

**PAIN AND PLACEBO ANALGESIA: THE ROLES
OF EMOTIONS AND GENDER**

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Everything should be made as simple as possible, but not simpler.
-Albert Einstein

It is easier to find men who will volunteer to die, than to find those
who are willing to endure pain with patience.
-Julius Caesar

(Thanks to all those who volunteered for the experiments that made this
thesis possible)

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LIST OF RESEARCH REPORTS

Report I:

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Report II:

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Report III:

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ABSTRACT

Placebo analgesia refers to the finding that pain is reduced after administration of a placebo that the patient or volunteer expects to reduce the pain. Expectation is considered a cognitive process, since it is closely related to the concepts of belief, learning, and memory. Placebo analgesia is also considered a psychophysiological process, as the expectation of pain relief leads to biological reactions that mediate the placebo analgesic response. Some researchers have suggested that the mechanisms underlying placebo analgesia involve emotional processes. The hypothesis proposed here is that administration of medication said to be an effective painkiller should reduce negative emotions, and these processes should mediate the placebo analgesic response.

This thesis describes three experiments that investigated the role of emotional modulation of, and gender effects in, pain and placebo analgesia. The aim of Report I was to test whether negative emotions, cortisol and circulating β -endorphin decreased after placebo administration. Expectancy was manipulated by providing positive versus neutral information about capsules administered prior to the pain stimulus. Emotions were manipulated by providing information about the effects of the pain stimuli versus no information about the pain stimulus. The results showed that positive information about the drug and information about the pain stimulus decreased pain, but only in male participants. Reduced pain after placebo administration was not related to negative emotions, cortisol or circulating β -endorphins. The conclusion from Report I was that reduction of negative emotions is not necessary to observe placebo analgesia. However, this finding was not termed conclusive, as placebo administration was performed before the pain stimulus was applied. Thus, initial levels of negative emotions were probably too low to observe decreases after placebo administration. Furthermore, all the experimenters were females, a factor

that might have biased the pain report in male participants since previous studies have shown that males report lower pain to female experimenters.

In Report II, the finding that male participants reported lower pain to female experimenters was further investigated. The experiment investigated whether males that report lower pain to female experimenters at the same time displayed less autonomic activation during pain. Six experimenters, three females and three males collected data. Heat pain (+48C°) was induced to the forearm through an aluminum thermode. Autonomic measures consisted of heart rate variability (HRV) and skin conductance levels. The results showed that male subjects reported lower pain intensity and arousal to female experimenters compared to male experimenters. However, there were no similar interactions in the physiological data, suggesting that the lowered pain report in male subjects reporting to female experimenters was due to a psychosocial reporting bias.

In Report III, the methodological shortcomings of Report I were adjusted and the hypothesis that reduction of negative emotions is a mechanism in the placebo analgesic response was further investigated. In a within-subjects design, subjects were tested on two separate days, one day for the placebo condition and one day for the natural history condition. Pain was induced by a thermode holding +46C°. Cardiac autonomic activation was measured by HRV. Eight experimenters, four females and four males collected data. Placebo was administered during the second of a total of four pain stimulations. The results showed a significant placebo effect on pain intensity and a concomitant reduction in stress and autonomic cardiac activity. Regression analyses revealed that subjective stress was the only predictor for the placebo response. Contrary to expectation, male subjects displayed higher placebo analgesia when a male acted as experimenter.

In sum, reduction of stress and autonomic arousal is concomitant with the placebo analgesic response. However, placebo analgesia can be observed without reduction of negative emotions if initial levels of negative emotions are low. Thus, reduction of stress seems to be one of several mechanisms in placebo analgesia. The finding that male subjects reported lower pain to female experimenters in Report II was probably due to a psychosocial reporting bias. However, the gender of the experimenter seems to be unrelated to placebo analgesia, given the divergent findings in Report I and III.

INTRODUCTION

In recent years, considerable progress has been made in the understanding of the placebo effect, and the majority of this knowledge arises from the study of placebo analgesia. Placebo analgesia is the reduction of pain after information that a painkiller has been administered, even if an inactive agent has been provided to the individual (Benedetti 1996; Levine and Gordon, 1984). Thus, placebo effects are beneficial effects of the treatment that are not caused by the biological action of the treatment, but by the individual's response to stimuli that signal that effective treatment has been administered. The study of the placebo response is most evident in pain research, even if robust placebo responses have been observed in other conditions such as depression, Parkinson's disease, alcoholism, gastro-intestinal disorders, cardiovascular disorders, asthma, and anxiety disorders. According to Hoffman et al. (2005), there are at least three reasons that pain is the most studied research area for the placebo response. First, in clinical studies, placebo induced pain reduction is the best verified instance of this general response. Second, experimental pain studies offer opportunities for stringent methodological research. Third, brain imaging studies have offered better insight into the neural mechanisms that underlie placebo analgesia compared to other placebo responses.

The magnitude of placebo analgesia is highly variable and dependent on contextual factors (Price et al., 2008), and some researchers question whether the placebo analgesic effect is clinically relevant (Hróbjartsson and Gøtzsche, 2001). It has been suggested that the placebo effect might be a result of spontaneous remission, regression to the mean (Fields and Levine, 1984) and other possible confounding variables such as demand characteristics (Hróbjartsson and Gøtzsche, 2001). However, meta-analyses have shown that the placebo effect is a true phenomenon in clinical trials (e.g. Vase et al., 2002) and several studies of the biological mechanisms of the placebo effect show that placebos have impact on biological systems (Colloca

and Benedetti, 2005). Due to the fact that clinical trials employ placebo administration as a control condition, it is reasonable to expect that placebo effects are smaller in clinical trials than in experimental studies designed to test hypotheses about the mechanisms of the placebo response (Price et al., 2008).

Placebo analgesic responses can be induced by verbal information that a painkiller has been administered, but placebo responses can also be induced by non-verbal signals that effective treatment has been provided, e.g. the ingestion of a tablet or capsule that has previously been associated with pain relief. Hence, both expectation and classical conditioning are viewed as major explanatory mechanisms for placebo analgesia.

The expectations about pain differ from other sensory expectancies by their affective component. The most widely used definition of pain is the one formulated by The International Association for the study of Pain; “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 1979). This definition states that pain has two core components, both a sensory and an emotional component. Thus, placebo treatment for pain may affect cognitive expectancies about whether stimuli are worthy of attention, and emotional expectancies about personal harm (Wager, 2005). It is, therefore, reasonable to assume that placebo analgesia involves emotional modulation as well as cognitive interpretations. If a person in pain receives information that a treatment that reduces the pain is administered, the expectation of reduced pain should reduce stress and negative emotions as well – and the decrease in negative emotions are parts of the placebo analgesic response. The reports in the present thesis investigate whether reduction of negative emotions are among the mechanisms in placebo analgesia.

BACKGROUND

Conditioning and expectancy

Placebo responses have been construed as arising from classical conditioning or from the individual's expectancy of a particular drug response. The classical conditioning theory states that the effects of drugs are unconditioned stimuli (US), and neutral stimuli reliably associated with the ingestion of a drug, e.g. its' taste and smell, can become conditioned stimuli (CS) (Ader, 1997). Such conditioned stimuli can elicit responses that are similar to or, under some conditions, opposite to the drug response (e.g. Ramsay and Woods, 1997). The association between the context in which the treatment takes place and the treatment that is being provided can be conditioned consciously through the expectation that the CS signals the presence or non-presence of the US (Rescorla, 1988; Benedetti et al., 2003).

The expectancy theory, on the other hand, states that placebo responses are mediated via an expectancy of a particular drug response (Montgomery and Kirsch, 1997). When information is provided to the individual that a particular drug has been administered, the expectancy of a specific drug-generated response can be induced, and this "response expectancy" can, in turn, generate a physiological and psychological response mimicking the drug response. In this view, expectancies are ongoing predictions about the potential threat and emotional value of the upcoming stimuli, and expectancies are linked to the situational context which includes prior experience with pain, drugs, and beliefs about the treatment (Kirsch, 1985). The information carried in expectancies may be integrated with incoming sensory input to shape subjective pain and emotion. This integration is, however, based on the fact that expectancies must be maintained in memory until the predicted sensory events occur (Wager, 2005).

It has been argued that conditioned placebo responses are mediated via expectancy (Montgomery and Kirsch, 1997). The few direct tests performed so far have provided mixed results. Montgomery and Kirsch (1997) cannot be considered a test of whether conditioned responses are mediated via

expectancy, since they applied the placebo (i.e. the conditioned stimulus) only once, which is probably sub-optimal for conditioning to occur. Price et al. (1999), in a conditioning study on placebo analgesia, found support for the expectancy theory, whereas Klinger et al. (2007) displayed results suggesting that both conditioning and expectancy were equally involved as mechanisms in the placebo response. However, the placebo response generated via conditioning showed longer lasting effects than placebo induced via expectancy. The available evidence suggests that expectancy induced by verbal information about treatment effects can generate placebo responses. The evidence further suggests that placebo responses can be generated by pharmacological conditioning without mediation of conscious expectancy (e.g. Benedetti et al., 1999; 2003). Benedetti et al. (2003) showed that placebo analgesia induced via conditioning could be completely reversed by verbal information, lending support to the expectancy theory. However, also in Benedetti et al. (2003), administration of the serotonin agonist sumatriptan was paired with a conditioned stimulus. The unconditioned effects of sumatriptan is to decrease cortisol and increase growth hormone. When the conditioned stimulus was applied alone, after being paired with sumatriptan, decreased cortisol and increased growth hormone could be seen, and these conditioned responses were not modified by instruction.

Thus, the results so far indicate that both expectancy and conditioning seem to be viable and independent explanations of placebo effects, but the role played by each mechanism could apply to different response systems. Expectancy could play a role in conscious processes like pain, whereas conditioning could have a role in unconscious regulation of e.g. hormonal secretion. The controversies over the relative roles of expectancy and conditioning have clearly shed light over the mechanisms in the placebo effect, however, there is reason to believe that there might be interacting effects between conditioning and expectancy that are at play, but yet poorly investigated. One such example could be possible interactions between expectancies created by verbal suggestion and expectancies generated from non-verbal environmental cues (Hoffman et al., 2005).

Biological basis of the placebo analgesic response

It is now established, beyond reasonable doubt, that placebo analgesia is partly mediated via endogenous opioids, since the opioid antagonist naloxone partly reverses the placebo response (Benedetti 1996; Levine and Gordon 1984; Grevert et al. 1983). Endogenous opioids, or endorphins, consist of at least three sub-classes: β -endorphin, the enkephalins, and the dynorphins. There are also different classes of endorphin receptors, the μ , δ , κ , ϵ , and σ receptors. The μ and δ receptors are involved in supraspinally mediated analgesia.

β -endorphin is an agonist, and naloxone acts as an antagonist at both the μ and δ receptors, but the affinity of β -endorphin and naloxone is stronger to the μ compared to the δ receptor. Interestingly, morphine is an agonist at the μ but considerably less so at the δ receptor. This line of reasoning suggests the involvement of β -endorphin and the μ -receptor in placebo analgesia.

The endogenous opioids act centrally to decrease pain impulses, since placebo analgesia can be specific to the site where, e.g., a placebo cream has been administered, and the placebo response cannot be observed at other sites where the cream was not applied (Benedetti et al. 1999; Montgomery and Kirsch, 1996). Moreover, circulating beta-endorphin was not related to placebo analgesia in three studies (Johansen, Brox and Flaten, 2003; Roelofs et al. 2000; Flaten et al., 2006).

It has been suggested that the circuitry underlying placebo analgesia is the same circuitry that modulates pain in animals (Fields and Price, 1997). The best studied of these systems is the periaqueductal gray (PAG) in the brainstem, with projections to an area in the ventral medulla. Injections of morphine-like substances in these areas produce analgesia, most likely because of inhibitory descending pathways to the spinal cord that inhibit transmission of pain signals. Electrical stimulation of the PAG or ventral medulla has the same effect. Thus, it is suggested that endogenous opioids activate the PAG or ventral medulla, causing inhibition of pain signals from the periphery

(Fields and Price, 1997). This view has been supported in imaging studies that shows that the PAG is activated during the anticipation phase after placebo administration (Wager et al., 2004; Liberman et al., 2004), suggesting that release of endogenous opioids might be activated prior the placebo response. Further evidence to support the role of endogenous opioids in placebo analgesia comes from studies of the endogenous peptide cholecystokinin (CCK) and a CCK-antagonist, proglumide (Benedetti et al., 1995; 1996). The CCK is simultaneously released with endogenous opioids and antagonizes their analgesic effects while proglumide enhances the opioid effect (Hoffman et al., 2005). Thus, the pharmacological basis of the placebo analgesic response might be a function of the balance between endogenous opioids and endogenous CCK.

Studies using positron emission tomography (PET) have found that the same brain regions are affected by both placebo and opioid antagonists, indicating that the mechanisms of placebo analgesia and opioid induced analgesia are to some extent similar (Petrovic et al., 2002). Furthermore, Wager et al. (2004), employing functional magnetic resonance imaging (fMRI), found that placebos decreased nociceptive signals along the pain pathways and in the thalamus, anterior insula and the caudal part of the rostral anterior cingulate cortex, regions that are central in pain processing in the brain and that have a high number of opioid receptors (Zubieta et al., 2001; 2003; Willoch et al., 2004). Moreover, these brain regions are termed the affective pain network (Wager, 2005), as they are closely linked to the subjective feeling of pain (Craig et al., 2000). In sum, neuroimaging studies of placebo analgesia have shown that psychological mediators of placebo analgesia are related to brain structures involved in emotional regulation (Price et al., 2008).

An important question is whether placebo administration alters nociceptive input, or if it only affects the judgment and evaluation of pain. Several studies have shown that placebo has an effect on cognitive processing of pain (e.g. Wager et al., 2004), but few have investigated if placebos have a suppressing effect on nociceptive processing prior to subjective evaluation, thereby showing that

placebo has an active psychobiological effect on pain transmission. Wager et al. (2006) and Watson et al. (2007) tested this hypothesis with laser evoked pain potentials and both studies found that early nociceptive signals were modulated by placebo information. These findings provide evidence that placebo analgesia is due to reduced pain transmission to the brain, which is consistent with the idea that expectations and conditioned stimuli generate activity in pain-inhibitory descending pathways.

Emotions and placebo analgesia

The majority of studies investigating the mechanisms in placebo analgesia have focused on the impact of expectation and conditioning, and there is little debate that these factors are important psychological factors in placebo analgesia. However, it is unlikely that expectation and conditioning are the only factors that are responsible for the placebo effect on pain given the close relationship between pain and emotions.

It has been proposed that reduction of negative emotions could be an important factor in experimental placebo analgesia (Price, 1999; Vase et al., 2003; 2005), and in clinical practice it is common to observe that anxiety increases pain experience (Tracey and Mantyh, 2007). Several studies have shown that negative emotions increase pain perception (Rhudy and Meagher, 2000; 2003; Keogh and Cochrane, 2002), although this may be dependent on the intensity of emotional arousal. In most studies investigating the impact of emotions on pain perception, emotions have typically been produced by films (Zillmann, et al., 1996), affective pictures (Meagher et al., 2001) and odours (Villemure et al., 2003), that were independent of the pain stimulus used to assess pain sensitivity (Rainville et al., 2005). Price (1999) proposed that pain related emotions are triggered by the immediate unpleasantness of pain as a function of the context and the cognitive interpretation of the meaning of pain and the anticipation of future consequences of the pain experience. Thus, according to Price (1999), pain related negative emotions should increase

concomitant with stimulus intensity, a prediction that has been supported in several studies (Flaten et al., 2003; 2006; Johansen et al., 2003). Pain itself is a potent stressor (Johansen et al., 2003), and high levels of negative affect and arousal from pain stimulation may activate the endogenous opioid system (Rhudy and Meagher, 2001). Thus, the relationship between emotional activation and pain can be described as an inverted U, where pain is perceived highest with moderate negative emotions and lowest with positive and highly negative emotions. According to Rhudy and Meagher (2001), negative emotions of low to moderate intensity may increase attention towards and amplify pain via neural circuits in the amygdala and PAG that also modulate startle responses. As in pure pain studies, attention could possibly also play a role in placebo analgesia. It is possible that administration of placebo induces an affective or motivational state that reduces the attention towards the painful stimuli. The motivational state that regulates attention can be partly under conscious control, and the effects of placebo serve as a safety signal and permit attention to be directed to other stimuli than pain (Wager et al., 2006). Consequently, attention may be conceived as a mediator of emotion effects rather than a confounding factor.

Studies by Vase et al. (2003; 2005) have shown that placebo analgesic responses may partially be mediated by reductions in anxiety levels. Similar results have also been obtained in pain studies, where subjects reporting higher levels of anxiety report increased pain compared to subjects scoring lower on anxiety measures (McGlashan et al., 1969; Staats et al., 2001). The reduction in anxiety levels, as observed in Vase et al's (2003; 2005) studies, was closely related to expectations, however less clear than the relation between pain ratings and expectations of treatment effect on pain. As shown above, reduced negative affect is associated with decreased pain, and it can be predicted that if information about a painkiller reduces stress and negative emotions, then pain should be reduced as well. However, Vase et al's (2003; 2005) findings

suggest that anxiety is just one of many possible emotional states that may modulate the placebo analgesic effect. This view is also supported in pain studies by Rhudy and Meagher (2001; 2003) where subjects react with various emotional feelings, ranging from fear to surprise under noxious stimulation. The latter notion fits well with results from neurobiological placebo studies that find activation of distinct, but overlapping networks involved in processing of sensory and affective aspects of nociceptive stimuli (Wager et al., 2004; Kong et al., 2006; Craggs et al., 2007), implying that a broad specter of emotions could be important for the placebo analgesic response. Petrovic et al. (2005) found that subjects with large placebo responses displayed decreases in neuronal activity in the emotional networks of the cortex, suggesting that placebo effects are strongly linked to neuronal emotional modulation.

In studies where patients were asked to rate their expected pain levels and their desire for pain relief (Vase et al., 2003; Verne et al., 2003), the results displayed that both factors independently, and the interaction between desire and expectation, explained about 40 % of the variance in pain intensity. In the studies by Vase et al. (2003) and Verne et al. (2003), anxiety levels were reduced after placebo administration, a finding that was supported in a later study by Vase et al. (2005). The findings from the studies by Vase et al. (2003; 2005) and Verne et al. (2003), that support the desire-expectation model proposed by Price and Barrell (1985; 2000), suggest a clear connection between placebo analgesia and emotional factors. A possible problem in studies like Vase et al. (2003; 2005) and Verne et al. (2005), where participants rate their expectation and emotional state before the experimental procedure, is the possibility that these ratings may be viewed as a sort of social contract (Wager, 2005). Thus, the reporting of expectations and emotions prior to the pain procedure may establish a norm and a commitment which shapes the later self reports during pain.

In contrast to findings that suggest that emotional modulation is important in placebo analgesia, Flaten et al. (2006) found that placebo analgesia might be observed without a concomitant reduction of negative emotions. This could especially be true when initial levels of negative emotions are too low to observe a decrease after placebo administration. Vase et al. (2003; 2005) suggested that the mechanism of emotional modulation in placebo analgesia has an effect on the sympathetic nervous system. This is plausible since several studies have established that pain sensations increase sympathetic activity as measured by skin conductance (Rhudy and Meagher 2003) and heart rate variability (Rainville et al., 2005). Pollo et al. (2003) tested the hypothesis that placebo analgesia is accompanied by modulations in the cardiovascular system by measuring heart rate variability. The results from Pollo et al. (2003) showed that the low frequency cardiac responses were decreased during placebo analgesia, suggesting that reduction of cardiac autonomic arousal is a part of placebo analgesia.

The hypothesis put forth in the present thesis is that, for a person experiencing pain, administration of a treatment together with information that it is a potent painkiller should reduce negative emotions and concomitant autonomic arousal, thereby decreasing pain sensation.

Gender effects in pain and placebo analgesia

There is general agreement that there are differences between females and males in perception and experience of pain (Berkley, 1997; Fillingim, 2000; Arendt-Nilsen, 2004). Females experience more pain related symptoms in greater frequency and in more bodily areas across the lifespan than males (Unruh, 1996). In the study of sex and gender differences there are terminological differences that are relevant; the term “sex” refers to biologically based differences, while the term “gender” refers to socially based phenomena (Greenspan et al., 2007). Thus, differences between females and males can be attributed to multiple factors, from genes

and reproductive hormones to socio-cultural and environmental factors. Findings from neuroimaging studies also indicate that there might be sex differences in cortical activation during pain stimulation (Paulson et al., 1998; Zubieta et al., 2002). In experimental studies, there are several findings showing that females have significantly lower pain thresholds and lower pain tolerance and rate equally intense stimuli as more painful than males do (e.g. Edwards et al., 1999; Fillingim, 1999). The sex differences in pain perception are also reflected in psychosocial attitudes towards societal gender roles; In general, gender roles refers to a society's widely assumed set of characteristics for each gender and may compromise beliefs regarding appropriate pain behaviors (Kállai et al., 2004).

Robinson et al. (2001) found evidence of stereotypical masculine and feminine pain behaviors and that members of both sexes believe that males are less sensitive to pain than women. Such gender role expectations have been found to significantly predict pain threshold, pain tolerance and pain unpleasantness (Wise et al., 2002). Moreover, several studies indicate that gender role expectations also influence pain report (Levine and De Simone, 1991; Robinson and Wise, 2003; Sanford et al., 2002). The stereotypical male role in western societies characterizes men as stoic and intending to impress women with their ability to withstand pain, while the female role expects women to exhibit increased sensitivity in order to evoke protective behavior in men (Levine and De Simone, 1991).

The main finding of gender role effects on pain report in western societies is that male subjects report lower pain to female experimenters compared to male experimenters (Levine and De Simone, 1991; Kállai et al., 2004; Aslaksen et al., 2007), while the results regarding females that report to male experimenters are mixed. A possible explanation for the lack of consensus on female subjects' pain report to male experimenters could be that gender roles are in change, at least in western societies. Aslaksen et al. (2007) tested whether the previous findings of gender

effects in pain reports could be explained by changes in autonomic parameters. The results showed the expected pattern, with male subjects reporting lower pain to female experimenters. However, the lower pain report in males could not be explained by autonomic factors, and it was therefore concluded that the effect of experimenter gender on pain reports probably was psychosocial. In studies where subjective pain reports are used, the possible interaction between experimenter and subject gender could threaten the reliability and the validity of the results, and it has been recommended (Greenspan et al., 2007) that the sex of the experimenter should be reported in scientific pain studies.

Given the robust findings in pain studies that males are less sensitive to pain than females, are there gender and sex differences in placebo analgesia?

Studies of post-operative pain have revealed that females experience more severe post-operative pain and require more morphine than men to achieve similar degree of pain relief (Cepeda and Carr, 2003; Aubrun et al., 2005). This might be explained to some degree by a decrease in μ -opioid receptor availability and suppression of endogenous opioid responses to pain during low oestrogen states (Zubieta et al., 2002; Smith et al., 2006). Placebo analgesia is, at least partly, mediated by endogenous opioids, and it is therefore likely to expect that there are gender differences in placebo analgesic responses due to differences in opioid responsiveness. In a review of studies on opioid analgesia (Craft, 2003) it was suggested that agonists which act preferentially at μ -receptors are more powerful in male rodents than females, but act in the opposite direction in humans. However, possible sex and gender differences in placebo analgesia are sparse in the literature (Klosterhalfen and Enck, 2008), and it is one of the present thesis goals to explore this issue further.

GENERAL RESEARCH QUESTIONS

The major concern in the work underlying the present thesis was to investigate the effect of emotional modulation as a mechanism in placebo analgesia. This approach is meant to be supplemental to the explanations of placebo analgesia as a phenomenon that arises from expectation and/or conditioning. During the time of the experimental work, the issue of psychosocial effects that affect the placebo response and pain report in the laboratory has been another major research question, and the impact of subject and experimenter gender on these variables have been included.

The following is a list of the main research questions addressed in the present thesis:

- 1) Is reduction of negative emotions a mechanism in the placebo analgesic response?
- 2) Is placebo analgesia dependent on the gender of the subject and the gender of the person obtaining the pain report?
- 3) Is the experimenter effect on pain reports mediated by autonomic factors?

Previous research on placebo analgesia allows formulation of this relatively simple model (Fig. 1), with the inclusion of emotional factors as possible mediators for placebo analgesia.

Fig. 1

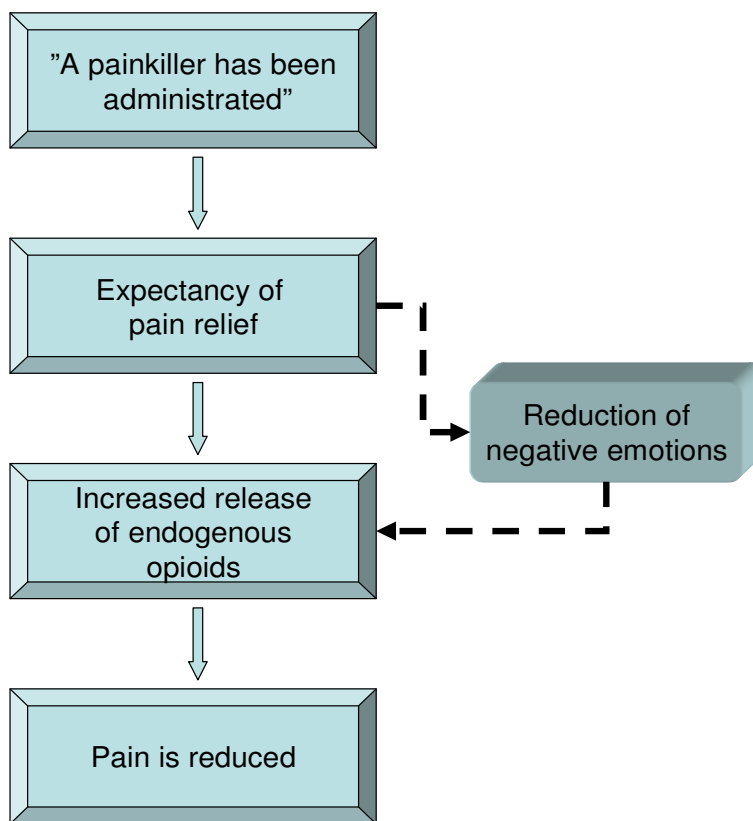


Figure 1. Model of elicitation of placebo analgesia that the present series of experiments aim to test. The new element in this model (dashed lines), relative to previous studies on placebo analgesia, is the inclusion of emotional factors thought to mediate the effects of expectancies on physiological processes related to pain modulation.

METHODS

Pain stimuli

One of the most common methods to study the nociceptive system and placebo responses in pain are noxious heat stimuli (Julius and Basbaum, 2001; Baumgartner et al., 2005). These systems, often based on the Peltier technique, activate nociceptive-specific transduction mechanisms in the nervous system. The most common way to transfer heat is via an aluminum thermode attached to the skin, which also is the main pain inducing method employed in this thesis (Reports II and III). Conductive heating allows computer control over the temperature at the stimulator-tissue interface, which make precise stimulations possible. A potentially confounding factor could be variations in the pressure between the thermode and the skin that make differences in conduction, and thereby heat transfer (Baumgartner et al., 2005). Another possible drawback of the conductive heat systems, due to slow temperature rise, is concomitant stimulation of low-threshold mechanoreceptors. Despite these shortcomings, pain induction through computer controlled conductive heat is seen as a reliable method to safely induce experimental pain in humans. Another relatively common method to induce pain is the submaximum effort tourniquet technique (Smith et al., 1966), which was used in Report I (Flaten et al., 2006). The tourniquet technique induces pain by lack of oxygen in muscle tissue due to inflation of a sphygmomanometer cuff and an esmarch bandage that is placed the arm of the subject (Smith et al., 1966; Benedetti, 1996; Flaten et al., 2006). Firstly, the blood is drained through an esmarch bandage, then the sphygmomanometer cuff is inflated to a certain level to stop the blood flow to the arm, and then the subject uses a hand exerciser to create ischemia. This ischemic pain is increasing as long as the cuff is applied, and this type of pain is known to mimic several types of clinical pain states (Johansen et al., 2003).

Measures of subjective pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, 1979). This definition implies that pain has both a sensory and an emotional component, and it is therefore necessary to measure both. In most studies, the sensory component is termed intensity and the emotional component is termed unpleasantness.

The visual analog scale (VAS) and the numerical rating scale (NRS) are the most common methods to assess subjective levels of pain (Price et al., 1983; Farrar et al., 2001; Rosier et al., 2002). The VAS has been shown to be more sensitive to small differences in perceived pain intensity and unpleasantness than scales with verbal descriptors of the pain sensation (Rosier et al., 2002). In study II and III, we employed pen-and-paper VAS for pain intensity and pain unpleasantness. The anchoring of the intensity scale was “no pain” and “unbearable pain” written under the left and right ends of the scale, respectively. The anchoring for the pain unpleasantness scale was “no unpleasantness” and – “unbearable unpleasantness”. The difference between pain intensity and pain unpleasantness was explained according to Price et al. (1983) in report II and III.

In study I, an 11-point NRS was used, mainly due to the fact that the subjects were attached to the sphygmomanometer cuff on one arm and had an indwelled veneflon on the other.

Emotional measures

Subjective stress and arousal were measured by four adjective pairs from the Short Adjective Check List (SACL) (Mackay et al., 1978) in Norwegian translation in all the experiments in the present thesis. The items from the SACL were chosen for their high factor

loadings on the stress and arousal factors on the SACL (e.g., O'Neill & Parrott, 1992; Parrot, 1995). The four adjective pairs taken from SACL were tensed – relaxed (stress), nervous – calm (stress), energetic – tired (arousal) and awake – sleepy (arousal). Previous studies have shown that stress and arousal measured by the SACL are separate dimensions (e.g. Surawy and Cox, 1987), and this conclusion is supported by factor analytic studies where stress and arousal emerged as orthogonal factors (Mackay et al., 1978). Arousal was also measured by the nine-point version of the Self-Assessment Manikin (SAM) arousal scale (Lang, 1980; Bradley and Lang, 1994) in Report II. Mood was measured by the nine-point version of the SAM (Lang, 1980; Bradley and Lang, 1994) in Report II and III. Both SAM scales had Norwegian instructions. The SAM scales are validated with the International Affective Picture System (IAPS; Lang, Öhman, and Vaitl, 1988) and are widely used to measure emotional valence (mood) and arousal in experimental settings (Bradley and Lang, 1994).

Physiological measures

Physiological arousal of emotions was measured by skin conductance levels and heart rate variability in Report II and III. Report I employed measurement of cortisol and circulating β -endorphin. Cortisol is known to be released under stress, and plasma cortisol is found to be elevated during pain (Johansen et al. 2003). The amount of circulating β -endorphins was in Report I assumed to be a possible indicator of physiological pain level, as the release of β -endorphin is known to increase as the pain increases (Flaten et al., 2006).

Heart rate variability is a reliable method to measure the contribution of autonomic control on cardiac function (Tousignant-Laflamme and Marchand 2006), and when accurately measured, it can be employed as an indicator of sympatho-vagal balance. High frequency heart rate (0.15-0.4 Hz) is largely attributable to variations in parasympathetic control of the heart

function (Berntson et al., 1997), while low frequency (0.04 – 0.15 Hz) reflects mainly the baroreflex-dependent sympathetic cardiac activity (Pomeranz et al., 1985), but also elements of parasympathetic activity (Akselrod et al., 1985). Malliani et al. (1991) recommended the use of the ratio of LF and HF instead of using the absolute value of either, a notion that was supported by Friedman and Thayer (1998), at least for physiological and psychological states that are known to be associated with increased sympathetic and decreased vagal activity. Experimental studies have shown that acute pain increases sympathetic activity (Rhudy and Meagher, 2003; Rhudy et al., 2004; Terkelsen et al., 2005; Rainville et al., 2005), and we employed the ratio of low frequent to high frequent activity as a measure of sympatho-vagal balance in Report II and III. In addition to heart rate variability, skin conductance levels were used in Report II. Skin conductance is a pure measure of sympathetic arousal as the sweat glands in the hands are innervated exclusively by the sympathetic branch, and previous studies have shown that pain stimulation increases skin conductance levels (e.g. Rhudy and Meagher 2003).

SUMMARY OF RESEARCH REPORTS

Report I (Flaten MA, Aslaksen PM, Finset A, Simonsen T, Johansen O. Cognitive and Emotional factors in placebo analgesia. Journal of Psychosomatic Research, 2006; 61:81-89.)

The aim of this study was to test whether the effect of expectancy on pain is mediated via reduction of negative emotions. First, we investigated whether the administration of a placebo reduced negative emotions. Second, we tested whether positive information about the drug produced higher pain relief than neutral information. Expectancy was manipulated by informing one group that the provided drug was a potent painkiller (Positive information), whereas one other group got information that that the drug would have only minor effect on pain (Neutral information). In addition, information about the effects of the pain stimulation (Tourniquet) was manipulated by informing half of the participants about the physiological effects of the pain stimulus, and the other half received no information about the pain stimulus. The experiment was run at the University Hospital of North Norway, and all the experimenters in this study were female nurses employed at the Department of Clinical Research.

Both male and female subjects were assigned in the study. The design of the study was a 2 Drug Information X 2 Pain Information X 2 Gender between-subjects design. All of the subjects received 500mg of acetaminophen, a dose that should not have any significant effects on pain given the relatively painful stimulus. Pain intensity, pain unpleasantness, stress and arousal were measured by numerical rating scales, ranging from 0 to 10. Physiological stress was measured by plasma cortisol. The tourniquet was applied for a maximum of 45 minutes or until the subjects reported 10 on the numerical rating scales on pain intensity or pain unpleasantness. In addition,

plasma levels of β -endorphin were measured to test whether circulating β -endorphin might have analgesic effects.

If the placebo response was mediated by a reduction in negative emotions, we expected that the group receiving positive information about the drug would display lower pain and lower levels of negative emotions compared to the group receiving neutral information about the drug. If information about the pain stimulus reduced negative emotions induced by the pain stimulation, then this information should also reduce pain.

The results showed that male subjects in the neutral information/no pain information group had lower pain tolerance compared to the other groups. There were no reductions in stress, arousal, β -endorphin or cortisol levels after information that a painkiller was administered. Thus, placebo administration did not decrease negative emotions in the present design. Information about the effects of the pain stimulus and information that a painkiller was administered decreased pain intensity, but only in male subjects.

The results from Report I cannot be termed conclusive about the possible effects of reduced negative emotions in placebo analgesia. Firstly, the placebo was administered prior to the application of the tourniquet. Thus, the initial levels of negative emotions might have been too low to observe a reduction in emotional parameters. Second, the experimenters had knowledge of which condition the participants were allocated to, that could have changed the experimenters' behavior toward the subjects. Thirdly, the pain inducing method employed produced an increasing pain due to ischemia as long as the tourniquet was applied, this could have caused difficulties in detecting a reduction in negative emotions, since the pain and stress were increasing as long the pain stimulus was applied. There was no effect of circulating β -endorphin on pain or emotions, and this finding is in line with previous studies (Johansen et al., 2003) that suggest that β -endorphin only has an analgesic effect in the central nervous system.

The finding that only males showed a placebo response raised interesting novel questions, as there have been few earlier attempts to explore possible gender differences in placebo analgesia (Klosterhalfen and Enck, 2008). Previous studies (Levine and De Simone, 1991; Kállai et al., 2004) have shown that male subjects report lower pain to female experimenters compared to when testing is done by male experimenters, and the findings on gender effects in Report I fits nicely with former studies. However, placebo analgesia was seen in males only after positive information, whereas pain scores after neutral information and no pain information was similar in male and female subjects. Thus, there was no main effect of gender, implying that the mere presence of a female was not the crucial factor.

Report II (Aslaksen PM, Myrbakk IN, Høifødt R, Flaten MA. The effect of experimenter gender on autonomic and subjective responses to pain stimuli. Pain, 2007; 129:260-68.)

In this study, we followed up the results from Report I on the experimenter effect on pain report. The aim of the study was to test whether previous observations (Levine and De Simone, 1991; Kállai et al., 2004, Flaten et al., 2006) of male subjects reporting lower pain to female experimenters have a physiological basis. More precisely, it was tested whether male subjects that report lower pain to female experimenters also display less autonomic activation during pain stimulation. Autonomic measures were heart rate variability and skin conductance levels. The design employed was a 2 subject gender X 2 experimenter gender X 15 pain tests mixed design. Six experimenters, three females and three males collected data. All experimenters were psychology students of the master or clinical program with the exception of one male that was a Ph.D student in psychology. Heat pain (+48C°) to the forearm was delivered through a contact

thermode via the computer controlled TSA II system. The duration of the stimuli were 12 seconds at +48C°. Pain intensity, pain unpleasantness, stress and arousal were measured on 10 point VAS scales. Mood was measured by the nine point Self-Assessment Manikin Mood scale (Lang, 1980, Bradley and Lang, 1994). The experimenters collected pain and emotional measurements at four occasions during pain testing.

The results showed that male subjects reported lower pain intensity to female experimenters, compared to male subjects that reported to male experimenters. Female subjects, on the other hand, reported the same level of pain intensity to both male and female experimenters. The subjective arousal data displayed a significant interaction between experimenter and subject gender, male subjects reported lower arousal when tested by female experimenters. Thus, the effect of experimenter gender was found for other variables than pain. The physiological data did not display the same interactions as the subjective data, that is, the lower pain and arousal reports in male subjects was not due to sympatho-vagal changes induced by the female experimenters. A limitation in Report II was that three minute period of R-R interval measurement, is in the lower area to obtain a reliable estimate of HRV. These findings gives partially support to the traditional gender role expectations where males are expected to report less pain and affect in the presence of a female. However, female subjects did not report higher pain to male experimenters as could be expected from the traditional gender role expectations. The studies that shows the impact of experimenter gender on pain report (Levine and De Simone, 1991; Kállai et al, 2004; Aslaksen et al., 2007) raises important methodological issues in pain research where subjective pain report is a central measure. Other studies have shown that different environmental factors, such as experimenter status (Kállai et al, 2004) or race (Weisse et al., 2005) also contribute to variance in pain report, and if these variables are not controlled, there may be threats to the reliability and the validity of pain research.

Report III (Aslaksen PM, Flaten MA. The relation of stress to placebo analgesia. Psychosomatic Medicine, In Press).

Flaten et al. (2006) tested the hypothesis that placebo analgesia is dependent on reduction of negative emotions. In that study, there was not found evidence that emotional modulation was necessary to observe placebo analgesia. However, the Flaten et al. (2006) study had methodological shortcomings that reduced the opportunity to be conclusive about the role of emotional effects in the placebo analgesic response. These shortcomings were identified and improved in Report III. The experiment in Report III was designed to capture reductions in negative emotions by employing a within subjects design, where subjects participated on two separate days, one day for the placebo condition and one day for the natural history control condition. To avoid a possible floor effect on emotional measures, as could have affected the results in Flaten et al. (2006), the placebo was administered during the second pain test. This would also be comparable to a clinical situation where uses of painkillers are motivated by the experienced pain. In report III, the experimenters were unaware of which condition the subjects were allocated to before the experiment started to avoid differences in the experimenters' behavior before the experimental procedure started (Gracely et al., 1985). In addition, the finding in Flaten et al. (2006) where only males reported a placebo effect was followed up by employing experimenters of both genders to test whether placebo analgesia may be modulated by gender interactions in the lab. Pain and subjective emotions were measured with the same methods as in Report II. Pain induction was performed with the TSA II. The duration of the stimuli was 240 seconds (+46C°) each, and subjective measures were performed after 180 seconds duration of the stimuli. Physiological responses to pain stimulation were measured by heart rate variability. Epoch sizes for heart rate variability were 180 seconds, to avoid that the interaction between the

experimenters and the participants during measurement of pain and emotions should affect the HRV measures.

The results showed that pain intensity and stress were decreased in the placebo condition compared to the natural history condition. Administration of placebo lowered the sympathetic component of cardiovascular activity (lowered LF/HF ratio), an effect that lasted until after the second post test. There were no placebo effects on mood or arousal. Analysis of predictors of the placebo effect on pain intensity revealed that subjective stress was the only direct predictor. In a control regression analysis, to test whether stress was decreased as a function of lowered pain, the results showed that pain reduction was not a significant predictor for the placebo effect on stress. Thus, lowered pain could not explain the observed stress reduction. In the analysis of predictors of stress, we found that improved mood and reduced cardiac sympathetic activity predicted the stress scores. The analysis of the effect of experimenter gender on placebo analgesia showed that male subjects tested by male experimenters reported a higher placebo effect than male subjects reporting to female experimenters. In the overall pain data, when the pain intensity ratings from both conditions were combined, male subjects tested by female experimenters reported lower pain compared to male subjects reporting to female experimenters.

The results from Report III suggested that modulation of stress is probably an important variable in placebo analgesia, at least when stress levels are high enough to observe a decrease. The HRV data showed a decrease in the LF/HF ratio after placebo administration. This effect lasted until the second post-test, after that point, the ratio increased

DISCUSSION

The conclusions from Report I and III suggests that placebo analgesia can be observed under various levels of initial emotional activation. In Report I, the information and administration of the placebo medication were given prior to the pain stimulation, at a time where emotional levels were low. Thus, as the results from Report I suggest, the desire to experience pain relief is probably not crucial to create an expectation of pain relief and thereby observe placebo analgesia. However, it could be argued that the timing of the placebo administration in Report I was not optimal to mimic a clinical setting where a patient seeks treatment for a painful symptom. In Report III, the timing of the placebo administration was changed to a point where subjects experienced both stress and arousal due to the pain stimulation. That timing made it possible to measure the reduction in emotional activation after placebo administration, and the results showed that the reduction in stress predicted the placebo response. Furthermore, the regression analyses displayed that the reduction in pain was not responsible for the decrease in stress, as could be argued since when pain is reduced, so is the stress levels.

The only emotional measure that was significantly related to the placebo response was stress. A possible explanation is that the measure of stress employed in the present thesis measure some core elements of negative affect. This notion is supported by a factor analytic study investigating the factor structure of the SACL (Mackay et al., 1978), where the adjectives measuring stress displayed the highest factor loadings on the negative affect factor. The other emotional measures that were employed were arousal and mood, and it is possible that these measures are less likely to be affected by placebo administration in a painful setting, that is, even if the pain decreases, it is still perceived as painful as shown by the pain ratings in Report III. However, in Report III, stress was significantly predicted by changes in the mood scale, showing a relation between the emotional measures employed. It could be argued that the subjective

emotional measures that were employed in the present thesis are somewhat restricted. Other similar studies have used more specific emotional measures as anxiety (Vase et al., 2003; 2005; Verne et al., 2003) to investigate the impact of emotional modulation in placebo analgesia. The measures that were employed in the present thesis are thought to be sensitive to changes in basic emotional states, and less sensitive to psychological traits, as a measure of anxiety could possibly be. However, the emotional measures employed in the present thesis are widely used and validated as measures of stress, arousal and emotional valence in emotional studies (Mackay et al., 1978; Parrott, 1993; Bradley and Lang, 1994; Backs et al., 2005; Åsli and Flaten, 2008). The divergent results concerning effects of emotional modulation in Report I and III supports the notion that there is not one single placebo effect, even for the placebo effect on pain (Colloca and Benedetti, 2005). Nevertheless, in both reports induced expectation of pain relief was shown to affect pain sensations, even if the context of the experimental procedure and the administration of placebo differed.

Report II and III relied on the ratio of low-frequency to high frequency heart rate variability (LF/HF) as a measure of sympathovagal balance, and it was assumed that an increase in this ratio should be related to an increase in sympathetic cardiac activity. It has previously been argued that the LF/HF ratio is a less precise marker of sympathetic cardiac control (Berntson et al., 1997) due to the fact that the LF activity to some extent also is modulated by parasympathetic activity. However, both Terkelsen et al. (2005) and Rainville et al. (2005) have shown that acute pain stimulation increases the LF component and decreases the HF component, and the results from the present thesis are in line with those studies. Theoretically, it is plausible that a stressor like pain stimulation should increase the sympathetic cardiac activity, given the findings that pain increases skin conductance levels, which is a clean measure of autonomic sympathetic activity (Rhudy and Meagher, 2003; Rhudy et al., 2004). Moreover, Pollo et al. (2003) found a decrease

in the cardiac LF activity after placebo administration, supporting the results from Report III regarding decreased sympathetic cardiac activity in placebo analgesia. There are, however, two possible interpretations of the reduced LF/HF ratio in Report III. First, the reduced pain itself could be the mechanism behind the reduction in LF activity. Second, endogenous opioids that were activated after placebo administration could have a direct inhibitory effect in the cardiovascular system (Pollo et al., 2003). The regression analyses in Report III showed that reductions in the LF/HF ratio was not a predictor for the placebo effect on pain, lending support to the possibility that endogenous opioids could have decreased the sympathetic component of cardiac activity. The effects of endogenous opioids are, however, known to be complex, and future research should investigate possible effects on emotional modulation created by release of endogenous opioids.

In sum, the measures in Report III of subjective stress and sympathetic cardiac activity points to the conclusion that perceived stress and concomitant autonomic arousal decreases after placebo administration. This finding showing emotional modulation in the placebo response could possibly be important for conditions other than pain. For instance, the knowledge that expectancies of positive treatment outcome reduce negative emotions could be important in treatment and caregiver-patient interactions in conditions that are known to have elements of negative emotions attached.

The conclusions in Report I and II regarding the effect of gender interactions could possibly have several implications for designs in pain studies. Firstly and mainly, the results show that experimental pain reports are dependent on the social context in the lab, and future studies should report and control these factors. At least, the possible error variance induced by the interaction between experimenter and subject gender should be kept under experimental control. Secondly, measurements of physiological effects of pain stimulation that allow objective

measurement of pain perception should be included in experimental studies in addition to subjective measures. Furthermore, the results from Report II suggests that also other feelings that are reported to an experimenter of the opposite gender might be biased, a finding that could be important for studies of other processes than pain and placebo. An important question is whether the findings of psychosocial influence on pain reports in experimental studies can be true for clinical situations. Obviously, the motivation to report pain to an experimenter differs from report to a health care professional, and future studies should test whether the findings from laboratory studies can be found in clinical settings. However, in a study performed in a pain clinic (Weisse et al., 2005), it was shown that psychosocial factors such as employment status and race affected pain report in patients.

The results in Report I suggested that there might be interactions between experimenter and subject gender on pain reports in placebo analgesia since only male subjects displayed a significant placebo response and that all the experimenters were females. However, the results in Report III did not support the hypothesis that placebo analgesia is larger in male subjects reporting pain to female experimenters. Nonetheless, when the pain scores in both the placebo and the natural history conditions were collapsed, the previous findings (Levine and De Simone, 1991; Kallai et al., 2004; Aslaksen et al., 2007) that male subjects' reports lower pain to female experimenters were supported. The divergent results regarding experimenter effects in placebo analgesia (Report I and III), suggests that factors other than the gender of the experimenter is important for placebo analgesia. It is a common observation that the magnitude of placebo analgesia shows large variability (Price et al., 2008), and further research could focus on individual differences that contributes to variability in placebo responses.

OVERALL CONCLUSIONS

The main findings in the present thesis can be summed up as follows:

- (i) Reduction of stress is found to be concomitant with the placebo analgesic response. This is supported by the finding that autonomic activation is decreased after placebo administration (Report III). However, placebo analgesia can be observed in the absence of reduced negative emotions if initial levels of negative emotions are sufficient low (Report I).
- (ii) Placebo analgesia is probably not systematically dependent on the gender of the subject or the gender of the experimenter, given the divergent findings in Report I and III.
- (iii) The effect of experimenter gender on pain report is probably a pure psychosocial effect, since there was no interaction between experimenter gender and subject gender in the autonomic data in report II.

REFERENCES

- Ader R. Processes underlying placebo effects - The preeminence of conditioning. *Pain Forum* 1997;6(1):56-58.
- Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart-rate fluctuation – A quantitative probe of beat-to-beat cardiovascular control. *Science* 1981;213(4504):220-222.
- Arendt-Nielsen L, Bajaj P, Drewes AM. Visceral pain: gender differences in response to experimental and clinical pain. *European Journal of Pain* 2004;8(5):465-472.
- Aslaksen PM, Myrbakk IN, Høifødt RS, Flaten MA. The effect of experimenter gender on autonomic and subjective responses to pain stimuli. *Pain* 2007;129(3):260-268.
- Aslaksen PM, Flaten MA. The relation of stress to placebo analgesia. *Psychosomatic Medicine*, In Press.
- Aubrun F, Salvi N, Coriat P, Riou B. Sex- and age-related differences in morphine requirements for postoperative pain relief. *Anesthesiology* 2005;103(1):156-160.
- Baumgartner U, Cruccu G, Iannetti GD, Treede RD. Laser guns and hot plates. *Pain* 2005;116(1-2):1-3.
- Benedetti F. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain* 1996;64(3):535-543.
- Benedetti F, Amanzio M, Baldi S, Casadio C, Maggi G. Inducing placebo respiratory depressant responses in humans via opioid receptors. *European Journal of Neuroscience* 1999;11(2):625-631.
- Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. *Lancet* 1995;346(8984):1231-1231.

- Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *Journal of Neuroscience* 2003;23(10):4315-4323.
- Berkley KJ. Sex differences in pain. *Behavioral and Brain Sciences* 1997;20(3):371-380.
- Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, VanderMolen MW. Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology* 1997;34(6):623-648.
- Bradley MM, Lang PJ. Measuring emotion – The self assessment mannequin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry* 1994;25(1):49-59.
- Cepeda MS, Carr DB. Women experience more pain and require more morphine than men to achieve a similar degree of analgesia. *Anesthesia and Analgesia* 2003;97(5):1464-1468.
- Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nature Reviews Neuroscience* 2005;6(7):545-552.
- Craft RM. Sex differences in opioid analgesia: "From mouse to man". *Clinical Journal of Pain* 2003;19(3):175-186.
- Craggs JG, Price DD, Verne GN, Perlstein WM, Robinson MM. Functional brain interactions that serve cognitive-affective processing during pain and placebo analgesia. *Neuroimage* 2007;38:720-729.
- Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. *Nature Neuroscience* 2000;3(2):184-190.
- Edwards RR, Fillingim RB, Yamauchi S, Sigurdsson A, Bunting S, Mohorn SG, Maixner W. Effects of gender and acute dental pain on thermal pain responses. *Clinical Journal of Pain* 1999;15(3):233-237.

- Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94(2):149-158.
- Fields HL, Levine JD. Placebo analgesia – A role for endorphins. *Trends in Neurosciences* 1984;7(8):271-273.
- Fields HL, Price DD (1997). Toward a neurobiology of placebo analgesia. In A Harrington (ed.) *The Placebo Effect*. Cambridge, MA: Harvard University Press (pp. 93-116).
- Fillingim RB. Sex, gender and pain: A biopsychosocial framework. *Sex, Gender, and Pain* 2000;17:1-6.
- Fillingim RB, Edwards RR, Powell T. The relationship of sex and clinical pain to experimental pain responses. *Pain* 1999;83(3):419-425.
- Flaten MA, Aslaksen PM, Finset A, Simonsen T, Johansen O. Cognitive and emotional factors in placebo analgesia. *Journal of Psychosomatic Research* 2006;61(1):81-89.
- Flaten MA, Åsli O, Blumenthal TD. Expectations and placebo responses to caffeine-associated stimuli. *Psychopharmacology* 2003;169(2):198-204.
- Friedman BH, Thayer JF. Autonomic balance revisited: Panic anxiety and heart rate variability. *Journal of Psychosomatic Research* 1998;44(1):133-151.
- Gracely RH, Dubner R, Deeter WR, Wolskee PJ. Clinicians expectations influence placebo analgesia. *Lancet* 1985;1(8419):43-43.
- Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, Gold MS, Holdcroft A, Lautenbacher S, Mayer EA, Mogil JS, Murphy AZ, Traub RJ, Cwgspsigiasp. Studying sex and gender differences in pain and analgesia: A consensus report. *Pain* 2007;132:S26-S45.

- Grevert P, Albert LH, Goldstein A. Partial antagonism of placebo analgesia by naloxone. *Pain* 1983;16(2):129-143.
- Hoffman GA, Harrington A, Fields HL. Pain and the placebo - what we have learned. *Perspectives in Biology and Medicine* 2005;48(2):248-265.
- Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New England Journal of Medicine* 2001;344(21):1594-1602.
- International Association for the Study of Pain (IASP). *Pain* 1979; 6:247-252.
- Johansen O, Brox J, Flaten MA. Placebo and nocebo responses, cortisol, and circulating beta-endorphin. *Psychosomatic Medicine* 2003;65(5):786-790.
- Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature* 2001;413(6852):203-210.
- Kállai I, Barke A, Voss U. The effects of experimenter characteristics on pain reports in women and men. *Pain* 2004;112(1-2):142-147.
- Keogh E, Cochrane M. Anxiety sensitivity, cognitive biases, and the experience of pain. *Journal of Pain* 2002;3(4):320-329.
- Kirsch I. The logical consequences of the common-factor definition of the term placebo. *American Psychologist* 1985;40(2):237-238.
- Klinger R, Soost S, Flor H, Worm M. Classical conditioning and expectancy in placebo hypoalgesia: A randomized controlled study in patients with atopic dermatitis and persons with healthy skin. *Pain* 2007;128(1-2):31-39.
- Klosterhalfen S, Enck P. Neurophysiology and psychobiology of the placebo response. *Current Opinion in Psychiatry* 2008;21(2):189-195.
- Kong J, Gollub RL, Rosman IS, Webb JM, Vangel MG, Kirsch I, Kaptchuk TJ. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance Imaging. *Journal of Neuroscience* 2006;26(2):381-388.

- Lang PJ. Behavioral treatment and bio-behavioral assessment: computer applications. In: Sidowski JB, Johnson JH, Williams TA, editors. Technology in mental health care delivery systems. Norwood, NJ: Ablex, 1980, pp.119-37.
- Lang PJ, Ohman A, Vaitl D. (1988).The international affective picture system. Gainesville FL: The Center for Research in Psychophysiology, University of Florida.
- Levine FM, Desimone LL. The effects of experimenter gender on pain report in male and female subjects. *Pain* 1991;44(1):69-72.
- Levine JD, Gordon NC. Influence of the method of drug administration on analgesic response. *Nature* 1984;312(5996):755-756.
- Lieberman MD, Jarcho JM, Berman S, Naliboff BD, Suyenobu BY, Mandelkern M, Mayer EA. The neural correlates of placebo effects: a disruption account. *Neuroimage* 2004;22(1):447-455.
- Mackay C, Cox T, Burrows G, Lazzerini T. Inventory for measurement of self-reported stress and arousal. *British Journal of Social and Clinical Psychology* 1978;17(sep):283-284.
- Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation in the frequency-domain. *Circulation* 1991;84(2):482-492.
- McGlashan TH, Evans FJ, Orne MT. Nature of hypnotic analgesia and placebo response to experimental pain. *Psychosomatic Medicine* 1969;31(3):227-246.
- Meagher MW, Arnau RC, Rhudy JL. Pain and emotion: Effects of affective picture modulation. *Psychosomatic Medicine* 2001;63(1):79-90.
- Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. *Pain* 1997;72(1-2):107-113.
- O'Neill ST, Parrott AC. Stress and arousal in sedative and stimulant cigarette smokers. *Psychopharmacology* 1992;107(2-3):442-446.

- Parrott AC. Stress modulation over the day in cigarette smokers. *Addiction* 1995;90(2):233-244.
- Paulson PE, Minoshima S, Morrow TJ, Casey KL. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. *Pain* 1998;76(1-2):223-229.
- Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. Placebo in emotional processing - Induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 2005;46(6):957-969.
- Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia - Imaging a shared neuronal network. *Science* 2002;295(5560):1737-1740.
- Pollo A, Vighetti S, Rainero I, Benedetti F. Placebo analgesia and the heart. *Pain* 2003;102(1-2):125-133.
- Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H. Assessment of autonomic function in humans by heart-rate spectral-analysis. *American Journal of Physiology* 1985;248(1):151-153.
- Price DD, Barrell JE, Barrell JJ. A quantitative-experimental analysis of human emotions. *Motivation and Emotion* 1985;9(1):19-38.
- Price DD, Barrell JJ. Mechanisms of analgesia produced by hypnosis and placebo suggestions. *Biological Basis for Mind Body Interactions* 2000;122:255-271.
- Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology* 2008;59:565-590.
- Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analog scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17(1):45-56.

Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 1999;83(2):147-156.

Rainville P, Bao QVH, Chretien P. Pain-related emotions modulate experimental pain perception and autonomic responses. *Pain* 2005;118(3):306-318.

Ramsay DS, Woods SC. Biological consequences of drug administration: Implications for acute and chronic tolerance. *Psychological Review* 1997;104(1):170-193.

Rescorla RA. Pavlovian Conditioning - Its Not What You Think It Is. *American Psychologist* 1988;43(3):151-160.

Rhudy JL, Grimes JS, Meagher MW. Fear-induced hypoalgesia in humans: Effects on low intensity thermal stimulation and finger temperature. *Journal of Pain* 2004;5(8):458-468.

Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. *Pain* 2000;84(1):65-75.

Rhudy JL, Meagher MW. Noise stress and human pain thresholds: Divergent effects in men and women. *Journal of Pain* 2001;2(1):57-64.

Rhudy JL, Meagher MW. Individual differences in the emotional reaction to shock determine whether hypoalgesia is observed. *Pain Medicine* 2003;4(3):244-256.

Robinson ME, Riley JL, Myers CD, Papas RK, Wise EA, Waxenberg LB, Fillingim RB. Gender role expectations of pain: Relationship to sex differences in pain. *Journal of Pain* 2001;2(5):251-257.

Robinson ME, Wise EA, Gagnon C, Fillingim RB, Price DD. Influences of gender role and anxiety on sex differences in temporal summation of pain. *Journal of Pain* 2004;5(2):77-82.

Roelofs J, ter Riet G, Peters ML, Kessels AGH, Reulen JPH, Menheere P. Expectations of analgesia do not affect spinal nociceptive R-III reflex activity: an experimental study into the mechanism of placebo-induced analgesia. *Pain* 2000;89(1):75-80.

Rosier EM, Iadarola MJ, Coghill RC. Reproducibility of pain measurement and pain perception. *Pain* 2002;98(1-2):205-216.

Sanford SD, Kersh BC, Thorn BE, Rich MA, Ward LC. Psychosocial mediators of sex differences in pain responsivity. *Journal of Pain* 2002;3(1):58-64.

Smith GM, Egbert LD, Markowitz RA, Mostelle F, Beecher HK. An experimental pain method sensitive to morphine in man – submaximum effort tourniquet technique. *Journal of Pharmacology and Experimental Therapeutics* 1966;154(2):324-332..

Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. *Journal of Neuroscience* 2006;26(21):5777-5785.

Staats PS, Staats A, Hekmat H. The additive impact of anxiety and a placebo on pain. *Pain Medicine* 2001;2(4):267-279.

Surawy C, Cox T. Smoking under natural conditions – a diary study. *Personality and Individual Differences* 1987;8(1):33-41.

Terkelsen AJ, Molgaard H, Hansen J, Andersen OK, Jensen TS. Acute pain increases heart rate: Differential mechanisms during rest and mental stress. *Autonomic Neuroscience-Basic & Clinical* 2005;121(1-2):101-109.

Tousignant-Laflamme Y, Marchand S. Sex differences in cardiac and autonomic response to clinical and experimental pain in LBP patients. *European Journal of Pain* 2006;10(7):603-614.

- Tracey I, Mantyh PW. The cerebral signature and its modulation for pain perception. *Neuron* 2007;55(3):377-391.
- Unruh AM. Gender variations in clinical pain experience. *Pain* 1996;65(2-3):123-167.
- Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 2002;99(3):443-452.
- Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients - An empirical investigation. *Pain* 2003;105(1-2):17-25.
- Vase L, Robinson ME, Verne GN, Price DD. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* 2005;115(3):338-347.
- Verne GN, Robinson ME, Vase L, Price DD. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. *Pain* 2003;105(1-2):223-230.
- Villemure C, Slotnick BM, Bushnell MC. Effects of odors on pain perception: deciphering the roles of emotion and attention. *Pain* 2003;106(1-2):101-108.
- Wager TD. Expectations and anxiety as mediators of placebo effects in pain. *Pain* 2005;115(3):225-226.
- Wager TD. The neural bases of placebo effects in pain. *Current Directions in Psychological Science* 2005;14(4):175-179.
- Wager TD, Dagfinn MB, Casey KL. Placebo effects in laser-evoked pain potentials. *Brain Behavior and Immunity* 2006;20(3):219-230.

Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004;303(5661):1162-1167.

Watson A, El-Deredy W, Vogt BA, Jones AKP. Placebo analgesia is not due to compliance or habituation: EEG and behavioural evidence. *Neuroreport* 2007;18(8):771-775.

Weisse CS, Foster KK, Fisher EA. The influence of experimenter gender and race on pain reporting: Does racial or gender concordance matter? *Pain Medicine* 2005;6(1):80-87.

Willoch F, Schindler F, Wester HE, Empl M, Straube A, Schwaiger M, Conrad B, Tolle TR. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [¹¹C]diprenorphine PET study. *Pain* 2004;108(3):213-220.

Wise EA, Price DD, Myers CD, Heft MW, Robinson ME. Gender role expectations of pain: relationship to experimental pain perception. *Pain* 2002;96(3):335-342.

Zillmann D, deWied M, KingJablonski C, Jenzowsky S. Drama-induced affect and pain sensitivity. *Psychosomatic Medicine* 1996;58(4):333-341.

Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu YJ, Koeppe RA, Stohler CS, Goldman D. COMT val(158)met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 2003;299(5610):1240-1243.

Zubieta JK, Smith YR, Bueller JA, Xu YJ, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science* 2001;293(5528):311-315.

Zubieta JK, Smith YR, Bueller JA, Xu YJ, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS. mu-opioid receptor-mediated antinociceptive responses differ in men and women. *Journal of Neuroscience* 2002;22(12):5100-5107.

Åsli O, Flaten MA. Conditioned facilitation of the unconditioned reflex after classical eyeblink conditioning. *International Journal of Psychophysiology* 2008;67(1):17-22.