Fear of Pain Reduces the Effect of a Placebo Intervention on Pain

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Fear of Pain Reduces the Effect of a Placebo Intervention on Pain

Abstract

Placebo analgesia refers to a reduction in pain after a placebo treatment has been provided. Fear of pain has been shown reduce placebo analgesic response. The present study investigated if experimentally induced fear of pain reduces the efficacy of a placebo intervention on pain. A balanced within-group design (n = 45) with a natural history, a placebo, and a placebo+fear condition was employed. In the placebo condition the participants were exposed to heat stimuli before and after administration of placebo capsules with information that they were given an analgesic. In the placebo+fear condition the participants were told, after the administration of the placebo capsules, that they would receive electric shocks before the next block of heat stimuli. On group level we found no placebo effects on reported pain intensity, pain unpleasantness and stress. We thus restricted our analysis to those who actually showed a reduction in pain after the administration of placebos (n = 18). In these respondents we observed that the placebo effect was diminished in the placebo+fear condition, however fear of pain did not predict placebo response in this group. In the startle reflex data we found a placebo effect on group level (n = 45). This placebo effect was reduced in the placebo+fear condition. The participants showed a potentiated startle reflex immediately after the induction of fear of pain, preventing a placebo response on pain to occur. Experimentally induced fear of pain thus seems to be related to a reduced placebo response.

Key words: *placebo, pain, pain unpleasantness, fear of pain, startle reflex, contact heat, electric shocks, psychobiology.*

Fear of Pain Reduces the Effect of a Placebo Intervention on Pain

Sammendrag

Placeboanalgesi vil si en opplevd smertereduksjon hos individer som har mottatt placebobehandling. Det har tidligere blitt vist at smertefrykt kan redusere placeboanalgesi. Denne studien undersøkte hvorvidt eksperimentelt indusert smertefrykt reduserer effekten av en placebointervensjon på smerte. Hypotesen ble undersøkt i et balansert innengruppedesign (n = 45) med tre betingelser: Kontroll, placebo og placebo+frykt. I placebo- og placebo+fryktbetingelsene ble deltakerne eksponert for smertefulle varmestimuli før og etter administrasjon av placebokapsler, sammen med informasjon om at de inneholdt et smertestillende legemiddel. Etter administrasjon av kapslene, fikk deltakerne i placebo+fryktbetingelsen, vite at de kom til å motta elektriske sjokk før neste blokk med smertestimulering. På gruppenivå (n = 45) så vi ingen signifikant placeboeffekt på smerteintensitet, smerteubehag eller stress. Analyser ble derfor utført på deltakerne som faktisk opplevde redusert smerte etter administrasjon av placebo (n = 18). I denne gruppen så vi en redusert placeboeffekt i placebo+fryktbetingelsen, men smertefrykt kunne ikke predikere placeborespons. I startle-dataene så vi en placeboeffekt på gruppenivå (n = 45). I placebo+fryktbetingelsen viste deltakerne en økt startle-refleks umiddelbart etter indusert smertefrykt, og dette forhindret placeboanalgesi ved påført varmesmerte. Eksperimentelt indusert smertefrykt ser derfor ut til å være relatert til en redusert placeborespons.

Nøkkelord: *placebo, smerte, smerteubehag, smertefrykt, startle refleks, kontaktvarme, elektriske sjokk, psykobiologi.*

Preface

The author was inspired by PhD-student Peter Solvoll Lyby to write a master thesis on the present topic. The present project was done on the basis of work by Lyby, Aslaksen, & Flaten, (2010) and contributes to a PhD-thesis about fear of pain and individual differences. Psychophysiological research has been the author's main area of interest since her bachelor thesis, and the present project has been a challenging, but also a very interesting and educational task.

Professor Magne Arve Flaten has supervised the project and this thesis. Flaten is leading a research group consisting of psychology students, PhD-students, post doctors and assistant professors. This study is one of severaly that Flaten supervises.

The author acted as experimenter in the study, together with Lyby and four research assistants. Lyby has been responsible for the design and software programming. Recruitment of participants, booking of the laboratory, training and supervising of the research assistants was done by the author. The data were analyzed by the author with guidance from Lyby, Espen Bjørkedal and Ole Åsli.

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Fear of pain reduces the effect of a placebo intervention on pain

The placebo effect has been a topic of interest in psychological and medical science for many years. From being considered a reporting bias, it is now a well documented phenomenon involving both biological and psychological factors. The word placebo means "I will please", and is defined as a psychophysiological response that follows the administration of pharmacological inactive substances, surgery or other kinds of treatment (Purves, et al., 2008). A number of studies have revealed that placebo treatment generates pain relief (Aslaksen & Flaten, 2008; Benedetti, 1996; Colloca & Benedetti, 2005; Flaten, Aslaksen, Finset, Simonsen, & Johansen, 2006; Levine & Gordon, 1984), and information that an effective analgesic medication has been administrated can be sufficient for a patient to feel pain relief. Placebo analgesia is the most studied and best understood placebo effect. Analgesia is a reduction in the magnitude of pain (Price, Finniss, & Benedetti, 2007) and placebo analgesia is the reduction in the magnitude of pain after administration of a placebo, i.e., an inert treatment.

Some researchers have constructed the placebo effect as being a reporting bias, and Hrobjartsson & Grotzsche (2001) suggested that the placebo in fact might be powerless. Even though the placebo phenomenon is a part of all treatment it is only in the last 30 years that advanced research designs and technology has given researchers the opportunity to study the placebo effect`s neurobiological and psychological mechanisms (Price, et al., 2007). The hypothesis that the placebo effect is a reporting bias has been challenged with increasing evidence that there are underlying neural mechanisms for the placebo analgesic effect (Scott, et al., 2008). Criticism has, however, been essential in the development of research designs and methods. Hrjobjartsson & Grotzsche`s (2001) criticisms contributed to an increasing use of brain mapping, (EEG/ERP; PET; fMRI) and pharmacological methods.

Placebo analgesia seems to be affected by emotional and motivational factors (Zubieta, Yau, Scott, & Stohler, 2006), suggesting a role for individual differences (Hoffman, Harrington, & Fields, 2005). Fear of pain has recently been reported to be negatively related to placebo analgesia (Lyby, Aslaksen, & Flaten, 2010). The results reported in the present study is an experimental test of the hypothesis put forth in Lyby et al. (2010), and investigates the effect of experimentally induced fear of pain on placebo analgesia.

Conceptualizations

Hoffman et al. (2005) criticized the literature for indiscriminately speaking of placebo effects and placebo responses as if it was the same thing. Based on prior work by the most distinguished researchers in the field, a distinction between the two terms has been drawn. In concordance with Hoffman et al. (2005) the term "placebo effect" will in this thesis be referred to as an average improvement in the condition of a group of participants that has received a placebo treatment. "Placebo response" will in contrast be referring to the change in an individual caused by a placebo manipulation.

Neurobiology of pain

A receptor that is activated by a stimulus that causes or could cause tissue damage is termed a nociceptor (Purves, et al., 2008). There are two types of neurons that respond to painful stimuli. The thin myelinated Aδ-fibers conduct quickly and are engaged in the response to sudden painful stimuli. The non-myelinated C-fibers are activated in slow and poorly localized pain (Brodal, 2007). Aδ-fibers terminate in the dorsal horn. In the dorsal horn the Aδ-fibers synapse with the neospinothalamic tracts dendrites. When pain signals are conducted in the synapse, the signal transmutes through the spinal cord. These axons travels to the ventral posterior nucleus of the thalamus and then to the somatosensory cortex (S1 and S2) (Brodal, 2007). C-fibers are terminated in substantia gelatinosa in the dorsal horn, and the signal is transmitted via these axons to the anterolateral pathway. Both Aδ and C-fibers terminate at different sites of the brainstem, the thalamus, medulla, pons and periaqueductal grey (PAG) (Price, 2002). The transmission pathway is illustrated on the left side in figure 1.

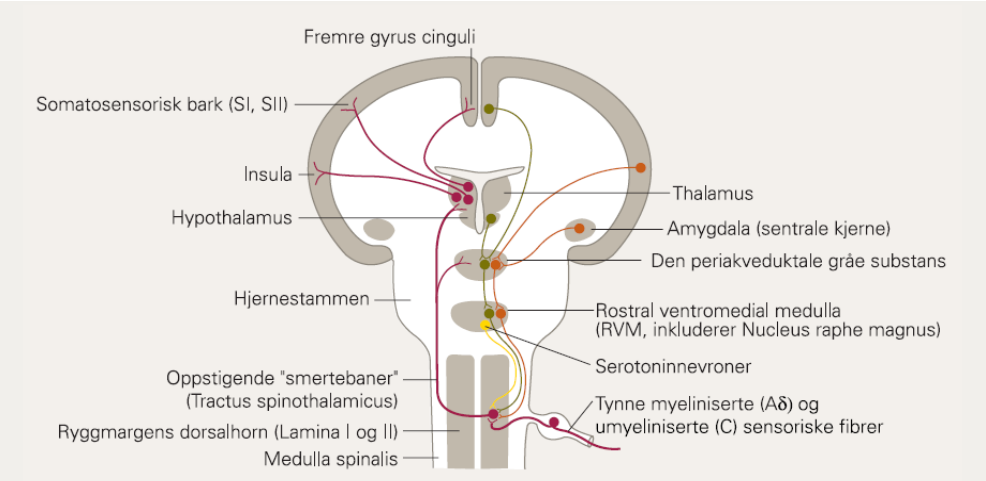

Figure 1: The transmission pathway from the painful stimulus to the cerebrum on the left side. Green: Pathway that inhibits pain transmission. Red: Pathway that increases pain transmission (Brodal, 2007, p. 229)

Pain intensity is the sensory experience conducted by nociceptive activation (Price, 2002; Purves, et al., 2008). In addition, pain has an emotional dimension termed pain unpleasantness (Price, McGrath, Rafii, & Buckingham, 1983). This includes the unpleasant feeling, the fear and anxiety, and the autonomic "fight or flight" reaction. The distinction between pain intensity and pain unpleasantness reflects the fact that the neurobiology of pain involves both sensory and affective structures. Brain areas known to be involved in pain are the primary and secondary somatosensory cortices (S1 and S2), the limbic system, the thalamus and the anterior cingulate cortex. Pain unpleasantness also include structures like the reticular formation, superior colliculus, PAG, rostal ventromedial medulla (RVM), the hypothalamus, and the amygdala (Purves, et al., 2008).

Pain and the modulation of pain by psychological factors

The International Association for the Study of Pain defines pain as a sensory and emotional experience that occurs because of potential or actual tissue damage. Pain can be modulated by ascending and descending pathways (figure 1), and emotional factors such as fear, anxiety and stress can affect these modulator mechanisms (Bradley, Silakowski, & Lang, 2008; Cuthbert, et al., 2003; Zubieta, et al., 2006). The traditional biomedical interpretation was that pain was a response to a noxious stimulus. Nociceptive signals were thought to travel directly by neural pathways to a pain centre in the brain, and tissue damage and pain

experience were thus closely connected (Purves, et al., 2008). According to this view placebo effects were considered anomalies and as a response bias.

A greater understanding of pain and the modulation of pain by psychological factors came with the gate-control theory (GCT), (Melzack & Wall, 1965). The biomedical model could not explain individual differences in pain, subjective complaints in the absence of injury and the modulation of pain by expectancies and emotions. There were no psychological aspects in the biomedical model. The gate-control theory challenged the existing understanding of pain and included the brain as a central and superior regulator of pain transmission (Melzack & Wall, 1965). The GCT showed how nociceptive signals could be transformed and modulated on their way from the periphery to the brain through specialized structures in the spinal cord. The GCT also showed that emotional and cognitive processes were central components in this modulation triggering either inhibitory or excitatory influences through descending neural pathways from the brain to the spinal cord. Pain today is considered a composite experience consisting of both psychological and biochemical components. Placebo analgesia is often referred to as the cardinal example of such mind-body interaction where expectation of pain relief after the administrating of an inactive treatment causes neurochemical changes in the brain resulting in an analgesic effect.

Underlying mechanisms in placebo analgesia

Understanding the placebo analgesic effect as a mind-body phenomenon implies that underlying mechanisms should be investigated both at the biological and psychological levels.

Placebo and neurobiological effects

It is established that placebo analgesia is partly mediated via endogenous opioids (Benedetti, 1996; Levine & Gordon, 1984; Levine, Gordon, & Fields, 1978). Endogenous opioid, or endorphins, consists of three sub-classes: β-endorphin, enkephalins and dynorphins. There are different classes of endorphin receptors, the μ, δ, κ, ε, and σ receptors. Levine, Gordon and Fields (1978) found that naloxone (a μ and δ receptor antagonist), partly blocked placebo analgesia. In a follow-up study Levine & Gordon (1984) investigated the placebo response in an open versus hidden model. After standardized surgery for the removal of third molars, the patients were randomly assigned to treatment with naloxone, physiological saline (0.9% NaCl solution), or morphine (μ and δ receptor agonist). In the two groups receiving

either open or hidden infusion of saline, the mean pain intensity decreased similarly. On the other hand mean pain intensity increased after hidden infusion of saline. Mean pain intensity also increased after administration of naloxone, regardless of how the administration occurred. Morphine decreased pain level regardless of administration route. The fact that the open infusion of naloxone produced an increase in pain whereas open infusion on saline had an opposite effect, suggests that there is a naloxone-antagonizable component of placebo-induced analgesia. Benedetti (1996) replicated these results.

Fields & Price (1997) proposed that placebo analgesia is due to activation of the pain inhibitory descending system (figure 1). The best studied of these systems is the PAG with projection to the central medulla. Morphine injected in these areas produce analgesia because of inhibitory descending pathways to the spinal cord that inhibit nociceptive signals. Electrical stimulation of the PAG and the RVM in animals has been shown to have the same effect (Brodal, 2007).

Further supporting the theory that placebo analgesia is mediated via endogenous opioids are studies of the endogenous peptide cholecystokinin (CCK) and proglumide (a CCK-antagonist). CCK is localized widely throughout the central nervous system and is shown to reduce the placebo analgesic effect (Benedetti, 1996) while proglumide enhances the opioid effect (Hoffman, et al., 2005). The placebo analgesic effect seems therefore to be a balance between endogenous opioids and endogenous CCK.

Psychological mechanisms: Conditioning and expectations

A substantial amount of work has been done to identify the underlying psychological mechanisms in explaining placebo focus on classical conditioning and conscious expectation (Benedetti, Rainero, & Pollo, 2003; Hoffman, et al., 2005; Montgomery & Kirsch, 1997). It has been argued that conditioned placebo response is mediated via expectancy (Montgomery & Kirsch, 1997). According to the classical conditioning model the placebo response occurs after an individual has been repeatedly exposed to pairing of neutral stimuli with an effective pain treatment. E.g. when a drug is administrated, the active substance represents the unconditioned stimulus (US) producing pain relief (unconditioned response, UR), whereas the shape, colour or taste of the capsules represents the conditioned stimulus (CS). After repeated associations, the shape, colour and taste elicit conditioned responses that mimic the response to the active treatment (CR) (Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999).

The expectancy theory, on the other hand, holds that placebo responses are mediated via conscious expectation of a particular drug response (Montgomery & Kirsch, 1997). When treatment is administrated an expectation can be generated, and the response expectancy can generate a response that mimic the original drug-response on both a physiological and psychological level. Several studies have shown that verbal information can create expectations which in turn can produce a placebo response (Benedetti, et al., 2003; Flaten, Simonsen, & Olsen, 1999; Johansen, Bronx, & Flaten, 2003) The effect of the treatment is also predicted by expectations the person had prior to the treatment (Kirsch, 1999). These expectations are mediated by context, prior experience with pain, drugs and belief about the treatment`s effectiveness.

Benedetti et al. (1999) showed that the placebo response can be generated by conditioning alone, without any mediating effect of expectancy. 60 lung surgery patients participated in the study on their third post-operative day. The first two days the patients received buprenorphine treatment (UR) as an infusion (US). A conditioning procedure was used to generate placebo respiratory depressant responses. A balanced design with four conditioning groups (natural history, placebo received open, naloxone received open, naloxone received closed) was employed. The patients who got open infusion (CS) were told that they got buprenorphine, and the group that got hidden infusion did not know that any injection was performed. The group that received placebo with open infusion experienced the most relief in pain (CR) compared to the other groups.

In sum, evidence suggests that both conditioning and expectancy represent independent psychological mechanisms that may act independently or in concert. Benedetti and colleagues has done extensive research on both models (Benedetti, et al., 1999b; Benedetti, Lanotte, Lopiano, & Colloca, 2007; Benedetti, et al., 2003) and are implying that the role played by each mechanism could imply to different response systems. Expectancy could play a role in conscious processes like pain (Benedetti, et al., 2003), whereas conditioning could have a role in unconscious processes (Benedetti, et al., 1999).

Emotions in pain and placebo

Experimental manipulations that have positive effects on emotional state, such as pleasant music, are generally shown to reduce pain perception (Good, 1996; Roy, Peretz, & Rainville, 2008). In clinical practice it is common to observe that anxiety increases pain

experience (Tracey & Mantyh, 2007). Meagher, Arnau, & Rhudy (2001) used affective pictures (IAPS) and a cold-pressor test to investigate how negative emotions (fear and disgust) influence pain perception. Viewing either fear or disgust slides before the cold-pressor test reduced pain intensity - and unpleasantness threshold ratings. These results suggest that both sensory and affective dimensions of pain are influenced by negative emotions. Several other studies have also connected negative emotions, such as fear, anxiety and stress to an increase in pain and reduced placebo analgesic effect (Benedetti, 1996; Benedetti, Amanzio, Vighetti, & Asteggiano, 2006; Benedetti, et al., 2003; Flaten, et al., 1999; Johansen, et al., 2003).

As described earlier the placebo analgesic effect is a balance between endogenous opioids and endogenous CCK. CCK predominance enhances a hyperalgesic effect. Nocebo hyperalgesia refers to an increase in pain due to anxiety or fear, and has been linked to CCK. Blocking of CCK receptors has been shown to abolish nocebo hyperalgesia (Benedetti, 1996). A nocebo effect induced by verbal suggestion was blocked by proglumide (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997). These results showed that nocebo hyperalgesia is mediated by CCK and that nocebo hyperalgesia might by due to CCK-depended increase in anxiety. Pharmacological blockade of CCK-receptors has also been shown to abolished nocebo hyperalgesia (Benedetti, et al., 2006). The conclusion based on these two studies was that hyperalgesic nocebo appears to be caused by a complex biochemical and neuroendocrine mechanism that links together cognition (expectation) and emotions, such as anxiety, and pain.

Bradley, et al. (2008) investigated the relationship between fear of pain and dental fear. Participants in the study with a high level of fear of pain displayed greater defensive reactivity than the participants with a low level of fear of pain. Defensive reactivity included potentiated startle blinks, heightened skin conductance, and cardiac deceleration in the context of a threat compared to no threat. Higher levels of fear of pain elevate levels of stress and negative emotions in situations where painful stimulation is highly probable (Lyby, et al., 2010).

Measuring the placebo analgesic effect

The neurobiological structures mediating the placebo analgesic effect has resent years been investigated using positron emission tomography (PET) and functional magnetic

resonance imaging (fMRI). A PET study using thermal pain investigated the neuronal circuitry implicated in placebo responding (Petrovic, Kalso, Petersson, & Ingvar, 2002). The researchers analyzed CNS activity by observing the effect of remifentanil (μ receptor agonist) and saline placebo. Similar brain regions were activated (significant overlap) with both solutions, including the anterior cingulate cortex and the rostral medulla/caudal pons. Wager et al. (2004) measured neuronal activity using fMRI. The participants were given placebo with expectations of analgesia while they were exposed to painful heat stimulus. Placebo effect was associated with decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex, and was associated with increased activity during anticipation of pain in the prefrontal cortex (figure 1).

The electroencephalogram (EEG) measures continuous brain activity as electrical impulses from the scalp. Event related potentials (ERP) are specific responses to a given stimulus (Luck, 2005). Pain evoked potentials reflects the processing of pain in the brain from an external stimulus (Granovsky, et al., 2008) . The EEG has high temporal resolution as it is measured in real time with millisecond resolution, and by using EEG/ERP in placebo studies the placebo response can be detected early in the pain signal transmission. Stimulation using contact heat activates both Aδ and C-fiber nociseptors.

The ERP-response correlates with stimulus intensity and with verbal pain report and can be used as an objective measurement of pain intensity (Granovsky, et al., 2008). This reduces reporting bias that is a problem with subjective reporting. If placebo analgesia is due to an anti-nociceptive process the ERP-response (N2/P2-waveform) should decrease after placebo treatment is given. Wager, Matre, & Casey (2006) examined how early in the signal transmission the placebo response occurred. Comparisons of the ERP-response before and after placebo treatment gave significant decreases in P2 amplitude. The N2 amplitude, however, did not respond to the placebo treatment. The conclusion was that the placebo analgesic response is a psychobiological process that occurs before the pain signal reaches the brain. The lack of change in N2 amplitude confirms that there are other components that also affects the placebo analgesic response (Wager, et al., 2006).

Watson, El-Deredy, Vogt, & Jones (2007) examined whether a placebo response were due to increased compliance or habituation. 31 participants were assigned to one of two groups (treatment group and natural history). The forearms were stimulated with laser stimuli

and laser evoked potential were recorded. After a pre-test of 20 moderately painful stimuli an inactive aqueous cream was applied to the participant's forearms with information that the cream would have analgesic effect. Prior to the next test the stimuli were reduced to a non-painful level on one of arms. The treatment group was unaware of this, but the natural history group was told that the stimuli were reduced. The participants then received 20 stimuli to each arm, and rated the level of pain to each stimulus. In the third test stimuli were increased back up to moderately painful. This was to investigate whether the apparent placebo effect would be observed on conditioned or unconditioned site. The findings were a significant placebo-induced reduction in pain rating and in both N2 and P2 amplitude in both the conditioned and the unconditioned arm. The reduction of pain was concluded to due to a placebo response and that it was unlikely to be due to sensory habituation or compliance to the experimental instructions.

Measurement of emotions: The startle reflex

The startle reaction consists of a series of muscular reactions, with includes eyeblinks and contraction of muscles in the neck, shoulders, upper back, arms and legs (Berg & Balaban, 1999). The startle reflex is measured by electromyography (EMG) by surface electrodes placed above the orbicularis oculi, the circular muscle surrounding the eye. The orbicularis oculi controls blinking that is the most reliable component in the startle reflex because it is the last component to habituate. The startle reflex is a defensive reflex elicited by abrupt stimuli with moderate to high intensity, and startle reflexes are increased when the individual is in a state of fear (Brown & Schwartz, 1980). When a probe is paired with a cue that predicts painful electric shocks, the startle reflex is also reliably higher with cues that simply indicate the threat of shock (Hamm, Greenwald, Bradley, & Lang, 1993). Bradley, et al. (2008) showed that startle blink magnitude was larger in the presence of threat of shocks, compared to periods with no threat.

Individual differences

Most studies on placebo analgesia are mainly designed to investigate the mechanisms and to pinpoint brain structures that mediate the placebo analgesic effect. However, often they do not investigate individual variations within the groups. Hoffman et al. (2005) points out that, in placebo studies there have always been both placebo responders and non-responders. In clinical studies the mean placebo effect is the result of some relatively large responses,

whereas the majority of individuals show no evident response to placebo manipulation (e.g. Benedetti, 1996). How many participants who do respond with placebo has varied across studies, e.g. 27% (Benedetti, 1996) and 56% (Petrovic, et al., 2002). It is critical to be able to identify those individuals who are responding and those who are not. By investigating the placebo response within individuals, researchers can gain more insight to psychological and neural mechanisms of placebo analgesia (Hoffman, et al., 2005; Kosslyn, et al., 2002).

Individual differences is present in both psychological (Flaten, et al., 2006) and physiological mechanisms (Davidson & Irwin, 1999). Flaten et al. (2006) investigated whether the effect of expectancy on pain is mediated via reduction of negative emotions. One group of participants was told that they received a potent analgesic medication (positive information) and the other group was told that the drug would only have minor effect (neutral information). Information about the pain stimulus and about its effect was also given to half of the participants (equally to the positive information and the neutral information groups). Pain expectancy and pain information decreased pain to the same degree, but independently. This was, however, only the case in the male participants. Social context and gender influences cognitive and emotional factors in individual differences.

The present study

The present study we investigated whether induction of fear of pain reduces the effect of a placebo intervention on pain. The study was based on Lyby, et al. (2010) which showed that fear of pain was positively related to stress both during pain and anticipation of pain, and negatively related to placebo analgesia. A balanced within-group design with a natural history, a placebo, and a placebo-fear condition was employed. The pain stimulation was delivered with a 30x30 mm contact thermode for a total of 60 stimuli in three blocks, with a temperature of 54°C and less of .1 second duration to the forearm. After the first block (pretest) of 20 stimuli there was a 15 min break and after the second block (posttest 1) a 10 min break.

Subjective pain intensity, pain unpleasantness, subjective stress and startle reflexes were recorded. At the beginning of the 15 min break the participants were, in the placebo condition and the placebo+fear condition, given two capsules containing an inactive ingredient (lactose) and told that it was an easily soluble analgesic that would reduce the pain within a few minutes. In the placebo+fear condition, after the placebo administration, the

participants were in addition told that they would receive a number of painful electric shocks within the end of the break. This was done to induce fear of pain and investigate if it would reduce the apparent placebo effect from the placebo condition.

Hypotheses

The following question was investigated in the present study: Does induced fear of pain decrease the placebo analgesic effect, both the biological effect and the subjective experience?

It was assumed that if placebo administration reduces subjective pain experience and stress, a lower startle reflex in the placebo condition compared to the natural history condition would be expected. In the placebo+fear condition it was assumed a reduced placebo analgesic effect compared to the placebo condition. Additionally an increased stress level both subjective and psychobiological, with an increased startle reflex (compared to the placebo condition) would be expected in the placebo+fear condition.

Method

Participants

Forty-five students (26 females, 19 males), age range 19-40 years (mean = 22,8 SD = 4,2) from the University of Tromsø participated in the study. The study was advertised through flyers, websites and by recruiting from lectures. The advertisement informed that the participants would participate in an experiment that tested the effects of induced negative emotions and pain treatment. All participants signed an informed consent form and were asked about their medical history of serious diseases and injuries. They were also instructed not to use caffeine or nicotine three hours prior to the experiment. The participants received a gift certificate of 500 NOK for the participation. All the participants completed the study. The study was conducted in accordance with the Helsinki declaration and was approved by the Norwegian Social Science Data Services and the Regional Committee for Medical Research in North Norway (project 20277).

Design

A balanced three condition (natural history, placebo, placebo+fear) x 3 tests within subjects design was employed. The participants were randomly assigned to a specific order of sequence and tested on three different days across a period of maximum 18 days.

Experimenters

Six experimenters, four females (mean age = 24) and two males (aged 25 and 32) conducted the experiment. Four of the experimenters (three females and one male) were students in the clinical psychology program, one female experimenter was a master student in psychology and one male experimenter was a PhD student in psychology. The experimenters were trained in the experimental procedures prior to the start of the experiment. All interaction between the experimenter and participant was standardized in a written protocol.

Apparatus and stimuli

Placebo capsules

The placebo capsules administrated during the experiment contained 75 mg of lactose each. The study was run double-blind and the experimenters were told that 25% of the capsules contained an analgesic medication.

Contact heat stimulation

A pc-controlled contact heat-evoked potential stimulator (CHEPS; Medoc, Israel) with a 30 x 30 mm thermofoil thermode was used to induce heat pain to the skin of the right medial forearm (dermatome C8). Baseline temperature was 32° C and the rise and fall rate was 70°C/s. Pulses (0.1 sec) at a temperature of 54° C was delivered at an interstimulus interval (ISI) of 7 to 15 seconds.

Startle reflex

A Bruel and Kjær 2235 Sound Level Precision Meter was used for calibration of startle-eliciting noise. Coulburn Human Startle System HSW v. 7500-00 run on a Dell PC with Windows XP operating system controlled the stimulus presentation and response recording. White noises with an intensity of 95 dB were delivered through Sennheiser HD 250 headphones. The noises had a rise time of 10 ms. Eyeblink electromyographic (EMG) responses were recorded from the right orbicularis oculi with two Ag/AgCl Sensor Medics miniature electrodes (2mm diameter) filled with Ultra Phonic conductivity gel. The reference electrode was placed over the right eyebrow.

Electrical stimuli

A Coulbourn finger stimulator E13-22 was used to present electric shock. Two electrodes placed on two fingers of the right hand applied shocks with an intensity of 1.4 milliampere. Software HMS-100 controlled the stimulus presentation.

Subjective recording

The participants rated the level of pain on a scale ranging from 0 (no pain), via 1 (pain threshold) and 5 (moderately painful) to 10 (highest imaginable pain).

The degree of unpleasantness of the startle reflex-eliciting noise was rated by the participants on a 100 mm pen-and-paper visual analogue scale (VAS). Subjective measure of stress and arousal was measured using the Norwegian translation of the Short Adjective Check List (SACL)(Mackay, Cox, Burrows, & Lazzerini, 1978). Four adjective pairs were used: tense-relaxed (stress), nervous-calm (stress), awake-sleepy (arousal) and energetic-tired (arousal). The pairs were reported on a 0-10 scale.

Questionnaires

The Fear of Pain Questionnaire-III (FPQ-III; (McNeil & Rainwater, 1998) is a self-report questionnaire that assesses fear of pain. It contains of 30 items involving three subscales: Severe pain, minor pain and medical pain. Each item is rated on a five-point Likert scale, were 1= no fear at all and 5 = extreme fear. The present study used a Norwegian translation of the FPQ-III questionnaire.

Fear of pain was induced experimentally with a threat that painful electric shocks would be given to two fingertips on the right hand. After the experiment the participants rated the effect of this fear manipulation. This was rated on a 5-point scale, where 1 indicated no effect and 5 indicated complete fear of pain.

Experience with pain medication

The participants rated their prior experience with over-the-counter (OTC) painkillers on a 5-point scale, where 1 indicated no pain relief and 5 indicated complete pain relief from such medications.

Procedure

All the participants were tested individually and had to attend three days of testing in the laboratory; one day for each condition. The orders sequences were randomly selected across the participants and the procedure varied between the conditions. Testing of all three conditions were to be completed within 18 days, and two conditions could not be tested within 24 hours of each other. All participants were tested between 8 AM and 6 PM.

The first day of the experiment the participants signed the informed consent form (Appendix A) and rated their previous experience with analgesic medication (Appendix C). Personal data was also collected (Appendix B). The experimenters then gave all the necessary information about the procedure and explained all the pen-and-paper measurements, the adjective pairs for the subjective measurement (SACL) (Appendix D) and VAS (Appendix E). The participants were then placed in a comfortable chair inside a steel cubicle, 2.8 x 2.8 meters large. This was done in order to isolate the participants from disturbing noises and electricity. The participants were also asked to leave mobile phones, watches and other electronic equipments outside the steel cubicle. The cubicle was placed in a larger room along with all the equipment necessary in the experiment was placed. Electrodes for registration of

startle reflex were attached around the participant`s right eye once inside the cubicle. Baseline measurements of stress and arousal (SACL) were then performed.

The participants were given three pain stimulations with the thermode attached to the right arm; a pretest and two posttests consisting of 20 pulses (54°C) each. After the pretest the participants were asked to rate pain intensity and pain unpleasantness together with SACL. The experiment then proceeded with a 15 min break prior to the next pain stimulation. The startle reflex stimulation pretest was given at this point and the participants rated the unpleasantness level on VAS. The procedure during the rest of the break was dependent on the condition tested: In the natural history condition the participants were told to relax until the next test. SACL was recorded prior to and after the two remaining pain stimulations. Pain intensity and pain unpleasantness were also recorded after the pain stimulations. After posttest 1 the participants had a 10 minute break before posttest 2. After the startle reflex stimulation posttest and VAS the participants were instructed to relax for the rest of the break.

In the placebo and the placebo+fear condition the procedure was identical to natural history condition prior to the startle reflex stimulation pretest during the 15 minute break. When the startle reflex stimulation pretest and VAS were completed, the participants were given two placebo capsules. They were told that each capsule contained 75 mg of a documented OTC analgesic, and that they would experience relief in pain from the thermode within a few minutes. After the placebo manipulation the participants were given startle reflex stimulation posttest 1 and VAS. From the pain stimulation posttest 1 the procedure proceeded identically to the natural history condition. At the end of the placebo condition day the participants were asked if they experienced an effect of the administrated capsules (Appendix F).

In the placebo+fear condition the participants received the capsules and the placebo manipulation at the same time as in the placebo condition. The fear manipulation was given immediately after the placebo manipulation. Two electrodes were attached on the two middle fingers of their right hand, and the participants were told that they would receive painful electric shocks within the end of the break.

After the placebo and fear manipulation the participants were given startle reflex stimulation posttest 1 and VAS. Two electric stimulations, barely noticeable, were given near the end of the 15 minute break. From the pain stimulation posttest 1 the procedure then

proceeded identically to the natural history and the placebo condition. After the experiment on the placebo+fear condition day, the participants were asked how they perceived the fear manipulation and what effect it had had (Appendix G). At the end of the third day regardless of condition the participants were asked to answer the fear of pain questionnaire (Appendix H).

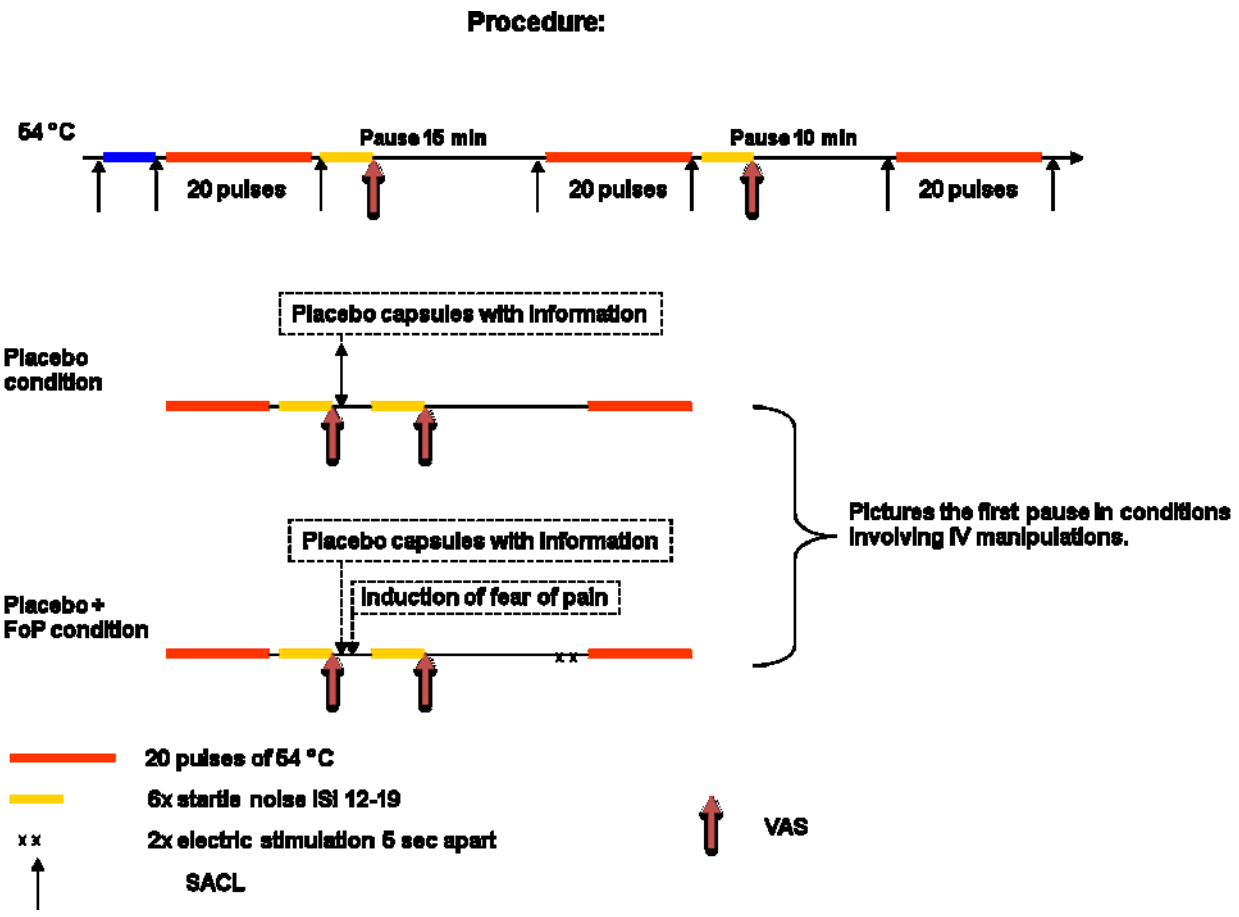

Figure 2: Timeline showing the experimental procedures.

Statistical Analysis

All statistical procedures were performed in SPSS 16.0 (SPSS, Inc., Chicago, Illinois). Follow-up tests were performed in Statistica 7.0. Data from the SACL, NRS, FPQ and startle reflex were entered in separate repeated measures and analysis of variance (ANOVA).

Tukey`s and paired sample t-test were used as follow-up tests. The hypothesis was tested with repeated measures ANOVA with three conditions (natural history, placebo and placebo+fear) three tests. Gender and order sequence were included as between subject factors in the model. A confirmation of our hypothesis was defined by two criteria: (1) A significant interaction between condition and test comparing the natural history condition with the placebo condition (i.e. placebo effect), (2) that the interaction between condition and test when comparing the natural history with the placebo+fear condition would not be significant (i.e. placebo effect reduced or neutralized). A regression analysis with continuous variables on placebo response on pain intensity, and with stress and fear of pain as independent variables was done to investigate if stress would interfere with the placebo response.

Results

Descriptive statistics of criterion and predictive variables

Descriptive statistics of means and standard error of the means of the predictor and criterion variables in the three conditions are presented in Table 1.

Table 1: Descriptive statistics for predictor and criterion variables, experienced placebo analgesic effect and fear of pain.

	Collapsed (n=45)		Natural history		Placebo		Placebo+fear	
Variable	Mean	S.E	Mean	S.E	Mean	S.E	Mean	S.E
Fear of severe pain	35.29	5.89						
Fear of minor pain	19.71	5.02						
Fear of medical pain	24.49	6.20						
Pain intensity	2.55	1.35	2.59	1.32	2.47	1.38	2.59	1.34
Pain unpleasentness	2.24	1.34	2.36	1.37	2.13	1.31	2.22	1.33
Stress level	2.41	1.56	2.51	1.71	2.31	1.56	2.39	1.41
Startle reflex	166.73	156.95	163.05	146.55	154.23	140.86	182.9	170.07

Pain intensity

There was a significant interaction between condition and order sequence ($F(10, 132) = 2.61$, $p = .009$), but the follow-up tests did not reveal any significant differences. No other significant effects were found in the pain intensity data.

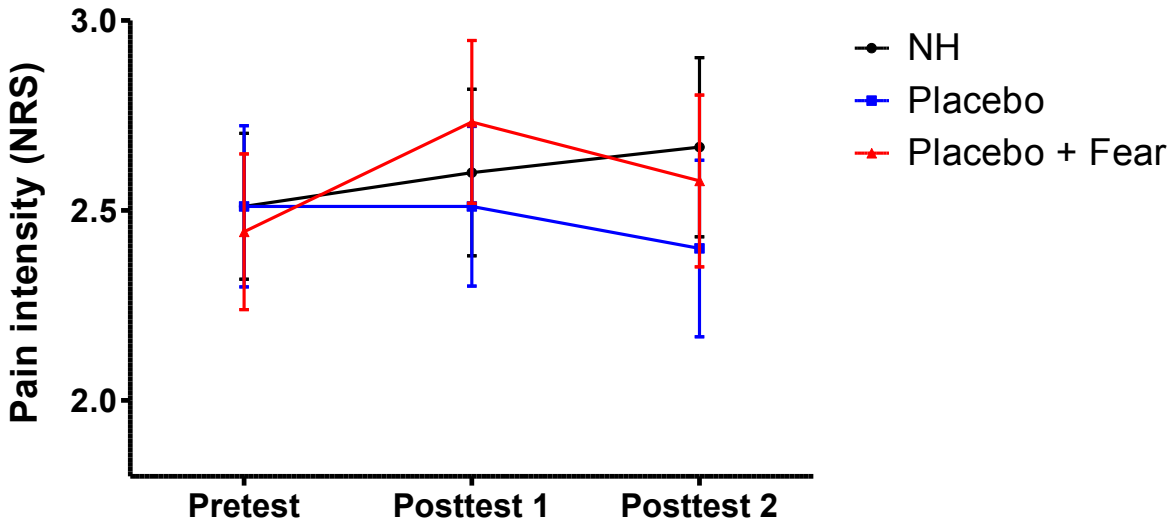

Figure 3: Condition x test on pain intensity. Vertical bars denote 1 standard error of the mean.

Pain unpleasantness

There was a significant interaction of condition and order sequence (F (10, 132) = 2.00, p = .047). No significant effect was found in the follow-up tests. No other significant effects were found in the pain unpleasantness data.

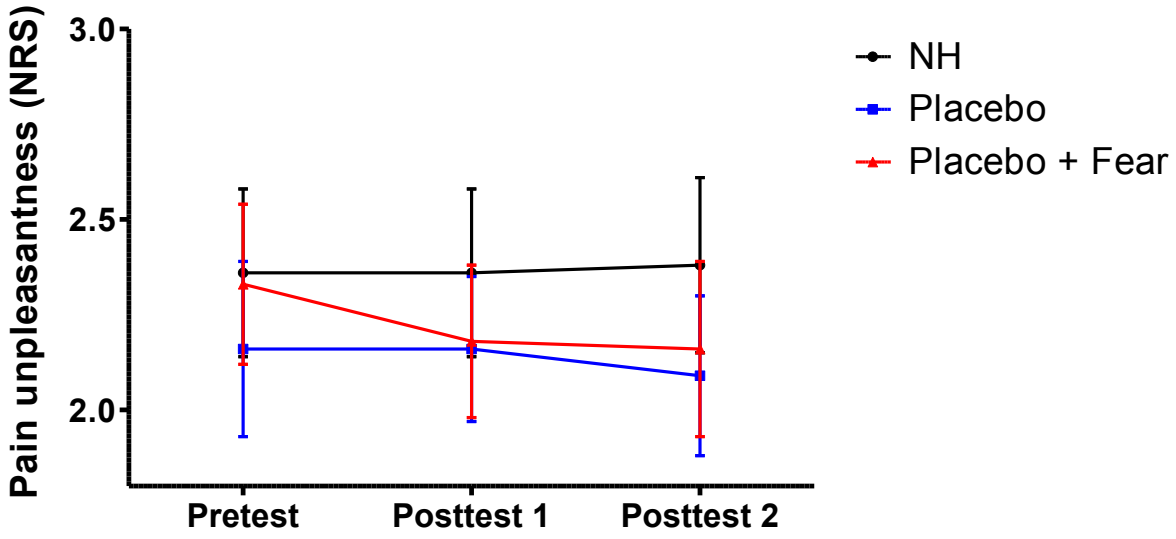

Figure 4: Condition x test on pain unpleasantness. Vertical bars denote 1 standard error of mean

Subjective stress

A main effect of condition (F(2,44) = 3.59, p = .03) was due to significantly lower stress in the placebo condition compared to the natural history condition (p = .02). An interaction of condition and order sequence (F (10,44) = 3.06, p = .003) was also found. There was no significant effect in the follow-up tests.

Furthermore, a main effect of test (F (2,44) = 9.93, p = .00), that was due to significantly decrease in stress level from the pretest to posttest 1 (F (12,44) = 2.75, p = .01), and from posttest 1 to posttest 2 (F (12,44) = 2.43, p = .02) in the placebo condition was found. In the placebo+fear condition there was a significant stress level increase from the pretest to posttest 1 (F (12,44) = 2.42, p = .02).

The participants experienced significantly higher stress level on the first day of testing, regardless of condition (F (2,88) = 15.18, p = .00). There was no difference in stress level between the second and the third day of testing.

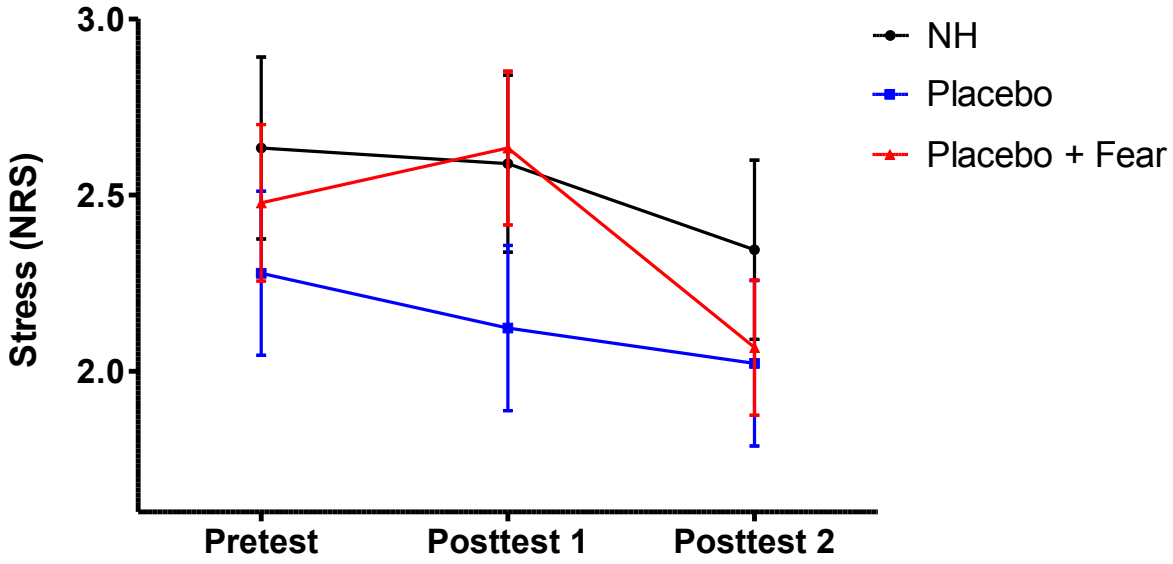

Figure 5: Condition x test on subjective stress. Vertical bars denot 1 standard error of mean.

Fear of pain, pain intensity/pain unpleasantness and stress in the natural history condition

A correlation between pain intensity and fear of medical pain (r^2 = .33, p = .03), and pain intensity and fear of total pain (r^2 = .37, p = .01) was found. Pain unpleasantness was also shown to correlate with fear of medical pain (r^2 = .30, p = .05) and fear of total pain (r^2 = .31, p = .04).

Subjective stress level in the natural history was shown to correlate with fear of minor pain (r^2 = .32, p = .03), fear of severe pain (r^2 = .38, p = .01) and fear of total pain (r^2 = .43, p = .00).

Startle reflex

A main effect of condition (F (2,44) = 4.32, p = .017) was due to a significantly lower startle reflex response in the placebo condition compared to the natural history (p = .013) and to a significantly higher startle reflex response in the placebo+fear condition compared to the placebo condition (p = .04).

There was a significant interaction of condition and test (F (4,132 = 2.96, p = .02). There were no differences between the conditions in the pre-tests. Follow-up test showed a difference between pretest and posttest 1 (p =.002), and between pretest and posttest 2 (p =.05) in the placebo+fear condition. There was also a difference between posttest 2 in the placebo condition and the placebo+fear condition (p =.01).

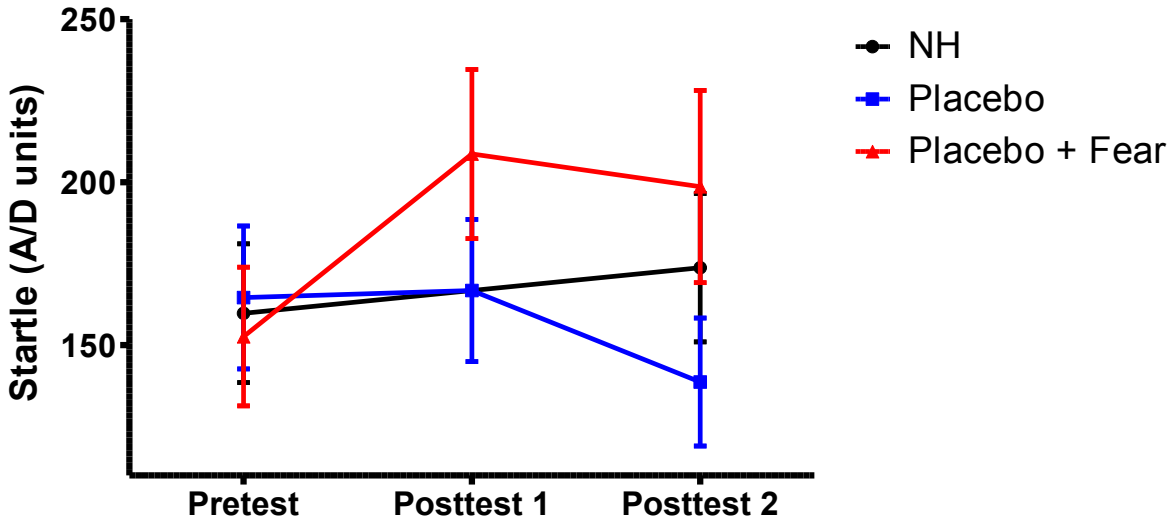

Figure 6: Condition x test on startle reflex. Post-test 1 in the natural history condition is measured at the same time as post-test 2 in the placebo condition and the placebo+fear condition. Vertical bars denote 1 standard error of mean.

Placebo responders on pain intensity and pain unpleasantness

There was no placebo effect at the level of the entire sample in the pain intensity and unpleasantness data. Therefore, to investigate the effect of fear of pain on placebo analgesic responding, further analyses were performed on the participants who responded with a reduction in pain after the placebo administration. Similar procedures have been used by e.g., Wager et al. (2006). 18 participants in the study experienced pain relief after the placebo administration (8 females and 10 males).

There was an interaction of condition and test on pain intensity ($F(4, 68) = 9.297$, $p = .00$). Follow-up tests were performed to confirm a difference between the conditions. A significant difference between the natural history condition and the placebo condition in the pre-tests ($t = -2.608$, $p = .02$) were found, and between the natural history condition and the placebo condition in posttest 2 ($t = 2.878$, $p = .01$).

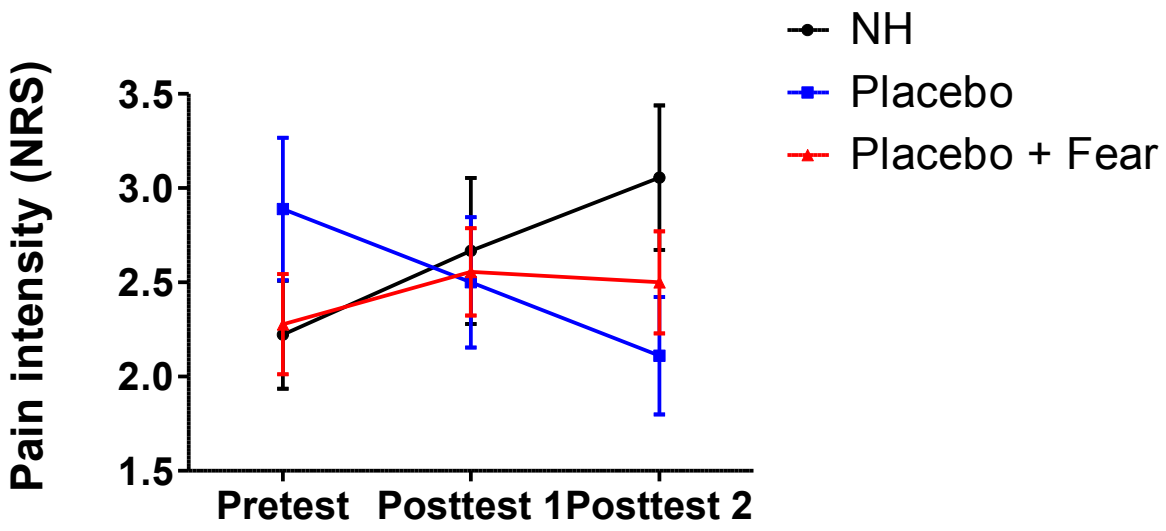

Figure 7: Condition x test. Pain intensity levels for the placebo responders. Vertical bars denote 1 standard error of mean.

There was also an interaction of condition and test on pain unpleasantness ($F(4,68) = 3.091$, $p = .03$). Follow-up test showed a difference between the natural history condition and the placebo condition in posttest 2 ($t = 3.220$, $p = .01$)

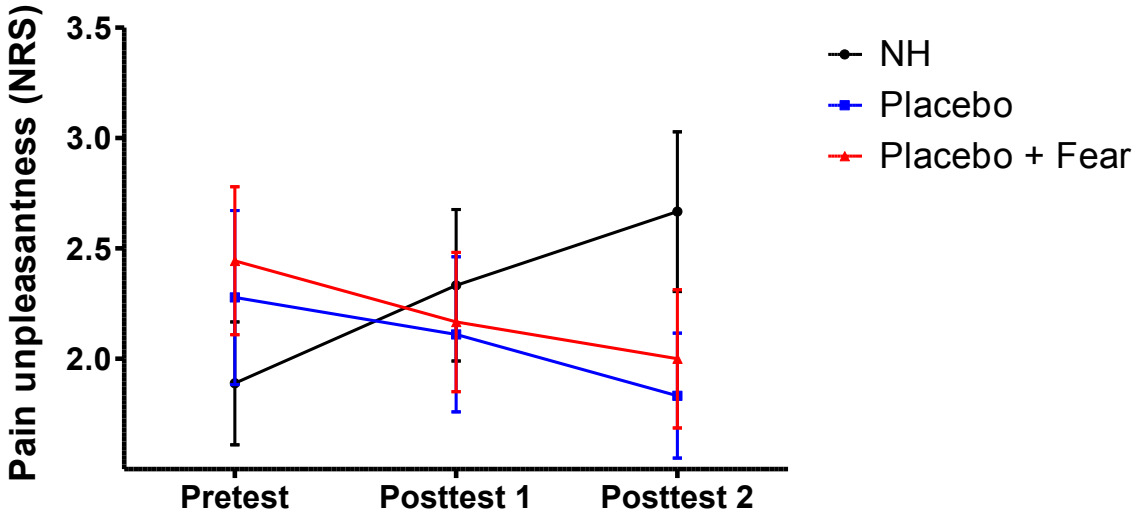

Figure 8: Condition x test. Pain unpleasantness levels for the placebo responders. Vertical bars denote 1 standard error of mean.

Regression analyses with placebo response on pain intensity and pain unpleasantness as dependent variables were performed. Gender, order sequence, baseline subjective stress in the placebo condition, baseline startle in the placebo condition, fear of pain, and placebo response on subjective stress, were included as predictors. Placebo response on stress predicted placebo response on pain unpleasantness ($\beta = .665$, $t = 2.559$, $p = .03$), but not on pain intensity.

Table 2: Multiple regression analysis predicting pain intensity and pain unpleasantness on the placebo responders.

Dependent variable	Predictor variables	R^2	β	t	p
Pain intensity	*Model 1*	.199		-.407	.692
	Gender		-.212	-.699	.499
	Condition sequence	.	.014	.044	.965
	Baseline stress, placebo condition		-353	-1.143	.277
	Baseline startle reflex, placebo condition		.005	.019	.985
	Response stress		.351	1.164	.269
	Fear of pain		-.017	-.055	.957
Pain unpleasantness	*Model 1*	.438		.946	.365
	Gender		.115	.454	.659
	Condition sequence		-.141	-.542	.598
	Baseline stress, placebo condition		-.367	-1.416	.184
	Baseline startle reflex, placebo condition		-.367	.263	.798
	Response stress		.665	2.559	.027
	Fear of pain		-.309	-1.204	.254

Discussion

The present study investigated whether experimentally induced fear of pain would reduce placebo analgesia. Lyby, et al. (2010) found a negative correlation between fear of pain and placebo analgesia.

Placebo effect on pain intensity and pain unpleasantness

A placebo effect on pain intensity and pain unpleasantness was not observed in the present study. However, the participants did not experience the heat stimulations as sufficiently painful, and this may be one factor as to why a placebo effect was not observed. Earlier studies (e.g. Granovsky, 2005) did use CHEPS as stimulator consistent with the present study, but higher pain levels was observed with a lower temperature (51° C). Granovsky et al. (2005) observed a mean pain intensity at of 3.30 (measured on VAS), compared to 2.55 (54°C) in the present study. It is possible for a placebo effect may occur with a mean VAS of 2.55, but as other researchers have pointed out it is difficult to measure a placebo effect if the overall pain intensity is not considered painful enough by the participants (Wager, et al., 2006). As a consequence, many placebo researchers use calibration procedures to make sure that the temperature is individually calibrated to a level 5 on the VAS, where it is more likely for a placebo response to occur. Such a calibration procedure was a part of the current study design.

The importance of sufficient pain intensity in placebo studies was demonstrated in a study by Vase, Robinson, Verne, & Price (2003) where one of the highest placebo effect sizes ever, was reported. The sample included 13 patients with irritable bowel syndrome (IBS) who reported mean pain intensity level at 5.5 (VAS) at baseline. Desire for pain relief was also measured, and was shown to account for a large portion in placebo analgesia. The conclusion was that motivation for pain relief must be considered as an important explanatory factor in placebo analgesic response. This has later been verified in a study on placebo analgesia using advanced methods (PET) to monitor μ-receptor availability after placebo administration (Zubieta, et al., 2006). In the present study pain threshold was defined as 1 on VAS, 5 as moderately painful and 10 as unbearably painful. One could argue that the reported pain intensity and pain unpleasantness was overall not high enough for our participants to cause a sufficient degree of desire for pain relief, thus making it less likely to observe a placebo effect on group level.

An alternative explanation for not observing a placebo effect on subjective pain levels might have been that the placebo procedure was too weak. In the present study verbal suggestion was used to induce expectations of pain relief. It is well established that greater placebo effects are obtained by verbal suggestions combined with a conditioning procedure, e.g. lowering the temperature of the stimuli after the administration of placebos in the manipulation trials (Benedetti, et al., 2003; Montgomery & Kirsch, 1997). However, in earlier placebo studies conducted in our lab, placebo effects on reported pain intensity and pain unpleasantness have been observed using only the expectancy paradigms (e.g. Lyby, et al., 2010; Aslaksen & Flaten, 2008; Flaten et al., 2006).

Placebo effect on subjective stress

The stress level decreases across tests in the natural history and the placebo condition. A placebo effect on stress was, however, not found. The decreased stress level reflects reduced impact of the stimulations and reduced stress over time in the experiment.

Placebo effect and order of sequence

An interaction effect of condition and order sequence was found in pain intensity, pain unpleasantness and subjective stress. The follow-up tests did not reveal a significant difference in pain intensity or pain unpleasantness across the study. However, visual inspection of scatter plot indicate that the participants that received the placebo condition on the first day of testing were more likely not to experience a decreased pain level after placebo treatment. This is consistent with Lyby et al. (2010) who found a greater placebo effect on the second day of testing compared to the first day.

The participants in the present study experienced the highest amount of stress on the first day of testing compared to the second and the third day regardless of condition sequence. This is a common methodological problem in placebo studies using within subjects design with testing on different days (e.g Lyby, et al., 2010; Price, 1999). Stress has been linked to release of CCK, which has been shown to have an antiopioid effect. CCK is the neurochemical mediator of nocebo hyperalgesia (Benedetti, et al., 2006) and CCK-antagonist proglimude have shown to boost placebo analgesia. Moreover, several new placebo studies show that higher stress levels are interfering with placebo response (Scott, et al., 2008; Zubieta, et al., 2006). A possible solution to this problem would be to include a familiarization day in the procedure for preliminary testing to familiarize the participants to

the stimuli and the laboratory. There was no difference in stress level between the second and the third day of testing.

Fear of pain, pain intensity/pain unpleasantness, and stress in natural history

It is well documented that emotions can modulate the experience of pain (e.g. Benedetti, 1996; Lang, Bradley, & Cuthbert, 1990; Cuthbert et al., 2003). In the present study, fear of total pain and fear of medical pain was shown to correlate with pain intensity and pain unpleasantness in the natural history condition. This is consistent with Lyby et al. (2010) who found that fear of medical pain predicted pain intensity and pain unpleasantness. Experimental studies investigating fear of pain on pain perceptions in healthy voluntaries are uncommon, but there are a few studies that support the findings in the present study (e.g George, Dannecker, & Robinson, 2006). George et al. (2006) investigated the validity of the fear-avoidance model of exaggerated pain, using among other the fear of pain questionnaire to consider the influence of fear of pain on pain perception. The participants underwent a cold-pressor procedure, and pain tolerance and pain intensity were measured. The findings demonstrated that pain intensity at both threshold and tolerance were significantly predicted by fear of pain.

An association between fear of pain and stress in the natural history condition was found in the present study. A positive relation between stress and fear of minor pain, stress and fear of severe pain and between stress and fear of total pain was found. A positive relation between fear of medical pain and stress has earlier been detected (Bradley, et al., 2008; Lyby, et al., 2010).

Placebo effect on the startle reflex

A placebo effect on startle reflex was observed in the placebo condition compared to the natural history condition. In line with Lang, et al. (1990) a lower startle reflex was expected in the placebo condition compared to the natural history condition. The present study confirmed this. After the placebo administration the participants responded with a lower startle reflex compared to before the administration (i.e. placebo effect). A placebo effect on startle reflex has not been observed in earlier studies. This implies that a reduction in negative emotional state can be considered as yet another supplement to placebo studies showing the importance of stress reduction as a mediator of placebo analgesic response (Aslaksen & Flaten, 2008).

The placebo effect observed in the placebo condition did not remain significant in the placebo+fear condition. Bradley et al. (2008) showed that individuals with substantial fear of dental pain responded with a larger blink reflex and heightened autonomic responses in context of threat of electric shocks, compared to individuals low in fear of dental pain. Electric shocks were used as threat in the present study as well, and thus a potentiated startle reflex after the fear of pain manipulation was expected. In line with Bradley et al. (2008) a greatly potentiated startle reflex was observed after the fear of pain induction compared to when the same reflex was elicited in the context of no threat. A defensive reactivity persisted even after the threat period was over, preventing the occurrence of a placebo effect.

Placebo responders

Hoffman et al., (2005) pointed out that in placebo studies there will always be both responders and non-responders. Eighteen of the 45 participants in the study experienced a decrease in pain after the placebo treatment (8 females and 10 males), and to be able to test our hypothesis the analysis were performed again on the group of placebo responders. A placebo effect on pain intensity and pain unpleasantness was found (figure 7 and 8). There was a significant difference between the pretests in the natural history condition and the placebo condition. A plausible explanation for this might be that the order sequence of conditions for the eighteen placebo responders was not balanced compared to the total sample. However, no differences between the pretests in the placebo condition and the placebo+fear condition were detected. The placebo responders did not experience a placebo effect in the placebo+fear condition. It was reduced to a non-significant level, indicating that the fear of pain manipulation influenced the placebo effect.

The next step was to investigate whether fear of pain predicted placebo analgesia and reduced stress level, respectively, as reported in Lyby et al., (2010). Regression analysis did not confirm a significant relation between fear of pain and stress. Reduced stress level was, however, confirmed to predict placebo analgesia. These findings supplement Aslaksen & Flaten (2008) who found that placebo analgesic response was associated with a decrease in stress.

Limitations of the present study

Restriction of range

Restriction of range is defined as the greater the variability in the distribution, the greater the opportunity for correlation coefficients or significant interactions to appear (Sedlacek & Hutchins, 1966). This will of course affect the results in the present study when using correlational methods i.e. regression analysis when investigating whether fear of pain predicted reduced stress level. The mean pain level on pain intensity and pain unpleasantness (table 1) in the conditions collapsed together were 2.55 (SE 1.35) and 2.24 (SE 1.34), respectively.

Double-blinding

The placebo medication administrated was capsules containing lactose. Two of the participants received capsules containing 75 mg paracetamol. In order to blind the experimenters to which substance they administrated, the experimenters were informed that 25% of the capsules contained analgesics. In order to improve the procedure and improving the experimenter's credibility when giving placebo manipulation, the experimenters should have received information about a 50/50% chance of distributing placebo or analgesic medication should have been given.

Reporting bias

The role of social context has been associated with reporting bias in placebo studies (Kirsch, 1999). The participants reporting behavior may have been affected if they realized that the experimenters expected a specific reaction. Aslaksen, Myrbakk, Høifødt, & Flaten (2007) concluded that psychosocial factors and social context in the lab could affect the reliability and validity of the pain report, especially when there is a male participant and a female experimenter. Psychophysiological recordings are included in placebo studies to include objective measures of pain and emotion, e.g. startle reflex.

Summary and conclusion

On group level no placebo effect on reported pain intensity, pain unpleasantness and stress was found. The hypothesis that fear of pain reduces a placebo intervention on pain, could not be tested without placebo respondents. Therefore, only the participants that did

report decreased pain levels in the placebo condition compared to the natural history condition were tested (n = 18). The placebo effect was reduced in the placebo+fear condition. This might have been due to an increase in stress after the induction of fear of pain, preventing a placebo response on pain to occur. However, fear of pain was not found to be related to placebo analgesia in the present study. This is not consistent with the findings in Lyby et al., (2010).

In the startle reflex data a placebo effect on group level (n = 45) was found. A significantly lower startle reflex was observed in the placebo condition compared to the natural history condition. The present study is, is to the author`s best knowledge, the first to register a placebo effect on startle reflex. In the placebo+fear condition a significantly potentiated startle reflex were observed immediately after the induction of fear of pain. The potentiated startle reflex level remained throughout the experiment, preventing a response on the placebo treatment.

An indication that experimentally induced fear of pain reduces a placebo intervention on pain was found in the present study. The startle reflex data did confirm this hypothesis on the biological level. The subjective data, however, was not equally conclusive, and a relation between fear of pain and placebo analgesia was not found on the entire sample. A possible explanation for the inconclusive subjective data might be restriction of range.

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Appendix A

Informed consent

FORESPØRSEL OM Å DELTA I FORSKNINGSPROSJEKT OVER BEHANDLING AV SMERTE

Eksperimentet undersøker effektene av eksperimentelt induserte negative emosjoner og medikamentell smertebehandling på subjektiv smerteopplevelse og smerteprosessering i hjernen målt ved elektroencephalografi (EEG). I tillegg undersøkes smertefrykt som måles ved spørreskjema. Eksperimentet gjennomføres ved at deltakerne gjennomfører smertetester samtidig som fysiologiske og subjektive reaksjoner måles. Smertetestene foretas i form av varme på en liten flate av huden på armene. Dette er relativt smertefullt, men stimuli er helt ufarlige og gir ingen ettervirkninger utover at huden på armen kan bli rød i opptil to dager etter eksperimentet. Legemiddelet er ufarlig i den dosen som gis i dette eksperimentet. EEG målinger foretas ved overflateelektroder festet på huden og hodebunnen, og medfører ikke ubehag utover at hodebunnen må vaskes etter hver gjennomføring av forsøket. Subjektive målinger foretas ved et kortfattet spørreskjema. Eksperimentet gjennomføres over tre dager med minimum to dagers mellomrom. Total varighet på eksperimentet vil være ca fire timer.

Vi søker etter forsøkspersoner av begge kjønn mellom 19 og 40 år. De som deltar må ha god helse og ikke ha eller ha hatt alvorlige sykdommer, ikke ha allergi mot legemiddel, og heller ikke bruke reseptbelagte legemiddel, med unntak av p-piller. Personer med høyt blodtrykk kan ikke delta. Kvinner som deltar skal ikke ha menstruasjon den dagen forsøket pågår, da dette kan endre nivået til visse hormon. Den som deltar må ha vært avholdende fra nikotin- og koffeinholdige substanser i minst tre timer før forsøket begynner. Dette forsøket er godkjent av Regional Komité for Medisinsk Forskningsetikk, Nord-Norge, og meldt til Personverneombodet for Forsking, Norsk Samfunnsvitskaplig Datatjeneste AS. Alle deltakerne er dekket av produktansvarsloven og av særskilt forsikring, så sant det foreligger adekvat årsakssammenheng mellom legemiddel og forsøksprosedyre, og eventuell skade. Det vil til en hver tid være personale tilstede som kan stoppe forsøket dersom deltakeren føler ubehag, eller av andre grunner ønsker å avbryte forsøket. Deltakelse i eksperimentet er frivillig, og forsøkspersonen kan når som helst avbryte forsøket uten å måtte gi noen grunn til dette. Deltakere som ønsker å avbryte forsøket kan kreve å få innsamlede data slettet. Resultatene fra eksperimentet vil ikke ha noen personlig nytte for deltakerne, men kan gi innsikt i hvordan et eksperiment gjennomføres. Resultatene lagres med en kode som igjen viser til en atskilt navneliste. Resultatene vil bli statistisk analysert og publisert på en slik måte at den enkelte deltaker ikke kan identifiseres. Datainnsamlingen avsluttes desember 2009 og da vil datamaterialet anonymiseres ved at navnelisten slettes. Dersom du ønsker

rapport fra prosjektets resultater, ber vi deg skrive din adresse på slutten av dette arket. Rapport vil bli tilsendt etter at prosjektet er avsluttet.
Forsøket foregår ved Institutt for psykologi, Teorifagsbygget, Hus 5, plan 3, rom 5.387. Hver person mottar et gavekort på kr 500,- for deltakelse i eksperimentet. Gavekortet kan brukes i de fleste forretninger i Tromsø sentrum.
Dersom du er villig til å delta i eksperimentet må du gi ditt skriftlige samtykke (neste side) i henhold til beskrivelsen gitt ovenfor.

For avtale om tidspunkt for deltakelse eller nærmere informasjon om forsøket: Kontakt stipendiat Peter S. Lyby på peterl@psyk.uit.no eller masterstudent June Thorvaldsen june.thorvaldsen@gmail.com

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

Rapport
Jeg ønsker å få tilsendt rapport over resultatene fra dette prosjektet:

Adresse: Postnummer: epost:

Appendix B

Personal data

PERSONALIA: **Dato/Eksperimentator:**

Forsøksperson nummer:

Lagret på software:

Kjønn:

Alder:

Studie:

Betingelse dag 1:

Betingelse dag 2:

Betingelse dag 3:

Nikotin/Koffein dag 1:

Nikotin/Koffein dag 2:

Nikotin/Koffein dag 3:

Deltatt i liknende studier før, hvis ja – hvilke?

Mobil/Klokke:

Samtykke levert:

Gavekort levert:

Appendix C

Previous experiences with OTC medications

Vi ønsker å vite hvordan dine tidligere erfaringer med <u>reseptfrie</u> smertedempende medikamenter har vært. Marker på tallrekken under hvor god <u>smertedemping</u> du har opplevd fra slike medikamenter:

Ingen smertedempede effekt.	Noe smertedempende effekt.	Middels smertedempende effekt.	God smertedempende effekt.	Svært god smertedempende effekt
1	**2**	**3**	**4**	**5**

Appendix D

The Short Adjective Check List (SACL) and Numerical Rating Scale (NRS)

REGISTRERING AV SMERTE, STRESS OG AKTIVERING

FP#:	FP. KJØNN:	EKSP. NAVN	DATO:	BETINGELSE

Si til FP: ”På en skala fra 0 til 10, der 0 er helt avslappet og 10 er maksimalt anspent, hvor avslappet eller anspent føler du deg”

”På en skala fra 0 til 10 der 0 her veldig søvnig og 10 er helt våken, hvor søvnig eller våken føler du deg”

”På en skala frå 0 til 10, der 0 er helt rolig og 10 er veldig nervøs, hvor rolig eller nervøs føler du deg”

”På en skala frå 0 til 10, der 0 er veldig trett og 10 er veldig energisk, hvor trett eller energisk føler du deg”

For smerte:

”På en skala fra 0 til 10, der 1 er smerteterskel og der 10 er uutholdelig smerte, hvor smertefull er varmen nå.

”På en skala frå 0 til 10, der 1 ikke er noe ubehag ved varmen og der 10 er maksimalt ubehag, hvor ubehagelig er varmen nå”.

FØR BASELINE EEG

INDIKÈR MED TALL MELLOM 0 OG 10:

AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

FØR SMERTESTIMULERING PRETEST

INDIKÈR MED TALL MELLOM 0 OG 10:

AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

PRETEST SMERTE: SPØR ETTER 20 STIMULI.

SMERTE-INTENSITET	SMERTE-UBEHAG	AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

ETTER MEDIKAMENT/HVILEPERIODE

AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

POSTTEST 1: SPØR ETTER 20 STIMULI

SMERTE-INTENSITET	SMERTE-UBEHAG	AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

ETTER HVILEPERIODE 2

AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

POSTTEST 2: SPØR ETTER 20 STIMULI

SMERTE-INTENSITET	SMERTE-UBEHAG	AVSLAPPA-ANSPENT	SØVNIG-VÅKEN	ROLIG-NERVØS	TRETT-ENERGISK

Appendix E

Visual Analogue Scale (VAS)

FP nr: _____

Test: _____

Marker med en strek på kryss av linjen under hvordan du vil rangere <u>STØYEN</u> på en skala fra "Ubehagelig" til "Behagelig":

Ubehagelig **Nøytral** **Behagelig**

Appendix F

Experienced medication effect

Hvordan opplevde du den <u>smertedempende</u> virkningen av medikamentet du fikk under dette forsøket? Marker på tallrekken under hvor god <u>smertedemping</u> du opplevde etter å ha fått medikamentet:

Ingen smertedempende effekt.	Noe smertedempende effekt.	Middels smertedempende effekt.	God smertedempende effekt.	Svært god smertedempende effekt.
1	**2**	**3**	**4**	**5**

Appendix G

Experienced induction of fear of pain

Hvordan opplevde du virkningen av prosedyren for induksjon av negative emosjoner? Marker på tallrekken under hvor effektfull prosedyren var:

Ingen effekt.	Noe effekt.	Middels effekt.	God effekt.	Svært god effekt.
1	**2**	**3**	**4**	**5**

Appendix H

Fear of Pain Questionnaire – III

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**	**Ekstremt**	
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 foten 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**	**Ekstremt**	
1	**2**	**3**	**4**	**5**	16. Få et objekt som sitter fast i øyet ditt fjernet av en lege
1	**2**	**3**	**4**	**5**	17. Få en injeksjon med en sprøyte i armen
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	**2**	**3**	**4**	**5**	21. Få en vorte på foten fjernet av en lege med et skarpt instrument
1	**2**	**3**	**4**	**5**	22. Kutte deg med en skarp barberhøvel når du barberer deg
1	**2**	**3**	**4**	**5**	23. Svelge en varm drikk før den er avkjølt
1	**2**	**3**	**4**	**5**	24. Få sterk såpe i øynene mens du dusjer eller bader
1	**2**	**3**	**4**	**5**	25. Få en dødelig sykdom som gir deg daglig 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