|---|---|---|
| **1** fjernet av | **2** | **3** | **4** | **5** | 16. Få et objekt som sitter fast i øyet ditt en lege. |
| **1** munnen. | **2** | **3** | **4** | **5** | 17. Få en injeksjon med en sprøyte i |
| **1** | **2** | **3** | **4** | **5** | 18. Bli brent i ansiktet av en sigarettglo. |
| **1** | **2** | **3** | **4** | **5** | 19. Kutte en finger på papir. |
| **1** | **2** | **3** | **4** | **5** | 20. Måtte sy sting i leppa. |
| **1** lege med | **2** | **3** | **4** | **5** | 21. Få en vorte på foten fjernet av en et skarpt instrument. |
| **1** når du | **2** | **3** | **4** | **5** | 22. Kutte deg med en skarp barberhøvel barberer deg. |
| **1** avkjølt. | **2** | **3** | **4** | **5** | 23. Svelge en varm drikk før den er |
| **1** eller | **2** | **3** | **4** | **5** | 24. Få sterk såpe i øynene mens du dusjer bader. |
| **1** daglig | **2** | **3** | **4** | **5** | 25. Få en dødelig sykdom som gir deg smerte. |
| **1** | **2** | **3** | **4** | **5** | 26. Få trekt en tann. |
| **1** | **2** | **3** | **4** | **5** | 27. Kaste opp flere ganger på grunn av matforgiftning. |
| **1** | **2** | **3** | **4** | **5** | 28. Få sand eller støv blåst inn i øynene. |
| **1** | **2** | **3** | **4** | **5** | 29. Bli boret i en tann. |

**1** **2** **3** **4** **5** 30. Få muskelkrampe.

Appendix D

## PANAS (oversatt av Peter Lyby)

**De følgende ordene beskriver ulike følelser og emosjoner.**

Vær vennlig å angi hvordan du føler deg akkurat nå ved å tegne en sirkel rundt det svaralternativet som passer best for hver følelse.

**1 = Svært lite eller ikke i det hele tatt**
**2 = Litt**
**3 = Moderat**
**4 = En god del**
**5 = Ekstremt (svært mye)**

**(1) = Svært lite eller ikke i det hele tatt** **(2) = Litt** **(3) = Moderat** **(4) = En god del** **(5) = Ekstremt (svært mye)**

| | **Svært lite/ikke i det hele tatt** | Litt | **Moderat** | **En god del** | Ekstremt (svært mye) |
|---|---|---|---|---|---|
| 1. Interessert | 1 | 2 | 3 | 4 | 5 |
| 2. Bekymret | 1 | 2 | 3 | 4 | 5 |
| 3. Oppstemt | 1 | 2 | 3 | 4 | 5 |
| 4. Oppskaket | 1 | 2 | 3 | 4 | 5 |
| 5. Sterk | 1 | 2 | 3 | 4 | 5 |
| 6. Skyldig | 1 | 2 | 3 | 4 | 5 |
| 7. Redd | 1 | 2 | 3 | 4 | 5 |
| 8. Fiendtlig | 1 | 2 | 3 | 4 | 5 |
| 9. Entusiastisk | 1 | 2 | 3 | 4 | 5 |
| 10. Stolt | 1 | 2 | 3 | 4 | 5 |
| 11. Irritabel | 1 | 2 | 3 | 4 | 5 |
| 12. Årvåken | 1 | 2 | 3 | 4 | 5 |
| 13. Skamfull | 1 | 2 | 3 | 4 | 5 |
| 14. Inspirert | 1 | 2 | 3 | 4 | 5 |
| 15. Nervøs | 1 | 2 | 3 | 4 | 5 |
| 16. Bestemt | 1 | 2 | 3 | 4 | 5 |
| 17. Oppmerksom | 1 | 2 | 3 | 4 | 5 |
| 18. Urolig | 1 | 2 | 3 | 4 | 5 |
| 19. Aktiv | 1 | 2 | 3 | 4 | 5 |
| 20. Engstelig | 1 | 2 | 3 | 4 | 5 |