UiT
THE ARCTIC
UNIVERSITY
OF NORWAY

FACULTY OF HEALTH SCIENCES
DEPARTMENT OF PSYCHOLOGY

Active Placebo

The relation of treatment expectancies to active analgesic treatments

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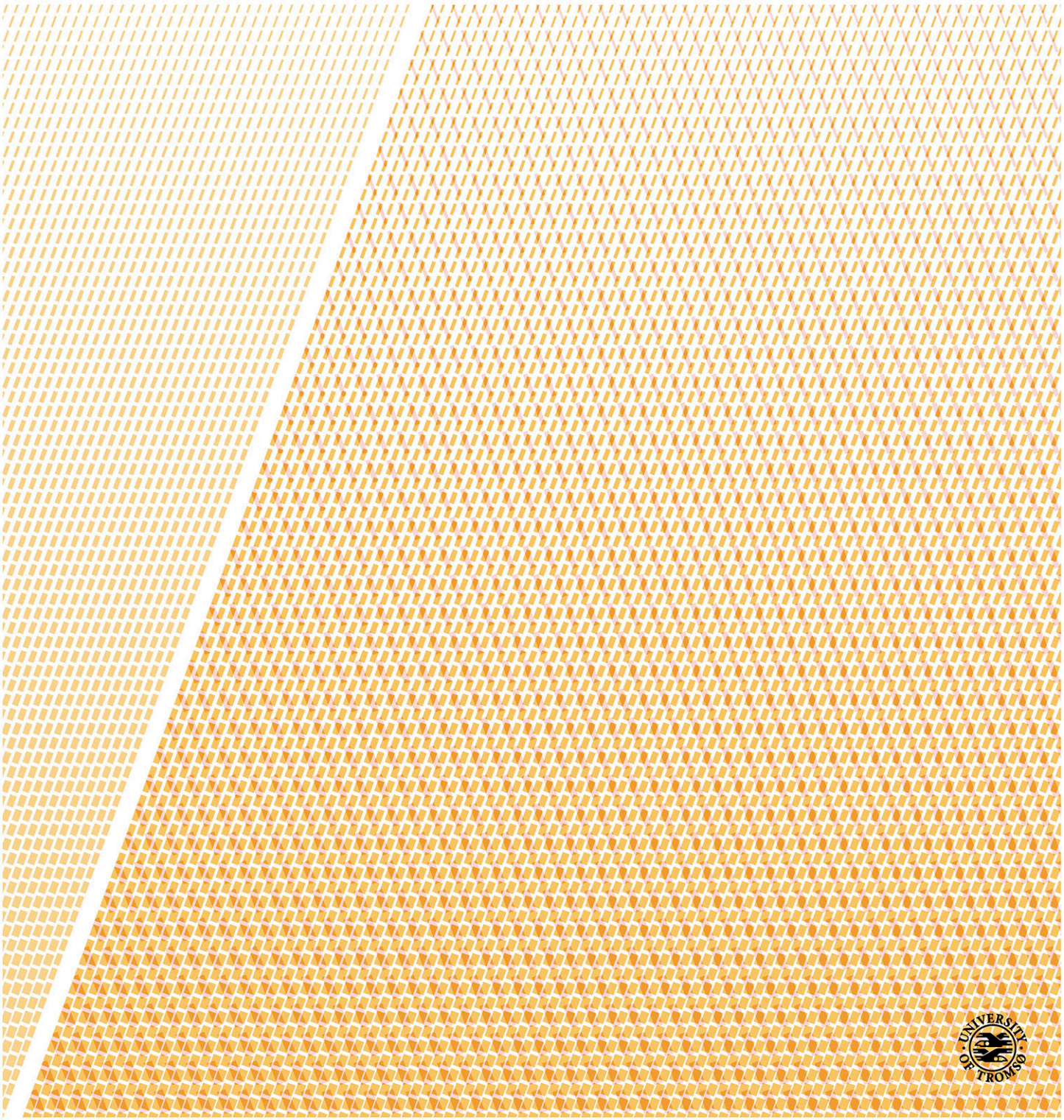
Espen Bjørkedal

A dissertation for the degree of Philosophiae Doctor – July 2016



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Espen Bjørkedal

Department of Psychology

Faculty of Health Sciences

UiT The Arctic University of Norway

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List of Papers

Paper I: Bjørkedal, E. & Flaten, M. A. Interaction between expectancies and drug effects: an experimental investigation of placebo analgesia with caffeine as an active placebo. *Psychopharmacology*, 2011, Jun; 215(3):537-48.

Paper II: Bjørkedal, E. & Flaten, M. A. Expectations of increased and decreased pain explain the effect of conditioned pain modulation in females. *Journal of Pain Research*, 2012; 5: 289–300.

Paper III: Aslaksen, P.M., Zwarg, M.L., Eilertsen, H-I.H., Gorecka, M.M & Bjørkedal, E. Opposite effects of the same drug: reversal of topical analgesia by nocebo information. *Pain*, 2015; 156 (1): 39-46.

Abstract

The placebo analgesic effect refers to the improvement in a group receiving an inert treatment compared to a group receiving no treatment. Conversely, nocebo hyperalgesia refers to the worsening in a group receiving an inert treatment compared to a no treatment control group. The hypothesis that active treatments, e.g. a drug, enhance the placebo effect has received some support but rarely been tested experimentally. In the present work this hypothesis was tested by administering caffeine or placebo to healthy subjects after induction of pain. Both caffeine and placebo were administered with information that they received a painkiller which would alleviate the pain or that they received a placebo with no effect. The effect of this manipulation was tested by comparing subjective and physiological responses to identical painful stimulation before and after treatment. It was predicted that the active drug would increase the placebo analgesic effect. The total treatment effect consists of the specific treatment response, e.g. the response to the pharmacological action of a drug, and the placebo response. Previous research indicate that the total treatment effect is modulated by placebo and nocebo responses, such that placebo responses increase the treatment effect and nocebo responses decrease it. The present work consists of two experiments that investigated the relation of placebo and nocebo responses to the treatment effect. In both experiments, pain was induced in healthy subjects before and after administering a known analgesic treatment with information that it was analgesic, hyperalgesic or with no specific information about its effect. We predicted that treatment effects would be enhanced by placebo information and reduced by nocebo information. The role of stress in placebo and nocebo responding was investigated by including subjective and physiological measures of stress. It was predicted that placebo responses was mediated by reductions in stress, while nocebo responses were mediated by increased stress.

The results showed that a placebo response was only present when caffeine was administered. This supports the hypothesis that active drugs enhance placebo responses. It was further observed that the analgesic effect of a topical analgesic cream was reversed in the nocebo group and had a hyperalgesic effect. Placebo and nocebo responses were related to reduced and increased anticipatory stress, respectively, and anticipatory stress was a predictor of subsequent pain.

The present work is relevant for both the design and interpretation of clinical trials and for clinical practice. Clinical trials assume that the only difference between drugs and placebos are the pharmacological action of the drug. However, if placebo responses are larger

in the presence of the active drug the assumption might not always hold. The modulation of treatment effects by placebo and nocebo responses is relevant for maximizing treatment effects in clinical practice. Increasing positive expectations and decreasing stress is important to maximize placebo responses and minimize nocebo responses.

Abbreviations

ACC	Anterior cingulate cortex
ACTH	Adrenocorticotropid hormone
AMH	A-delta mechano heat sensitive nociceptor
BPD	Balanced placebo design
CCK	Cholecystokinin
CMH	C-fibre mechano heat sensitive nociceptor
COVAS	Computerized visual analogue scale
CPM	Conditioned pain modulation
CR	Conditioned response
CPT	Cold pressor test
CS	Conditioned stimulus
DLPFC	Dorsolateral prefrontal cortex
DNIC	Diffuse noxious inhibitory controls
ECG	Electrocardiogram
EEG	Electroenchephalogram
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
FPQ	Fear of pain questionnaire
LEP	Laser-evoked potentials
LOT-R	Life orientation test – revised
MCC	Midcinculate cortex
Nd:YAP	Neodymium yttrium aluminum perovskite laser
NRS	Numerical rating scale
NSAID	Non-stereoidal anti-inflammatory drug
OFC	Orbitofrontal cortex
PAG	Periaqueductal gray
PET	Positron emission tomography
PFC	Prefrontal cortex
rACC	Rostral anterior cingulate cortex
RDBPC	Randomized, double-blind, placebo-controlled trial
RVM	Rostral ventromedial medulla
SI	Primary somatosensory cortex

SII	Secondary somatosensory cortex
SACL	Short adjective check list
sgACC	Subgenual anterior cingulate cortex
UR	Unconditioned response
US	Unconditioned stimulus
VAS	Visual analogue scale

Introduction

Are the effects of analgesic treatments dependent on the state of mind of the patient? The present thesis investigates issues bearing on that general question. It was investigated whether a drug can enhance the placebo effect, and whether placebo and nocebo effects modulate treatment effects.

The placebo effect is the improvement in a group receiving an inert treatment compared to a group receiving no treatment. This point is important, since there can be several reasons why subjects receiving a placebo improve. First, the improvement in symptoms or illness could have occurred even if no treatment where given, due to natural progression of the symptom or disease. Second, symptom severity tend to fluctuate around a stable mean. Thus, if patients are given treatment when their symptoms are at the worst, later measures of symptoms will tend to be closer to the mean value and it would seem as if they had improved. This is referred to as regression to the mean. Third, enrollment in a study means increased medical attention, care and support that might have beneficial effects on the symptom. Therefore, in order to assess true placebo effects it is necessary to include a control group that have the same symptom severity and receives the same medical attention. While the placebo effect refers to a difference between a group receiving a placebo treatment and a group receiving no treatment, the term 'placebo response' refers to the symptom improvement in an individual (Wager & Fields, 2013).

The term 'placebo' is often used to refer to a "substance or procedure that has no inherent power to produce an effect" (Stewart-Williams & Podd, 2004, p. 326). Since the placebo is inert, it is not the inherent properties of the substance or procedure that cause the placebo effect, but the set of accompanying psychosocial stimuli in the treatment context. These stimuli may include the words of the doctor or nurse, the sight of the syringe, capsule or whatever vehicle is used for treatment delivery, smells and other contextual factors (Benedetti, 2014).

The common explanations for why placebo effects occur are that the treatment context induce expectations of improvement that lead to symptom reduction, and/or that cues in the treatment context previously associated with treatment effects lead to symptom reduction via the principles of classical conditioning. Either way, the placebo effect is also potentially present whenever active treatment is being administered, since the same, or similar, psychosocial stimuli accompany the administration of active treatments.

In the present thesis, placebo is understood in a broad sense that includes the psychosocial stimuli accompanying the act of administering a treatment. The point of administering a placebo is to mimick the treatment context, in order to control for its effect or take advantage of it.

The act of administering a treatment can also be accompanied by negative expectations or cues in the treatment context that activate memories of negative treatment effects. This negative impact in the symptoms in a group receiving a placebo compared to a no treatment control group is termed a nocebo effect. Similarly as for the placebo effect, nocebo effects are also potentially present whenever active treatments are being administered.

The total clinical benefit of a treatment can be measured as the difference in a group of patients receiving the treatment and a no treatment control group. From now on, this effect will be referred to as the total treatment effect. The total treatment effect is due to the specific action of the treatment and the placebo effect. While the placebo effect can be measured as the difference between a placebo group and a natural history group, the specific treatment effect is measured as the difference between a treatment group and a placebo group. The logic of finding the specific treatment effect by subtracting away the effect in a placebo group implies a certain assumption termed the additivity assumption. It is assumed that the specific treatment effect and the unspecific effects in the placebo group are independent of each other and added together to yield the total treatment effect.

An example will illustrate this principle. Suppose we wanted to test the efficacy of the imaginary drug auxilium for pain. According to the logic of RDBPC we randomize patients to a group receiving the drug or a group receiving a placebo. If the drug is administered in a pill, the placebo pill will be made of all the same incidental ingredients that went into making the active pill, except for the active ingredient auxilium. Since both groups are being administered a pill, and no one knows which group they belong to, all unspecific effects, including the placebo effect should be equal in the groups. Therefore, the only difference between these groups is the presence of auxilium in the treated group and any difference in outcome between the groups can therefore be ascribed to the pharmacological action of auxilium.

However, the additivity assumption, as illustrated in this example, can be questioned on logical grounds. Apart from the specific effect of the active treatment on the outcome, there are also other differences between the treated group and the placebo group. Active treatments, like psychoactive drugs, have widespread effects on the central nervous system. Side effects of drugs or treatments are effects not directly related to the primary outcome, but

that nevertheless induce an additional difference between the treatment arm and the placebo arm. Sticking with the above example, imagine that auxilium in addition to reducing pain also has certain other effects, like increasing blood pressure or heart rate, inducing drowsiness or alertness or other possible effects. Thus, logically, the improvement in the treatment arm compared to the placebo arm could be due to a direct specific effect of the treatment on the outcome, or could in principle also indirectly be due to the side effects of the treatment. Some empirical evidence supports this notion. For instance, in order to avoid the problem of drug side effects, some clinical trials compare the drug to an active placebo. An active placebo is a drug, that has no effect on the outcome one is interested in, but which induce similar side effects as the drug being tested. Further, an active placebo response can be defined as a placebo response that is due to the action of the active placebo. An active placebo effect could thus be measured as the difference between a placebo group and an active placebo group. Thomson (1982) compared the relative efficacy of tricyclic antidepressants in clinical trials using inert placebos vs. trials using active placebo (atropine). A larger number of trials showed a significant drug effect when inert placebo was the control arm, compared to when active placebo was the control arm. This suggests that the active placebo enhanced the placebo response, i.e. an active placebo response.

In another study, Flaten, Simonsen, and Olsen (1999) gave subjects either the muscle relaxant carisoprodol or placebo (lactose) crossed with information that they received a relaxant drug, a stimulant drug, or no drug-relevant information. Carisoprodol administered without information did not increase tension. Lactose administered with information that it was a stimulant increased tension compared to control. This placebo effect was enhanced when subjects received carisoprodol with information that it was a stimulant drug. This is remarkable in light of the fact that carisoprodol normally has relaxant effects and that it had no effect on tension in the study. The enhanced effect was mainly seen in the time interval when carisoprodol serum concentrations rose. Since the drug had no effect on tension when administered without information but increased tension more compared to placebo when both were administered with stimulant information, it is a reasonable interpretation that the drug enhanced the placebo response, i.e. an active placebo response.

The above considerations suggest that active drugs can enhance the placebo effect and therefore that the additivity assumption might not always hold. The first paper in the thesis tested the additivity assumption by comparing the effect of an active placebo to an inert placebo in a balanced placebo design. If the effect of the active placebo would be larger

compared to the inert placebo, then the additivity assumption would be challenged. As described above, this is because such a finding would imply that the side effects of active drugs induce a difference between the drug arm and the placebo arm that is not due to the specific effects of drugs on the outcome variable.

Even if the additivity assumption does not hold, the total treatment effect still consists of specific treatment effects and the placebo effect. This fact is well illustrated by the open-hidden design (Benedetti et al., 2003). In the open-hidden design treatments are administered for some symptom either unknowingly to the patient or with standard information. These studies show that treatments are less effective when patients are unaware that treatments have been administered compared to when they know the time of administration (Amanzio, Pollo, Maggi, & Benedetti, 2001; Benedetti, et al., 2003; Bingel et al., 2011). The difference can be attributed to the placebo effect. Conversely, hidden interruption of a treatment prolongs the treatment effect compared to open interruption (Bingel et al., 2011). This difference can be attributed to the nocebo effect.

In clinical practice, the goal is to maximize the total treatment effects. Thus, understanding the mechanisms behind placebo and nocebo effects are important for clinical practice. Thus, the second and third paper in the thesis, investigated how treatment expectancies modulated the total treatment effect. All three studies investigated either placebo analgesia or nocebo hyperalgesia and their relation to active treatments or procedures reducing pain.

Background

Pain

Pain is a subjective experience. It is characterized by an intensely unpleasant sensation. This sensation is of varying quality (stinging, burning, aching, throbbing etc.), more or less precisely localized and almost always accompanied by a desire to end the experience. The standard definition of pain acknowledges all of these components: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." (Bonica, 1979, p. 250).

Acute pain signals that tissue is about to be damaged and that the organism has to respond in order to avoid injury and thereby increase chances of survival. Persons born without the ability to feel pain frequently get injured and often die at a young age (Nagasako, Oaklander, & Dworkin, 2003). The signaling function of pain involves detection of

potentially tissue damaging stimuli. Specialized neurons, distributed throughout the skin, muscles, tendons and internal organs, respond to potentially tissue damaging stimuli. These neurons are called nociceptors and they respond to potentially damaging temperatures, pressures and chemical agents. Pain, understood as a signal for potential tissue damage, is normally produced by activity in these nociceptors. While pain is subjective, nociceptive activity is objectively observable. Nociceptors respond to noxious stimulus energies and transduce these energies to an electrical signal in the peripheral nervous system. This electrical signal is then transmitted to the central nervous system via dedicated nerve fibers.

Nociceptors have free nerve endings located at the end of thinly myelinated or unmyelinated nerve fibres termed a-delta and c-fibres respectively. These nerve fibres send their axon to the dorsal horn of the spinal cord. At this location the first synapse in the nociceptive pathway occurs. Here a reflexive motor response can be produced via interneurons connecting the sensory input to a motor neuron. Apart from these spinal reflexes, adaptive responses are produced via the cerebral cortex. From the spinal cord, distinct pathways transmit the signal further up the central nervous system. It reaches the thalamus via the spinothalamic tract, the hypothalamus via the spinohypothalamic tract, the reticular system via the spinoreticular tract, and several other areas receives the signal in parallel. The signal reaching thalamus has received most focus since it underlies the conscious perception of pain. In the thalamus the second synapse in the nociceptive pathway occurs. Several areas of the thalamus receives the signal, but two have received special attention, since they are thought to underlie sensory and affective components of pain. The lateral part of thalamus receives nociceptive input from the spinal cord and transmits it further to the somatosensory cortex. The function of this route is thought to be sensory discrimination, i.e. to provide information about where and how intense the stimulus is. The medial part of the thalamus also receives nociceptive input, but transmits it further to the cingulate cortex and insula. The function of this pathway is thought to be affective-motivational, i.e. provide information about how unpleasant it is and motivate a response. The subjective experience of pain is probably the result of parallel processing in a distributed network of brain areas involving somatosensory cortex, the insula, cingulate cortex and prefrontal cortex. These areas are not specific for pain, but are similarly active in other sensory modalities as well (Mouraux, Diukova, Lee, Wise, & Iannetti, 2011).

While pain is often tied to objectively observable nociceptive activity as explained, there are many instances of nociceptive activity without the experience of pain and

probably of pain without nociceptive activity, as for instance in stress-induced analgesia and phantom limb pain. The signaling of potential tissue damage is clearly adaptive. Nevertheless, there are times when other motives are more important than the motivation to stop a current activity to tend to the painful event. If the organism is fleeing from a predator, is in the pursuit of food or waiting for other strong rewards, it might be more adaptive to suppress nociceptive transmission including reflexive responses produced in the spinal cord (Fields, 2007). A large number of research papers have identified such a descending modulating system. Stress-induced analgesia refers to the suppression of pain during or after an unconditioned or conditioned stressful stimulus (Butler & Finn, 2009). Furthermore, not only aversive stimuli can produce analgesia. Animals receiving or anticipating a natural reward (sucrose) display pain inhibition (Blass, Fitzgerald, & Kehoe, 1987; Dum & Herz, 1984). Remarkably, stress and negative emotions can also enhance pain. For instance, pictures with negative emotional content increase pain and spinal nociceptive reflexes compared to neutral and positive pictures (Kenntner-Mabiala & Pauli, 2005; Rhudy, Williams, McCabe, Nguyên, & Rambo, 2005). Uncertainty about the intensity of an upcoming painful stimulation can induce anxiety and increase pain (Ploghaus et al., 2001). These examples show that the context within which pain is experienced is crucial for its subjective experience. Context can modulate pain by recruiting a descending pain modulatory pathway. One important paradigm for studying how contextual information triggers descending control of pain is placebo analgesia and nocebo hyperalgesia.

The Psychology of Placebo Analgesia

Expectancy theory and classical conditioning are the two most common theories of placebo analgesia. Even though there has been some debate about their relative roles in placebo effects, they are not mutually exclusive and both are often at work simultaneously (Stewart-Williams & Podd, 2004).

The general idea behind the expectancy theory is that administration of a treatment together with verbal suggestions about its effect generate treatment expectancies, and these treatment expectancies are a causal factor in the placebo effect (Kirsch, 1999).

The expectancy theory has received extensive empirical support. Studies that have measured expectancies have found expectancies of reduced pain in the placebo condition and these expectancy ratings correlate with the placebo analgesic response (de Jong, van Baast, Arntz, & Merckelbach, 1996; Goffaux, de Souza, Potvin, & Marchand, 2009; Goffaux, Redmond, Rainville, & Marchand, 2007; Montgomery & Kirsch, 1997; Price et al., 1999;

Vase, Robinson, Verne, & Price, 2005; Vase, Robinson, Verne, & Price, 2003). Other studies have induced different degrees of expectations by manipulating the subjective probability of receiving active medication vs placebo (Geers, Helfer, Weiland, & Kosbab, 2006; Pollo et al., 2001). Vase, Riley III, and Price (2002) compared the placebo effect in clinical trials where there is a 50% chance of receiving active treatment with experimental studies where subjects were informed that they received active treatment. These studies find that the placebo effect increase with increasing subjective probability of receiving the active treatment, i.e. with increasing expectations.

Thus, a widely held explanation of placebo responses is that the administration of a placebo, together with verbal suggestions, will induce treatment expectancies and that these expectancies are necessary to produce the placebo response.

Other researchers have argued that the placebo response can be understood as an instance of classical conditioning (Herrnstein, 1962; Wickramasekera, 1980). According to this view, every visit to the doctor can be considered as a learning trial following the principles of conditioning. In the instance of complaints of pain, the administration of a painkiller is such a learning trial. The active ingredient in the medication is the unconditional stimulus (US) that elicits an unconditional response (UR), the reduction of pain. The medication vehicle, a capsule, syringe or whatever, or other cues in the treatment context can become a conditional stimulus (CS) through the association with the US. Now, the CS in absence of the US, e.g. a placebo pill, can by itself elicit a response that is similar to the UR, a conditioned response (CR), i.e. reduction of pain. This is the stimulus substitution model of classical conditioning.

Conditioned placebo responses have typically been investigated with two paradigms. On the one hand, some have administered active drugs on several trials and later replaced the drug with a placebo. On the other hand, some have paired a placebo with surreptitiously changing stimulus intensity so as to mimick a true drug effect. In the testing phase the stimulus intensity is restored to pre-learning levels and the conditioned placebo response is measured.

Both verbal suggestions and classical conditioning can produce placebo responses. However, it has been shown that the combination of verbal suggestions and conditioning produce stronger placebo responses compared to either alone (Amanzio & Benedetti, 1999; Benedetti et al., 2003; Colloca et al., 2008; Voudouris, Peck, & Coleman, 1985, 1990). For instance, Amanzio and Benedetti (1999) investigated the separate and combined effects of

expectancies (induced by verbal suggestions) and drug conditioning on placebo analgesia. Subjects were either conditioned with an opioid or a non-steroidal anti-inflammatory drug (NSAID). One group was not conditioned but given verbal suggestions in order to induce treatment expectancies. The opioid antagonist naloxone was administered in some groups to see whether any effects were mediated by endogenous opioids. The results showed that treatment expectancies without any conditioning induced a placebo analgesic response that was blocked by naloxone. Opioid conditioning without verbal suggestions also induced naloxone reversible placebo response. Opioid conditioning together with verbal suggestions induced a placebo analgesic response that was blocked by naloxone and was larger than conditioning or verbal suggestions alone. The same pattern of results were observed for the NSAID except that these placebo responses were not completely blocked by naloxone. Thus, both treatment expectancies (induced by verbal suggestions) and drug conditioning can produce naloxone reversible placebo effects. Importantly, conditioning together with verbal suggestions induce larger placebo responses compared to either alone.

The stimulus substitution model of conditioning has been challenged by more recent cognitive interpretations of conditioning (Stewart-Williams & Podd, 2004). On the cognitive account, conditioning depends on the information value of the CS and not on merely on pairing a CS with a US. The occurrence of the CS predicts the occurrence of the US. Thus, conditioning is considered as a way of generating expectancies. Accordingly, the question of whether conditioned placebo responses are mediated by conscious expectancies have long been debated, and is still unresolved (Jensen et al., 2012; Montgomery & Kirsch, 1997; Price et al., 1999; Schafer, Colloca, & Wager, 2015; Voudouris et al., 1985; Voudouris et al., 1989; Voudouris et al., 1990).

There is evidence that conditioning is mediated by conscious expectations (Benedetti et al., 2003; Montgomery & Kirsch, 1997; Price et al., 1999). For instance, Montgomery and Kirsch (1997) found that informing subjects that pain had been surreptitiously reduced during conditioning abolished the conditioned placebo analgesic response. They also observed that conditioning increased conscious expectations and that these expectations mediated the conditioned response. Similar results have been observed after preconditioning with active drugs (Benedetti et al., 2003). Benedetti et al. (2003) investigated the effects of conditioning alone, positive and negative treatment expectancies and their combination. Injection of placebo with suggestions of positive treatment effects produced placebo analgesia. Placebo with suggestions of increased pain produced nocebo hyperalgesia. Drug conditioning with an

NSAID together with positive suggestions increased the placebo analgesic response. However, when drug conditioning was combined with negative suggestions the placebo analgesic response disappeared, indicating that conditioning was mediated by conscious expectations. Thus, treatment expectancies are important in placebo analgesia, and conditioning seem to be one way to enhance treatment expectancies.

Contrary to this view, recent studies show that unconscious cues can be conditioned to induce analgesia and hyperalgesia, suggesting a separate route for conditioned placebo effects not mediated by expectancies (Jensen, Kirsch, Odmalm, Kaptchuk, & Ingvar, 2015; Jensen et al., 2014; Jensen et al., 2012). Another recent study investigated whether conditioned responses were still present after revealing that a placebo had been administered and that intensity reduction had been used to mimick a drug response (Schafer et al., 2015). One group received a long acquisition phase (4 days) while another received a short acquisition phase (1 day). They found that placebo analgesia was still present after reveal in the long acquisition group, indicating that conditioning is independent of conscious expectancies after longer acquisition. Interestingly, Benedetti et al. (2003) suggested that placebo effects on conscious responses are mediated by expectations while effects on nonconscious responses are mediated by conditioning. In support of this, it was shown that verbal expectations of hyperalgesia reversed conditioned analgesic responses, while verbal suggestions did not counteract conditioned placebo responses on cortisol growth hormone.

Summing up, treatment expectancies are an important factor in placebo analgesia and conditioning can enhance treatment expectances compared to giving verbal suggestions alone. On the other hand, there is evidence that nonconscious cues can elicit placebo and nocebo responses, and that longer acquisition induce conditioned placebo responses that are unmediated by expectancies. This suggests two separate mechanisms in placebo analgesia, one mediated by conscious expectancies and one operating nonconsciously.

Physiological and Neurobiological Effects of Placebo

It has been claimed that placebo effects are only present in subjective measures and not on physiological outcomes (Hróbjartsson & Gøtzsche, 2001). Pain reports are subject to reporting bias and this could be an explanation of placebo effects in many studies (Aslaksen, Myrbakk, Høifødt, & Flaten, 2007). Reporting of pain in the treatment context can be subject to social influence, for example compliance to the doctors communicated suggestions of treatment outcome. This implies that reductions in self-reported pain after administration of a

placebo could be a consequence of compliance and not reflect changes in the experience itself, i.e. the pain experience is really unchanged but the subject reports that it has changed in order to comply. If subjective measures are the only outcomes in a study, it cannot be ruled out that reporting bias has an influence. One way to exclude this explanation is to include a biomarker of the subjective state and observe placebo induced changes in this outcome. The search for valid and reliable biomarkers for pain is for these reasons a very important target in pain research. Autonomic measures (heart rate, heart rate variability, blood pressure and skin conductance) and measures of cerebral (fMRI, PET, EEG/ERP) or spinal activity (spinal reflexes, spinal fMRI, microneurography) have been used as biomarkers for nociception and pain (Eippert, Finsterbusch, Bingel, & Buchel, 2009; Loggia, Juneau, & Bushnell, 2011; Martini, Lee, Valentini, & Iannetti, 2015; Rhudy, Williams, McCabe, Russell, & Maynard, 2008; Wager et al., 2004; Zubieta et al., 2005). Another important source of knowledge for understanding placebo analgesia have been pharmacological manipulations (Amanzio & Benedetti, 1999; Eippert et al., 2009; Levine, Gordon, & Fields, 1978).

A lot of converging evidence have made it clear that placebo analgesia have neurobiological effects. Levine et al. (1978) observed that naloxone, an opioid antagonist, blocked the placebo analgesic response indicating that placebo analgesia reduce pain by releasing endogenous opioids. This finding has been replicated several times (Amanzio & Benedetti, 1999; Eippert et al., 2009; Grevert, Albert, & Goldstein, 1983) and the idea that endogenous opioids are involved in placebo analgesia were supported by PET-studies (Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). Imaging studies show that administration of a placebo increase activation in prefrontal cortex (PFC) and reduce activation in areas of the brain responsive to nociceptive input and pain (Wager et al., 2004). It has also been shown that placebo analgesia is associated with increased activation of rostral anterior cingulate cortex (rACC) together with increased coupling between rACC and periaqueductal grey (PAG)(Eippert et al., 2009). The increased coupling predicted behavioural placebo responses and activity in rostral ventromedial medulla (RVM). These effects were abolished with naloxone. Both PAG and RVM are part of a descending pain modulatory system that can modulate pain all already at the first synapse in the dorsal horn (Fields, 2004). Thus, the involvement of PAG and RVM suggests that the descending pain modulatory system is activated in placebo analgesia, with endogenous opioids playing a key role. Opioid receptors are present in many areas implicated in placebo analgesia, including the insula, amygdala, PAG, RVM and spinal cord dorsal horn, and injection of opioid agonists at

each of these locations can inhibit responses to nociceptive stimuli (Fields, 2004). Consistent with this, placebo analgesia is also associated with reduced activation in the dorsal horn of the spinal cord, the area of the first synapse of nociceptive processing and also a target for the descending pain modulatory network (Eippert et al., 2009).

In light of the observations above, placebo analgesia can be conceived of as a top-down mechanism whereby conscious expectations maintained in prefrontal cortex can modulate afferent input from the nociceptive system by activating a descending pain modulatory system in which endogenous opioids play a key role. For instance, Wager et al. (2004) found that increased activity in dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex (OFC) after placebo administration, during the anticipation of pain, was associated with reduced responses to painful stimulation in pain processing areas of the brain. Also, placebo responses are reduced in Alzheimer's disease and by temporarily disrupting bilateral DLPFC activity with transcranial magnetic stimulation (Benedetti et al., 2006; Krummenacher, Candia, Folkers, Schedlowski, & Schönbächler, 2010).

If placebo analgesia reduce or block nociceptive transmission at spinal level one would expect widespread inhibition in cerebral areas involved in pain processing as well because the transmission of nociceptive information to these areas would be reduced. Contrary to these expectations, evidence suggest that only a limited part of cerebral structures show inhibition in placebo analgesia, mainly in medial regions (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2013; Atlas & Wager, 2012). Further, Martini et al. (2015) used laser-evoked potentials (LEP) to test the hypothesis of widespread inhibition. LEPs recorded as electroencephalographic (EEG) activity time-locked to a noxious laser stimulus, reflect cortical responses to these stimuli with high temporal resolution. The early N1 component (maximal at central electrodes contralateral to stimulation side) is modulated by stimulus intensity and is probably generated in somatosensory cortex reflecting the earliest nociceptive input to the cortex. The later N2 and P2 components (maximal at vertex), which correlate with reported pain, are generated in insula and ACC. If placebo analgesia reduce pain by inhibiting nociceptive processing in the spinal cord one would expect placebo responses on all of these components. The results showed that only the late components were reduced after conditioned placebo analgesia, suggesting that placebo analgesia was mediated by intracortical modulation and not spinal inhibition. Thus, the notion that placebo analgesia reduce pain by inhibiting early nociceptive processing is still debated. Alternatively, placebo analgesia could be mediated by higher order sensory processing of nociceptive stimuli, affective responses to

pain or cognitive evaluations of pain without modulating early sensory processing. It is currently not known under what specific conditions, if any, spinal inhibition by placebo occurs.

Placebo Analgesia and Emotion

While expectations may modulate pain processing directly, many have suggested that placebo analgesia could be mediated by other psychological variables (Buhle, Stevens, Friedman, & Wager, 2012; Flaten, Aslaksen, Finset, Simonsen, & Johansen, 2006; Johansen, Brox, & Flaten, 2003; Johnston, Atlas, & Wager, 2012). Several psychological variables modulate pain, and placebo analgesia could be mediated by these variables, e.g. emotions and attention.

Studies of how emotions modulate pain have mostly induced emotions by presenting pictures with emotional content; positive, neutral or negative. These pictures vary according to valence (pleasant-unpleasantness dimension of emotion) and arousal (intensity dimension of emotion). Generally, unpleasant pictures increase pain report, nociceptive spinal reflexes and autonomic responses and pleasant pictures decrease them (Rhudy et al., 2005; Rhudy et al., 2008; Roy, Piche, Chen, Peretz, & Rainville, 2009). However, this relationship depends on the level of arousal as intense negative emotions can result in stress-induced analgesia (Rhudy & Meagher, 2000). It has also been shown that uncertain expectations of the intensity of upcoming pain increase anticipatory anxiety and pain compared to certain expectations (Ploghaus et al., 2001).

Pain is a stressor that induces negative emotions (unpleasantness, fear, anxiety) and the expectation of pain can induce negative emotions as well (fear and anxiety). Consequently, if placebo administration induces expectancies of reduced pain, then placebo analgesia could be mediated by reduced anticipatory fear and anxiety, and reduced emotional reactivity to painful stimulation.

In line with this hypothesis it was found that administration of a placebo with information that it will relieve pain reduced subjective stress after placebo administration and before painful stimulation (Aslaksen, Bystad, Vambheim, & Flaten, 2011). The reduction in anticipatory stress predicted a placebo analgesic response in males only. In addition, the P2 component of the event related potentials to painful stimulation was reduced in males only. The probable generator of the P2 component is the ACC and the insula, areas involved in the affective component of pain (Garcia-Larrea, Frot, & Valeriani, 2003). This suggests that the

placebo effect on pain was related to reduced processing of nociceptive information in the anterior cingulate and insula.

Further support for this hypothesis came from the observation that administration of a placebo reduces the startle response after placebo administration and prior to painful stimulation (Lyby, Forsberg, Åsli, & Flaten, 2012). Importantly, by inducing fear by threatening to shock the participants after administration of placebo, it was observed that the placebo effect on startle was abolished. A placebo analgesic effect was not observed in that study, but the data showed a trend towards a placebo analgesic effect, and this trend was abolished by the fear induction. These studies suggest that administration of a placebo reduce anticipatory stress and that the reduction in stress mediates placebo analgesia.

It has also been demonstrated that emotional reactivity to painful stimulation is reduced after placebo. Pollo, Vighetti, Rainero, and Benedetti (2003) measured cardiac activity during pain and placebo analgesia. They found that pain increased heart rate and sympathetic control of heart rate, while these responses were reduced in a placebo group. The placebo effects on pain and cardiac activity were antagonized by naloxone, while the beta-blocker propranolol antagonized only the cardiac response to ischemic pain. In contrast, blocking parasympathetic control of heart rate with atropine had no effect on placebo analgesia or cardiac responses to ischemic pain. One possible explanation for these results is that expectations of analgesia triggered the release of endogenous opioids that reduced both pain and cardiac activity. Alternatively, endogenous opioids affected pain directly and cardiac activity indirectly via the reduction in pain.

Similar results were obtained by Aslaksen and Flaten (2008). They observed lower sympathetic cardiac activity during pain after administration of a placebo compared to natural history. The reduced sympathetic activity predicted reduced subjective stress during pain in the placebo condition, which again predicted placebo analgesia. In a later publication, the same dataset was reanalyzed to investigate the relation of fear of pain to placebo analgesia (P. Lyby, Aslaksen, & Flaten, 2010). It was found that fear of pain was related to reduced placebo analgesic responses.

However, in contrast to these results, two studies measured circulating cortisol and endorphin during pain in a placebo and control group. If placebo analgesia is mediated by reduced stress, then one should observe reduced cortisol release in the placebo group. They found no difference in cortisol levels between the groups even though a placebo analgesic response was observed (Flaten et al., 2006; Johansen et al., 2003).

In conclusion, evidence for the mediating role of stress in placebo analgesia is mixed even in experiments designed to test the hypothesis and further studies are needed.

Nocebo Hyperalgesia

While there has been a lot of research on placebo analgesia, the opposite response, nocebo hyperalgesia has received less attention. Similarly to the placebo response, a nocebo response is defined as the worsening in symptoms in a group receiving an inert treatment compared to a group receiving no treatment. Also, expectancies and classical conditioning are widely recognized as important factors in nocebo responses. Recently a meta-analysis of the nocebo hyperalgesic response was conducted (Petersen et al., 2014). The primary variables of interest were measures of the magnitude of the nocebo responses, the heterogeneity of results and whether nocebo effect sizes were different for studies using conditioning or verbal suggestions. They found medium to large effects sizes with considerable variation across studies. Parallel to the pattern of results for placebo reviewed above, there were larger nocebo effects after verbal suggestions together with conditioning compared to verbal suggestions alone as the manipulation. Interestingly, the inclusion criteria and design of the included studies were similar to a meta-analysis of placebo analgesic effects and they could therefor compare nocebo and placebo effects. Both the overall effects sizes and the difference between verbal suggestions and conditioning were comparable between nocebo and placebo studies. Thus, placebo and nocebo effects seem to be elicited by similar manipulations with comparable magnitudes of responses (Petersen et al., 2014).

Nocebo hyperalgesia is related to anxiety and cholecystokinin (CCK). Verbal suggestions of increased pain induce anxiety and fear (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006; Bingel et al., 2011; Tracey, 2010). Johansen et al. (2003) showed that circulating cortisol increased in a nocebo group during ischemic pain. This was replicated by Benedetti et al. (2006) who showed that adrenocorticotropid hormone (ACTH) and cortisol increased in a nocebo group. Administration of diazepam prior to nocebo manipulation blocked both nocebo hyperalgesia and the increase in ACTH and cortisol, while administration of the CCK antagonist proglumide blocked only nocebo hyperalgesia. Importantly, neither diazepam nor proglumide had any analgesic effects when administered alone. A previous report also observed that nocebo hyperalgesia induced by verbal suggestions can be blocked by the CCK antagonist proglumide (Benedetti, Amanzio, Casadio, Oliaro, & Maggi, 1997). These studies indicate that nocebo hyperalgesia is mediated by an anxiety-induced release of CCK. Elaborating on these results, Benedetti, Amanzio, and Thoen

(2011) found that a CKK agonist abolished the conditioned placebo analgesic response. This suggests that emotions play a role in placebo and nocebo responses by determining the balance between endogenous CCK and opioids.

However, Schmid et al. (2013) found increased expectations of pain after nocebo suggestions and this increased pain, but no increase in state anxiety, tension or cortisol was seen. Furthermore, Vase et al. (2003) found no nocebo hyperalgesic response after verbal suggestion, but found a large placebo analgesic response. Thus, nocebo hyperalgesia induced by verbal suggestions can also be elicited without increased anxiety.

Nocebo responses can be elicited by verbal suggestions alone, but can be enhanced by learning. For instance, Colloca, Petrovic, Wager, Ingvar, and Benedetti (2010) investigated how the number of learning trials during acquisition affected nocebo and placebo responses and observed that placebo and nocebo responses lasted through the extinction phase in the group with longer learning but not in the group with single session learning. Colloca, Sigaudo, and Benedetti (2008) found that nocebo hyperalgesia and nocebo induced allodynia was induced by both verbal suggestions and conditioning with no significant differences between the two procedures. In the same study, no placebo analgesic effect was observed after verbal suggestions, but conditioning induced a placebo effect.

Geuter and Büchel (2013) induced nocebo hyperalgesia through verbal suggestions and conditioning while performing fMRI. The nocebo manipulation increased pain and decreased pain threshold compared to control. Pain catastrophizing, social desirability and anxiety were not related to the nocebo hyperalgesic response. Nocebo hyperalgesia led to stronger activation of pain induced spinal cord activity in the ipsilateral dorsal horn compared to control. This spinal effect did not correlate with the behavioural nocebo response. The authors argued that this could be due to additional modulation of the signal at supraspinal sites.

In sum, nocebo and placebo responses are triggered by treatment expectancies induced by either verbal suggestions alone or conditioning, and are enhanced by combining these manipulations. Nocebo hyperalgesia is possibly mediated by an anxiety induced release of CCK. Considering the observations that the threat of shock attenuates placebo effects on startle and pain, and that a CCK agonist abolishes placebo responses, it is possible that emotional state modulate the balance between endogenous CCK and opioids, and thereby mediate placebo analgesia and nocebo hyperalgesia.

Drugs and Placebos

Most experimental research on the placebo or nocebo effects have investigated the difference between a placebo condition and no treatment condition. But, as implied in the RDBPC design, the placebo effect is one component of the total treatment effect of an active treatment. The basic fact is illustrated in the open-hidden paradigm. In an open-hidden design an active treatment is administered under two conditions. In the open condition, the treatment is administered in full view of the patient and with standard suggestions about the therapeutic effect. In the hidden condition, the patient is not aware of the timing of drug administration and has therefore no expectations about any changes in symptoms. Additionally, one can extend this design by including an open interruption condition (Benedetti, et al., 2003; Bingel et al., 2011). In open interruption, the subject is still administered the treatment but is informed that the treatment has been interrupted and that it will lose its effect. As a consequence, the subject expects that symptoms will worsen. Therefore the open-hidden design allows the investigation of how placebo and nocebo responses modulate the total treatment effect of active treatments.

Studies of the open-hidden design have shown that treatments tend to have greater effect in the open compared to the hidden condition, while open interruption can block the treatment effect as measured by hidden administration. For instance, Bingel et al. (2011) investigated the analgesic effect of the fast acting opioid remifentanil under neutral, positive and negative expectations. After a baseline measurement of pain, remifentanil was administered to healthy volunteers without their knowledge and pain was measured again after 30 minutes (hidden condition). The dose of remifentanil was kept constant while the subjects were informed that remifentanil would be administered to relieve pain (open condition). Thereafter, while still on remifentanil, the subjects were informed that remifentanil infusion had stopped and that they would now be monitored for possible increases in pain (open interruption). With this design, they were able to show that hidden administration of remifentanil was effective in relieving pain and activity in pain processing areas of the brain, but not as effective as open administration. Most interestingly, the analgesic effect of remifentanil was completely abolished during open interruption. The expectancy manipulations also modulated ratings of anxiety prior to painful stimulation. Suggestions of analgesia decreased anxiety ratings while suggestions of hyperalgesia increased anxiety ratings. Similar results were observed under open/hidden administration/interruption of morphine for post-operative pain, deep-brain stimulation for

treatment of Parkinson, and diazepam for reduction of state anxiety (Benedetti et al., 2003), Therefore, the psychological state, e.g. expectations and emotions, of an individual taking a drug might influence the total treatment effect, and possibly the pharmacological action of the drug itself. It is important to disentangle the circumstances under which these effects might take place and to identify possible mechanisms underlying these effects.

Other designs have also been used to investigate the modulation of total treatment effects by placebo and nocebo. Some studies have administered an active treatment with suggestions that are congruent or incongruent with the supposed action of the treatment (Dworkin et al., 1983; Goffaux et al., 2009; Goffaux et al., 2007). If active treatment is modulated by expectations, then one would expect different treatment effects under congruent and incongruent expectancies. Several studies have found that analgesic treatments can be blocked when administered with negative treatment expectancies (incongruent) compared to positive treatment expectancies (congruent) (Dworkin et al., 1983; Goffaux et al., 2009; Goffaux et al., 2007; Varelmann, Pancaro, Cappiello, & Camann, 2010). For instance, Goffaux et al. investigated the effect of positive and negative treatment expectancies on conditioned pain modulation (CPM). Conditioned pain modulation refers to the modulation of pain response to a test stimulus by a second painful stimulation applied simultaneously, or just prior to the test stimulus, at another body site. Application of a second painful stimulus inhibits nociceptive processing and pain in animals and humans (Le Bars, Villanueva, Willer, & Bouhassira, 1991). If the analgesic effect of CPM differs under opposing expectancies, then this is evidence that an effective analgesic procedure is modulated by expectancies. Goffaux et al. (2007) measured pain, spinal nociceptive reflexes and somotasensory evoked potentials to electrical shock (test stimulus) to the foot before and during submersion of the contralateral foot in ice water (conditioning stimulation). One group was told that the conditioning stimulation would reduce pain, while another group was told it would increase pain. The conditioning stimulation reduced pain, spinal reflex amplitudes and somatosensory evoked potentials in the analgesia group, and these CPM effects were blocked in the hyperalgesia group. It is noteworthy that while expectations modulated spinal reflexes, suggesting inhibition of nociceptive information to the cortex, only the P260 component of the somatosensory evoked potentials where modulated by expectations. If nociceptive information were attenuated at the spinal level one would expect a reduction also at the earlier N100 component. This is in line with the observations of Martini et al. (2015) who also found that expectancies modulate the P2 component of laser evoked potentials and not the N1

component. The probable generators of the P260 and the P2 components are in the ACC. The dorsal ACC has consistently been activated during pain and this area also consistently show reduced activity during placebo analgesia in fMRI studies (Wager & Atlas, 2015). Thus, expectancies may modulate intracortical processing of nociceptive input separately from spinal inhibition.

These studies contribute to the understanding of how placebo and nocebo effects modulate total treatment effects and are therefore relevant for understanding how to maximize treatment effects in clinical practice. In routine clinical practice the goal is to maximize the total treatment effect, i.e. the improvement compared to no treatment at all. This involves maximizing both active treatment effects and placebo effects, and minimizing nocebo effects. The present thesis investigates the modulation of total treatment effect by expectations in two different treatment models (Report II and Report III).

Another related issue that cannot be answered on the basis of the designs reviewed above is the question whether placebo and nocebo effects interact with the specific treatment effects. Analgesic drugs or treatments are directed at modulating nociceptive signaling either peripherally or in the central nervous system. Similarly, placebo and nocebo responses can also modulate nociceptive signaling in the same pathways as drugs or other kinds of treatments. This raises the question of how placebo effects and specific treatment effects combine to affect total treatment outcomes. Are placebo and drug responses additive, or do they interact?

The balanced placebo design (BPD) allows a test of the additive hypothesis. In the BPD, subjects are either given an active treatment (T+) or a placebo (T-). Treatment expectancies are manipulated in each group by informing half of the subjects in each group that they get the active drug (E+), or they are told that they get a placebo (E-). This creates four groups. Open treatment (T+E+), hidden treatment (T+E-) placebo (T-E+), and control (T-E-). With these groups one can investigate whether there is an interactive or additive relationship between drug and placebo: If the difference between the open treatment and the hidden treatment is unequal to the difference between the placebo and control, then there is an interaction. If they are equal, there is an additive relationship.

Previous studies with the BPD have found mixed results regarding the interaction of expectancies and drug effects. For instance, Benedetti, Amanzio, and Maggi (1995) used a variant of the BPD where the CCK antagonist proglumide or placebo (saline injection) were administered either openly (with information that it was a potent painkiller) or hidden (no

knowledge of administration). Open injection of placebo induced a placebo analgesic response. Open injection of two different doses of proglumide enhanced this response in a dose-response dependent manner. However, hidden administration of proglumide was ineffective for all doses. Therefore, proglumide only had an effect when subjects expected analgesia and this effect was larger than the placebo effect after open saline injection. One possible interpretation of these results is that an opioid mediated placebo analgesic response was induced and that the CCK antagonist potentiated the effect of endogenous opioids. This seems reasonable considering the fact that CCK agonists can block placebo analgesia (Benedetti et al., 2011). Another possible explanation, is that proglumide induced side effects that were noticed by the subjects and thereby increased treatment expectancies when they were present (in the open groups).

Similarly, as previously mentioned, Flaten et al., (1999) found that the muscle relaxant carisoprodol enhanced a placebo effect on reported tension. Possibly, carisoprodol acted as an active placebo, by inducing an internal stimulus that were interpreted in accordance with the treatment expectancies. In a later replication they administered carisoprodol, caffeine or placebo crossed with information that a stimulant, relaxant or that no drug was administered (Flaten et al., 2004). They observed that calmness decreased as serum levels of carisoprodol increased in the group receiving carisoprodol with information that they got a stimulant. This partly replicated their previous finding. However, no other interactions were observed between expectancies and drug effects. The authors argued that this might be related to the weak placebo responses in that study, and that enhancement of placebo responses by drugs requires that placebo responses are already present before the drug effect occurs, i.e. the presence of a placebo response before the drug effect is a necessary condition for active placebo responses to occur.

Opioid drugs are likely candidates for interaction with treatment expectancies since placebo analgesia can trigger the release of endogenous opioids in the descending pain modulatory system. Possibly, endogenous and exogenous opioids compete for the same receptors and interact. The first study to investigate this issue was Atlas et al. (2012). They administered the fast acting opioid remifentanil or placebo in a BPD. Treatment expectancies were manipulated by informing subjects that they had received either remifentanil or placebo. The results showed that both treatment expectancies and the drug reduced pain and that these effects were additive. Atlas et al. (2012) also performed an fMRI study where remifentanil was administered in an open-hidden design. This was not a BPD, but the brain concentration

of remifentanil was modeled and allowed the assessment of the contribution of treatment expectancies after infusion, but before drug concentrations began to rise in both the open and hidden condition. Again, both remifentanil and treatment expectancies reduced pain, but in an additive manner. Even though a placebo response was present before drug concentrations reached peak levels, there was no enhancement of the placebo response by the drug. Thus, the presence of placebo responses before the drug effect occurs is not a sufficient condition for active placebo responses to occur.

In sum, the evidence regarding possible interaction between treatment expectancies and active treatments are equivocal. Proglumide possibly enhance the placebo analgesic response by facilitating the effect of endogenous opioids triggered by expectancies. Thus, a prerequisite for proglumide acting as an active placebo is that a placebo response is already present before the drug effect occurs. There are some indications that drugs produce internal stimuli that can interact with treatment expectancies and modulate the placebo response. However, this is not a consistent result and many factors are probably involved. In general, more research in this area is needed.

Aim of Studies

The present thesis aimed to investigate the hypothesis that drugs can act as internal stimuli that enhance treatment expectancies and thereby the placebo response (Report I) (Dinnerstein, Lowenthal, & Blitz, 1966). Further, it was investigated whether positive and negative treatment expectancies modulate the total treatment effect and whether changes in stress are mediating these effects.

The present work addressed these three research questions:

i) Do drug effects provide an internal stimulus that reinforce response expectancies and enhance the placebo response to create placebo x drug interaction? (Report I)

ii) Do negative treatment expectancies attenuate or block treatment effects and are these effects mediated by increased stress and arousal? (Report II and III)

iii) Do positive response expectancies enhance treatment effects and are these effects mediated by decreased stress and arousal (Report I, II, and III).

Methods

Treatment Models

Caffeine. In report I 4 mg/kg body weight of caffeine (caffeine powder; Coffeinum 0.15 mm; Apotekproduksjon AS, Oslo, Norway) was administered in grapefruit juice. Grapefruit juice has no effect on the pharmacokinetic or pharmacodynamics effects of caffeine (Maish, Hampton, Whitsett, Shepard, & Lovallo, 1996). Caffeine is nearly totally absorbed from the gastrointestinal tract after about 45 minutes and peak plasma concentration occurs between 15-120 minutes in humans (Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999; Nehlig, Daval, & Debry, 1992). Since caffeine is hydrophobic there is no blood-brain barrier to caffeine and free passage from plasma to blood (Fredholm et al., 1999). In the experiment (Report I), subjects waited 30 minutes after caffeine administration before the posttest started. Thus, the posttest measures of arousal, stress, pain and LEPs were done 30-35 minutes after caffeine consumption. The plasma half-life of caffeine is variable, but the average value is about 4 hours (Meyer & Quenzer, 2005). The main mechanism involved in caffeine's psychostimulant effects is due to blockade of adenosine A_1 and A_{2A} receptors, at least within the normal doses consumed through beverages. At very high, close to toxic doses, other mechanisms could be at play (Fredholm et al., 1999). For the dose administered here, it is reasonable to assume that the effects of caffeine were mediated by its pharmacological action at adenosine receptors.

The effect of caffeine on pain was not crucial to our experiment. Although caffeine is used as an adjuvant in some analgesics, it is not generally considered to have analgesic effects in itself. Still, there are reports of small analgesic effects of caffeine in man (Keogh & Witt, 2001), although the general impression is that besides some evidence for an effect on headache, there is little support for any analgesic effects (Fredholm et al., 1999). On the other hand, it was important to use a drug with noticeable psychostimulant effects, and caffeine was chosen for this reason. The effects we were primarily interested in were consciously reportable arousing effects. Caffeine increase reports of arousal, alertness, positive moods and feelings of high compared to placebo (Childs & de Wit, 2006; Flaten & Blumenthal, 1999). Physiological effects include elevated systolic and diastolic blood pressure, skin conductance level and responses, and increased startle reflex amplitudes (Childs & de Wit, 2006; Flaten & Blumenthal, 1999). There have been some debate whether the stimulant effects of caffeine are just present in regular consumers with withdrawal symptoms (Nehlig et al., 1992). In these subjects, consumption of caffeine would adjust arousal to normal levels. In non-abstinent

subjects, however, caffeine would have no psychostimulant effects. This hypothesis is probably incorrect, since caffeine induce arousal, positive mood, feelings of high, and increase blood pressure in light, nondependent caffeine users (Childs & de Wit, 2006). Still, withdrawal symptoms are present in regular caffeine consumers which disappear after caffeine consumption, e.g. drowsiness, headache, anxiety, and others (Nehlig et al., 1992).

Conditioned pain modulation. Conditioned pain modulation (CPM) refers to the modulation of pain in which one noxious stimulus (the conditioning stimulus) modulate another (the test stimulus). Although the phenomenon that pain inhibits pain have been part of common knowledge a long time, it was research on animal models that identified the mechanism that form the basis of the effect (Lebars, 1979a, 1979b). In rat models, a spinal-bulbo-spinal loop has been identified as the key mechanism (Lebars, 1979a). Noxious input from the conditioning stimulus is conveyed to wide dynamic range neurons in the dorsal horn. These secondary neurons transmit a signal to the nucleus reticularis dorsalis in the caudal medulla. From here a descending inhibitory signal is sent back to the secondary neurons of the dorsal horn. The descending signal is widespread, causing inhibition at distant body parts (Lebars, 1979a; Nir & Yarnitsky, 2015). In animals the mechanism is termed diffuse noxious inhibitory controls (DNIC), while the behavioural correlate in humans is termed conditioned pain modulation (Yarnitsky et al., 2010). In experimental settings, CPM is perhaps the most studied model of endogenous analgesia.

CPM was applied in report II to investigate the effects of opposing verbal suggestions while a known pain inhibitory mechanism (DNIC) was activated. From this perspective CPM could be viewed as a substitute for an analgesic drug, since analgesic drugs also activate pain inhibitory mechanisms. Knowledge about how verbal suggestions modulate CPM could, therefore, be relevant for understanding how verbal suggestions modulate drug effects (Goffaux et al., 2007).

Lidocaine/prilocaine. In report III we used a local anaesthetic cream (EMLA) to reduce afferent nociceptive input to the CNS. The active ingredients in EMLA are lidocaine 2.5% and prilocaine 2.5%. Upon application of the cream lidocaine and prilocaine enters the epidermis, the outermost layer of the skin (Friedman, Mafong, Friedman, & Geronemus, 2001). Nociceptive nerve fibres terminate in free nerve endings in the epidermis. Free nerve endings contain specialized receptors that respond to noxious input. EMLA's anaesthetic action is mainly to stabilize the membranes of neurons by inhibiting the flux of ions across the

cell membrane. Thereby, the threshold for activation of action potentials is increased (Friedman et al., 2001).

The dose used in the experiment was 3 g applied to an area of 25 cm^2. The application period was 18 min. Thus, EMLA had been applied for 18 minutes before posttest 1 and 20-21 minutes before posttest 2. The recommended application time for total analgesia is 60 min (Friedman et al., 2001). However, significant increases in pain threshold assessed at the dorsum of hand with argon laser was observed after 15 min application (Arendt-Nielsen & Bjerring, 1988). The threshold increased steadily for 30 more minutes after removal of the cream before it declined. Application time for immediate pain block and total sensory blockade in that study were 80 minutes and 100 minutes respectively. Thus, the application time in our experiment should be sufficient to inhibit afferent activity in peripheral nociceptive nerve fibers.

Pain Models

In all three papers noxious thermal stimulation was applied to healthy volunteers to induce pain. In paper one a Nd:Yap 1340 nm laser was used to cause a rapid rise in skin temperature to selectively activate A-delta and C-fibres for the recording of pain and laser-evoked potentials in the electroencephalogram. In paper two a peltier-thermode (Thermosensory Analyzer II) was used for prolonged noxious heat stimulation of the skin together with a water bath as a cold pressor test. In paper three a peltier-thermode (Pathway) was used for noxious heat stimulation.

A rise in skin temperature above a certain threshold that is potentially tissue damaging are detected by two types of nociceptors, A-delta mechano heat sensitive nociceptors (AMH) and C-fibre mechano heat sensitive nociceptors (CMH). Activation of these underlie the perception of first and second pain respectively, due to the different conduction velocities of A-delta and C-fibres. In all our experiments the stimulus was applied to hairy skin, which is innervated by both AMHs and CMHs. Probably, this is the case also for glabrous skin (Iannetti, Zambreanu, & Tracey, 2006). Two types of AMH nociceptors have been identified. Type I AMHs have relatively low threshold for pressure and high threshold for temperature (median >53°C), and fast conduction velocities (mean 25 m/s). Type II AMHs have relatively high threshold for pressure and lower threshold for temperature (43-47°C, median 46°C), and slower conduction velocities (mean 15 m/s) (Iannetti et al., 2006). There are also several classes of C-fibres, but CMH are the most important for transduction of noxious heat. CMHs respond in the range 39-51°C with increased firing rate for higher temperatures. Thus, with

the temperatures applied in our experiments, the main contributors to afferent input were probably type II AMHs and CMHs. While type II AMHs adapt to repeated stimulation, CMHs sensitize (Dubin & Patapoutian, 2010).

Stimuli below approximately 15 °C can induce cold pain with a predominant aching quality (Davis & Pope, 2002). Noxious cold stimuli activate A-delta and C-fibres which increase in firing rate with decreasing temperatures between 20 – 0 °C, thus correlating with the linear increase in cold pain within this range (Schepers & Ringkamp, 2009).

Radiant heat and laser-evoked potentials. In the first experiment heat pain was induced with an infrared neodymium yttrium aluminum perovskite laser (Nd:YAP, Stimul 1340 nm, El.En. Group, Firenze, Italy). The laser radiates heat to a focused area without touching the skin. It therefore allows the selective activation of A-delta and C-fibres and avoids the concomitant activation of A-beta fibres. Concomitant activation of A-beta fibers might produce overlapping responses that masks pain specific brain responses and might also modulate nociceptive processing itself (Inui, Tsuji and Kakigi, 2006).

Another advantage is that laser stimulation allows the recording of brain responses time-locked to noxious stimulation. The rapid rise in skin temperature caused by laser stimulation ensures synchronization between stimulus onset and neural responses. As a result the brain responses that are time locked to stimulus onset can be identified by averaging EEG activity in a short time window following stimulus onset. EEG activity not related to the stimulus will show random fluctuations within the window and dissipate through averaging, while stimulus related activity will show up as positive or negative deflections in the EEG. When these potentials are triggered by laser stimulation they are called laser-evoked potentials (LEP). Stimuli that are perceived as painful evoke a typical negative-positive deflection that is maximal at scalp vertex (Carmon, Mor, & Goldberg, 1976). This biphasic vertex response is termed N2-P2, with latencies around 180-280 ms and 310-410 ms respectively, for hand stimulation. An earlier negative deflection, termed N1, preceding the typical biphasic vertex potential can also be observed with a different montage (Kunde & Treede, 1993). This deflection has maximal amplitude over temporal electrodes contralateral to the stimulated side. Its latency is around 130-170 ms after hand stimulation. These latencies are compatible with activation of A-delta fibers.

The plausible brain generators of these potentials have been investigated with dipole source modelling (Garcia-Larrea et al., 2003). The scalp potentials are probably generated by the combined activity of operculo-insular regions and anterior cingulate cortex. While the N1

probably is the result of mostly opercular activity (SII and possibly SI), the N2-P2 complex is the result of mostly insular and ACC activity (Garcia-Larrea et al., 2003).

The functional significance of LEPs is currently debated (Baumgärtner & Treede, 2009; Mouraux & Iannetti, 2009; Mouraux, Plaghki, & Iannetti, 2009). With regard to LEPs there is consensus that the N1 component reflects the brains earliest response to ascending nociceptive input and is more related to stimulus intensities than perception, while the N2-P2 components are more related to the perception of pain (Lee, Mouraux, & Iannetti, 2009). Several studies have found correlations between N2-P2 amplitude and reported pain intensity (Carmon, Dotan, & Sarne, 1978; García-Larrea, Peyron, Laurent, & Mauguière, 1997). Since the N2-P2 response correlates with perceived pain intensity it has been suggested that the generators of the N2-P2 complex are involved in pain intensity coding in the brain. However, N2-P2 responses are attenuated over time when the interstimulus interval is short and constant, while pain perception is not attenuated (Iannetti, Hughes, Lee, & Mouraux, 2008). Iannetti et al. (2008) investigated whether the correlation between N2-P2 and pain perception remained when three identical laser stimuli were presented with short and constant interstimulus intervals. While pain perception remained constant across the three stimulations both N1, N2 and P2 responses were reduced with stimulus repetition. If N2 and P2 responses reflect pain intensity coding this would not be expected. Iannetti et al. (2008) suggest that these laser-evoked responses instead encode stimulus saliency, since the attenuation of LEPs occurred between the first and second stimulus in the series with no further reduction between stimuli two and three. The first stimulus was less predictable both with regard to timing and intensity and was thus more salient. This hypothesis was further elaborated by Mouraux and Iannetti (2009). By randomly presenting auditory, visual, non-nociceptive and nociceptive stimuli they sought to disentangle neural activities contributing to evoked-potentials that were multimodal, somatosensory specific and nociceptive specific. They found that multimodal neural activity explained 76 ± 13 % of the LEP waveform contributing first and foremost to the biphasic waveform at scalp vertex (N2-P2 complex). This multimodal activity correlated positively with subjective ratings of stimulus saliency and was localized to the ACC and left-right operculo-insular regions. Surprisingly, they did not identify nociceptive specific neural activity. Since laser stimuli selectively activate A-delta and C-fibers that transmit nociceptive information through nociceptive specific pathways to the brain it is plausible that there exist nociceptive specific processing in the brain that is a component of the brains representation of pain. However, this nociceptive specific processing is possibly not detectable through classic

averaging techniques of laser-evoked potentials, with the possible exception of the N1 component. Therefore, a modification of N2-P2 LEPs could be interpreted as a modification of the saliency of the laser stimulus, thus involving modification of multimodal attentional processing and not nociceptive specific brain responses (Baumgärtner & Treede, 2009; Legrain, Iannetti, Plaghki, & Mouraux, 2011; Mouraux & Iannetti, 2009; Mouraux et al., 2009).

In our experiment we were primarily interested in measuring LEPs to rule out the possibility that the observed effects were due to reporting bias. Therefore, we focused on the N2-P2 components that are related to the perception of pain. Since these components are greatly attenuated or completely absent if the stimulus is not perceived as painful, we chose to calibrate the laser stimulus to ensure that all subjects would experience it as painful. The stimulus intensity used in the experiment was set to 1.5 x pain threshold. Calibration also has the advantage that all subjects experience comparable levels of pain.

Contact thermode. In study II and III thermal pain was induced with a peltier thermode of 30 x 30 mm (Study II: TSA II Neurosensory Analyzer, Medoc; Study III: Pathway, Medoc). This device monitors and controls stimulus temperature to ensure a constant stimulus temperature through internal circulating water pumped to and from a heated aluminum heat source. The peltier thermode allows a constant baseline temperature to reduce the influence of baseline temperature on pain threshold. In study II and III baseline temperature was set to 32 °C. Some studies have reported a relationship between the rise rate of stimulus temperature and pain threshold with higher thresholds for higher stimulus rates. In study II and III a rise rate of 10 °C/s was chosen. Psychophysical studies of pain in man and in animals have found that contact heat pain threshold occurs around 43-46°C, with some variability across different areas of the body and with somewhat lower threshold for women and increasing age (Neziri et al., 2011; Price, McHaffie, & Stein, 1992). Stimulus intensities was identical for all subjects in study II and III and were set to 46°C (duration 150 seconds) and 48°C (duration 12 seconds) respectively.

Cold-pressor test. In paper II we used the cold pressor test (CPT) as a conditioning stimulus to induce CPM under different expectations. The cold pressor test consists of submerging an extremity (hand or foot) in cold water. The water bath was a Jeio Tech Lab Companion RW-3025G bath and circulator (Jeio Tech, Gimpo, Republic of Korea) that maintains the water temperature at a constant level. The constant temperature was set to 8°C, well below the normal threshold for cold pain at around 15°C and below temperatures

observed to induce CPM, e.g. 12°C (Granot et al., 2008). CPM is not correlated with the perceived painfulness of the conditioning stimulus, although it is related to the intensity of the stimulus (Chalaye, Devoize, Lafrenaye, Dallel, & Marchand, 2013; Granot et al., 2008). The stimulated area was the dominant hand submerged to just above the wrist with a duration of 150 seconds. Importantly, we made sure that the body region submerged in water was identical across subjects in order to avoid any differences in spatial summation.

A cold water bath cools skin temperature and thereby initiates two separate but related physiological processes. First, the cooling of skin temperature results in vasoconstriction with a concomitant increase in heart rate and blood pressure. Second, the cooling of skin to potentially tissue damaging temperatures activates nociceptive fibres involved in the perception of pain. Chalaye et al. (2013) found that increased systolic blood pressure during CPT was associated with larger CPM. Based on the literature we were confident that the stimulus parameters used would be sufficient to induce CPM.

Pain Measures

In study I, subjects reported pain intensity after each laser stimulus on a numerical rating scale (NRS) where 0 represented “no sensation”, 4 represented “barely painful” and 10 “unbearable pain”. (Brown et al. 2008; GarciaLarrea et al. 1997; Leandri et al. 2006; Watson et al. 2007).

In study II pain intensity and unpleasantness were recorded by numerical rating scales (NRS) where the subject indicated vocally how intense and unpleasant the pain was on a scale from 0 (no pain) to 10 (unbearable pain or the most unpleasant pain imaginable). The difference between pain intensity and pain unpleasantness was explained by the radio metaphor recommended by Price, McGrath, Rafii, and Buckingham (1983), where intensity corresponds to the loudness of the sound and unpleasantness to how it affects you.

In study III the participants reported their pain intensity during each stimulus on a Computerized Visual Analogue Scale (COVAS; Medoc) from 0 to 100, where 0 represented “no pain” and 100 represented the “most intense pain imaginable.” Pain intensity was electronically recorded after each pain stimulus.

Measures of Expectancies

Expectancies were measured in study I and II. In study I two types of expectancies were recorded: certainty of pain relief and expected pain reduction. Research on expected pain and the match/mismatch between expectation and experience, indicate that the certainty

of expectations is an important factor in how a match/mismatch between expectation and experience affects future responses (Arntz & Lousberg, 1990). Thus, both expected pain reduction and the certainty of those expectations were measured.

On the days the subjects were told they received the drug, certainty of pain relief was measured by asking "Answer as exact as possible what your expectations were just before the posttest. On a scale from 0–100 were 0 means 'not certain at all' and 100 means 'completely certain' , how certain were you that the pain relieving drug you received today would be efficient in relieving the pain" (Arntz & Lousberg, 1990). Certainty/uncertainty about pain intensity has been found to mediate top down influences on pain perception (Brown, Seymour, Boyle, El-Deredy, & Jones, 2008). Expected pain reduction was measured on all days by asking: "Did you expect the pain to decrease in the posttest compared to the pretest? YES/NO. If you were expecting a decrease: on a scale from 0–100 were 0 means 'no reduction' and 100 means 'total reduction', how much reduction in pain did you expect?". If subjects answered "NO" to the first question, a value of zero was entered.

In study II Subjects in the analgesia group were asked how much percent decrease (0-100%) in heat pain they expected as a result of putting the hand in cold water. Subjects in the hyperalgesia group were asked how much percent (0-100%) increase in heat pain they expected as a result of putting their hand in cold water.

Cardiovascular Measures

In study II electrocardiography (ECG) was recorded continuously at 1000 Hz from two electrodes attached to the lower ribs and one reference electrode over the right hip-bone by a Biopac MP 150 system with Biopac Acqknowledge 3.7.1 software (Biopac Systems Inc, Goleta, CA) according to the manufacturer guidelines. The rationale behind measuring ECG was to obtain measures of heart rate and heart rate variability (HRV) at baseline, before pain stimulations and during pain. Measures of HRV was intended as an index of stress to investigate whether CPM and placebo/nocebo effects were related to cardiovascular activity and stress (Aslaksen & Flaten, 2008). However, due to recording failure we obtained only measures of HR during the painful stimulations.

In study III, blood pressure was measured with a standard electronic blood pressure device (Microlife, Widnau, Switzerland). Blood pressure was measured to test the hypothesis that placebo and nocebo effects are mediated by changes in stress, since acute stressors increase blood pressure.

Subjective Stress and Arousal

In all three studies subjective stress and arousal was measured with four adjective pairs from the Short Adjective Check List (SACL) (Mackay, Cox, Burrows, & Lazzerini, 1978) in Norwegian translation. Subjective stress was measured by two NRSs anchored by the two adjective pairs tense–relaxed and nervous–calm, where a score of zero indicated completely relaxation/calmness and a score of 10 indicated maximum tension/nervousness. Subjective arousal was measured by two NRSs anchored by the two adjective pairs energetic–tired and alert–drowsy, where a score of zero indicated completely tiredness/drowsiness and score of 10 indicated maximum alertness/energetic. Stress and arousal were expressed as the mean of the two NRSs used for reporting of subjective stress and arousal. The items from the SACL were chosen for their high factor loadings on the stress and arousal factors on the SACL, similar to earlier research on stress and arousal (O'Neill & Parrott, 1992).

In study I the measures were obtained immediately prior to the pretest and the posttest, in study II they were obtained upon arrival and during all pain stimulations, while in study III they were obtained before the pretest, immediately after the administration of Emla/placebo, and immediately after the posttests.

Questionnaires

Fear of pain might increase pain sensitivity and attenuate placebo responses (Lyby et al., 2011; Lyby et al., 2012). Optimistic or pessimistic life orientation as assessed by the revised Life Orientation Test (LOT-R) might be related to placebo and nocebo responses (Morton, Watson, El-Deredy, & Jones, 2009). Hence, in study II, fear of pain and optimism–pessimism were measured in order to rule out group differences in these variables.

To assess fear of pain related to specific situations the Fear of Pain Questionnaire (FPQ-III) was administrated. The questionnaire consists of 30 items rated on a five-point Likert scale (1 = not at all, to 5 = extreme). The questionnaire was translated into Norwegian and the sum score of all items was used as a dependent variable (Lyby et al., 2010).

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

Summary of Papers

Paper I: Bjørkedal, E. & Flaten, M. A. Interaction between expectancies and drug effects: an experimental investigation of placebo analgesia with caffeine as an active placebo. *Psychopharmacology*, 2011, Jun; 215(3):537-48.

We investigated whether interoceptive cues, induced by the administration of 4 mg/kg body weight of caffeine, would enhance the placebo analgesic response. Subjects received either 0 (T-) or 4 mg/kg (T+) body weight of caffeine in grapefruit juice and were either told that the drink contained a powerful painkiller (E+) or that it contained no drug (E-) in a within-subjects double-blind balanced placebo design. We hypothesized that the psychostimulant effect of caffeine would enhance the certainty of expectations of drug effects and thereby the placebo analgesic response. Measures of subjective arousal were obtained to investigate the psychostimulant effects of caffeine. Subjects reported their expectations of drug effects. Pain was induced with a Nd:YAP 1340 nm laser that selectively activates A-delta and C-fibers in order to measure ERP components related to the cortical processing of nociceptive information.

Twenty-three subjects participated in the experiment. All subjects were regular caffeine consumers. Three subjects were excluded from the analysis because they did not experience the laser stimulus as painful. Thus, 20 subjects (7 females) were included in the final analysis. There were no differences on any of the variables measured at arrival or in the pretests. The results showed that subjects expected larger reductions in pain after information that they received a painkiller compared to information that they received placebo. Caffeine increased arousal compared to no caffeine. Thus, the manipulations were successful. Contrary to our hypothesis increased arousal after caffeine administration did not increase certainty of expectations in the active placebo condition (T+E+) compared to the placebo condition (T-E+). Caffeine reduced pain intensity compared to placebo. The drug effect on N2 was marginally significant, with caffeine showing larger reductions compared to placebo, indicating that caffeine reduced both pain and nociceptive processing in the cortex. There was no main effect of treatment expectancies on pain or LEPs and the predicted interaction between drug and treatment expectancies was not observed on either reported pain or LEPs. No other effects on LEPs and no effects on stress were observed.

Since caffeine reduced pain and this was congruent with treatment expectancies in the active placebo condition (T+E+) but incongruent in the caffeine condition (T+E-), we tested

whether the analgesic effect of caffeine changed over time as a function of treatment expectancies. We had obtained 20 pain ratings in the pretest and 20 in the posttest and these were divided into 4 blocks. The mean of the 5 stimuli in each block was computed. Then we subtracted the mean of each block in the pretest from the mean of each block in the posttest and included block as a factor in the ANOVA. The results showed that an interaction between treatment expectancies and drug developed over time. Pain reduction in the active placebo condition (T+E+) at the last block was significantly larger than in the caffeine condition (T+E-), suggesting that caffeine acted as an active placebo. The difference in pain reduction between the active placebo condition and the caffeine condition correlated with certainty of expectancies, i.e. higher certainty of pain relief from the drug was associated with larger reduction in pain in the active placebo condition (T+E+) compared to the caffeine condition (T+E-).

These results provide evidence of a placebo effect only when an active drug is administered. A possible explanation is that the drug effect was congruent with treatment expectancies in the active placebo condition and this might have resulted in an updating and boosting of expectations. Conversely, the drug effect was incongruent with information provided in the caffeine condition and this might have induced uncertainty.

Paper II: Bjørkedal, E. & Flaten, M. A. Expectations of increased and decreased pain explain the effect of conditioned pain modulation in females. *Journal of Pain Research*, 2012; 5: 289–300.

The aim of the study was to test whether expectancies of either increased or decreased pain modulate conditioned pain modulation (CPM). It was also investigated whether changes in stress during CPM was associated with effects of treatment expectancies and whether there were any sex differences in these effect. A contact thermode holding 46°C was either applied to the arm alone or simultaneously with submerging the contralateral hand in ice water to induce CPM. Subjects were allocated to one of three groups that received different information about the effect of the conditioning stimulus on the pain induced by the test stimulus. One group were not given any information (control group), another group was told that it would reduce pain (analgesia group), and the third group was told that it would increase pain (hyperalgesia group). The groups were balanced according to sex and order of administration of conditioning stimulation (test stimulus alone first, or CPM first) by stratified randomization. The experimenters were uninformed about the effects of CPM. Pain intensity

and unpleasantness, stress and arousal were measured during pain. Treatment expectancies were measured after the information about treatment effect. The electrocardiogram was recorded in order to test whether expectancies had any effect on heart rate variability prior to pain and during pain. All subjects underwent a pretest to get experience with the test stimulus, three trials with the test stimulus alone and three trials with CPM. We hypothesized that CPM would reduce pain and that this effect would be larger in the analgesia group compared to the control group, and smaller in the hyperalgesia group. Due to divergent findings in the literature, we had no a priori hypothesis regarding sex differences.

There were no differences between the groups on any of the measures at arrival, in the pretest or in the trials with test stimulus alone. There was no main effect of CPM, but there was a significant effect of order of presentation, such that CPM decreased pain when administered last, but not when administered first. A significant group x test x sex interaction was observed. This was due a significant main effect of CPM for males but not for females. For males there were no differences between the groups. For females there was a significant difference between the analgesia group and the hyperalgesia group. CPM increased pain in the hyperalgesia group for females and decreased pain in the analgesia group. Thus, treatment expectancies modulated CPM in females only. Subjective stress increased during CPM compared to test stimulus alone, but there were no group differences. However, females in the hyperalgesia group reported increased stress during CPM compared to the other groups. HRV data were lost due to technical failure and only HR data during pain were recorded. CPM increased heart rate compared to test stimulus alone. The effect of order of presentation was significant such that HR was lower during test stimulus alone when presented after CPM compared to when test stimulus alone was presented first. Correlation analyses showed that treatment expectations were positively correlated with change in pain, i.e. expectations of reduced pain was associated with larger reductions in pain with CPM. Lower stress during CPM was associated with larger pain reductions during CPM.

In conclusion, treatment expectancies had an effect in females, but not in males. Conditioning stimulation increased stress, but not heart rate in females in the hyperalgesia group. An additional novel observation was that CPM is sensitive to order effects.

Paper III: Aslaksen, P.M., Zwarg, M.L., Eilertsen, H-I.H., Gorecka, M.M & Bjørkedal, E. Opposite effects of the same drug: reversal of topical analgesia by nocebo information. *Pain*, 2015; 156 (1): 39-46.

The observation that hyperalgesic suggestions can reverse the effect of CPM indicates that the effect of analgesic drugs can also be reversed by negative information. We investigated whether negative treatment expectancies modulated the effect of a local anaesthetic cream on contact heat pain and whether these effects were mediated by subjective and physiological stress. Subjects were randomized to one of six groups. In three groups the local anaesthetic cream EMLA (lidocaine/prilocaine) was administered with verbal suggestions that it was analgesic (EMLA group), hyperalgesic (EMLA nocebo group) or no specific information (EMLA reduced information). In two groups a placebo cream was administered with suggestions of analgesia (placebo group) or hyperalgesia (nocebo group). The last group was a natural history group. Heat pain was administered to healthy subjects before and after application of EMLA cream. Pain was continuously recorded during stimulation with a computerized visual analogue scale (VAS). Subjective stress and blood pressure was recorded before the pretest, after treatment, and after the posttest. We predicted that treatment expectancies would modulate the effect of EMLA such that EMLA with positive treatment expectancies would be superior to EMLA with reduced treatment expectancies and placebo with positive treatment expectancies, and that negative treatment expectancies would block the effect of EMLA. Stress and blood pressure were measured and we hypothesized that the effects of information were mediated by changes in stress and blood pressure.

The results confirmed that the local anaesthetic had an analgesic effect, since EMLA with positive treatment expectancies was better than placebo with the same expectations. EMLA with positive treatment expectancies was not significantly different from EMLA with reduced treatment expectancies, showing that there was no placebo response when EMLA was administered. No placebo analgesic response was observed in the placebo group either. The drug's analgesic effect was reversed into nocebo hyperalgesia when administered with negative treatment expectancies. Interestingly, the nocebo response with EMLA was not different from the nocebo response with placebo, even though an effective treatment was working in the opposite direction. Finally, the nocebo hyperalgesic effects were mediated by increased stress and systolic blood pressure.

In conclusion, the results showed that treatment expectancies can reverse the analgesic effect of a topical analgesic cream and that this was related to the level of stress.

Discussion

The present work provided three main findings: i) caffeine interacted with treatment expectancies and produced a placebo response in the presence of caffeine but not in the presence of placebo; ii) the analgesic effect of EMLA was reversed to hyperalgesia by negative treatment expectancies, and this effect was mediated by increased levels of stress; iii) the effect of CPM was modulated by treatment expectancies in females only.

In report I, we hypothesized that verbal suggestions would induce expectations of analgesia and a placebo analgesic effect when both inert placebo and active placebo was administered. We expected that the arousing effects of caffeine would produce an internal stimulus that would be interpreted as evidence that a real painkiller had been administered and boost the placebo analgesic effect. The assumption behind this line of reasoning, is that subjects enrolled in a clinical trial, or being treated by a doctor, have more or less certain expectations about the effects of treatments and will search for cues to confirm or disconfirm their expectancies. A corollary of this assumption is that expectancies will continuously be updated based on experiential evidence. Previous research show that expectancies that are confirmed will increase the certainty of these expectations (Arntz & Lousberg, 1990), and certain expectancies are stronger modulators of perception compared to uncertain expectancies (Brown et al., 2008). Thus, the subjects reported what their expectancies were just before the posttest were to begin, 30 min after drug administration. Even though caffeine increased arousal compared to placebo, this did not lead to increased expectations of pain relief, neither the amount of expected reduction nor the certainty of these expectations. Therefore, the prediction that increased arousal would enhance treatment expectancies in the active placebo condition was not supported, and increased arousal seems unlikely as an explanation for the active placebo effect.

On the other hand, the experience of reduced pain after caffeine could interact differently with the prior expectancies in the two conditions receiving caffeine. There is a line of research showing that expectancies of upcoming stimuli are updated based on prior matches or mismatches between experienced pain and predicted pain (Arntz & Lousberg, 1990; Arntz, van den Hout, van den Berg, & Meijboom, 1991; Rachman & Arntz, 1991). In the active placebo condition, there was a match between the experience of reduced pain and treatment expectancies. Thus, the expectancies were reinforced over time. Arntz and Lousberg (1990) observed that certainty of expectations increased linearly over time with increasing number of confirmatory evidence. This might explain why the active placebo effect

was present towards the end of the posttest; for each trial that confirmed the initial expectation the certainty increased linearly. In the caffeine condition, there was a mismatch between experience and treatment expectancy and thus a need for updating expectancies. Why this should lead to increased pain over time in the caffeine condition is unclear. In fact, previous research show that experiencing more pain than expected (underprediction) leads to subsequent increases in pain responses, uncertainty, anticipatory fear and skin conductance responses (Arntz et al., 1991). On the other hand, experiencing less pain than expected (overpredictions) has little effect on subsequent behavior and physiological responses, possibly because it is less aversive to prepare for the worse than to underpredict pain (Arntz et al., 1991). In a balanced placebo design with d-amphetamine as the drug, it was observed that anxiety increased in the conditions were there was a discrepancy between what they expected and what they got (Mitchell, Laurent, & de Wit, 1996). Similarly, in the caffeine condition, the discrepancy between what they expected and what they experienced might have increased anxiety or other emotions interfering with pain. However, we have no data to back this up and future research should investigate how matches and mismatches affect placebo and nocebo responses, by measuring expectancies, pain and the emotional impact of match/mismatch on a trial by trial basis both after placebo and drug.

The observation that a placebo effect was present only when the active drug was administered is in line with Schenk et al., (2014). They studied the effect of EMLA on pain in a within-subjects balanced placebo design and found a placebo effect only when active drug was administered. In report I it was argued that the effect could be due to the analgesic effect of caffeine providing feedback that enhanced expectancies over time. Unfortunately, we did not measure expectancies before every trial and could not test this explanation. However, Schenk et al. (2014) measured expectancies before every trial and observed increased expectancies over time in the open drug condition and decreased expectancies over time with placebo. Related to this point, Vase et al. (2005) found that placebo analgesia increased over time in patients with irritable bowel syndrome that were administered an inert placebo or lidocaine for their pain. Expected pain was measured both after 5 and 22 min and these expectancies explained more of the variance in placebo responding 25–40 min after administration of placebo compared to 5–20 min after. The authors suggested that the initial decrease in pain during the first 20 min matched and enhanced subject's expectancies over time. Thus, there is converging evidence suggesting that drug effects can reinforce expectancies that are congruent with these effects.

Flaten et al. (2004) suggested that active placebo responses require that a placebo response is already present before the drug effect occurs. The results from Report I does not support this, nor does the observations by Schenk et al. (2014). In addition, Atlas et al. (2012) found that a placebo response was present before the drug effect occurred, but the drug did not enhance the placebo response. Therefore, it seems that the presence of a placebo response before the drug effect is neither necessary, nor sufficient for active placebo responses to occur. On the other hand, Benedetti et al. (1995) found that a CCK antagonist enhanced the placebo analgesic response that was already present. CCK antagonists have been found to enhance morphine analgesia (Wiesenfeld-Hallin, Xu, Hughes, Horwell, & Hökfelt, 1990). Thus, although speculative, it is possible that drugs interfering directly with neurotransmitters involved in placebo analgesia require that a placebo response is already present in order to enhance this response. Hypothetically, a CCK antagonist would only enhance placebo analgesia if endogenous opioids were already released by a prior placebo analgesic response. Indeed, if this hypothesis is correct, it suggests that interaction between active treatment and treatment expectancies, in some instances, does not require the drug effect to be consciously detected. This line of reasoning suggest a classification of two types of interactions between active treatment and treatment expectancies. For some treatments, not interacting directly with the neurotransmitters involved in placebo analgesia, the conscious detection and interpretation of drug effects would be necessary for an active placebo response to be elicited. For other treatments, interacting directly with the neurotransmitters involved in placebo analgesia, an active placebo response would not require conscious detection and interpretation. These hypotheses are difficult to test, but would be interesting to pursue.

The active placebo effect was small. In the final block, the mean pain reduction of 5 pain stimuli in the active placebo condition was 1 unit on the NRS, while the corresponding reduction in the caffeine condition was about 0.2 units, i.e. there was a difference of 0.8 units of NRS. Considering that the partitioning of pain scores into blocks to look for time trends was not planned, it should be interpreted with some caution. Even though it was theoretically justified, since caffeine had an unexpected analgesic effect and prior research indicated that expectancies can be reinforced over time (Arntz & Lousberg, 1990; L. Vase et al., 2005), the experiment should be replicated. A future replication should measure expectancies, pain, arousal and their physiological correlates at several points in time before and after administration of caffeine or placebo.

Related to the results of Report I, one would expect that effective analgesic treatments provide feedback that decrease nocebo hyperalgesic responses, i.e. that initial nocebo responses decrease over time as the analgesic effect is experienced. Contrary to this, we observed a reversal of the analgesic effect of EMLA in the nocebo EMLA group in report III. This is remarkable if we assume that EMLA reduced afferent inpunt to the spinal cord and cortex, as indicated by the drug effect. Similar results were obtained by Bingel et al. (2011) who demonstrated that the analgesic effect of remifentanil was blocked by expectations of increased pain. The effect was even more pronounced in our study, since analgesia was reversed into hyperalgesia. Actually, this shows that nocebo responses not only subtracts the placebo response away from the treatment effect, but that it may block the treatment effect altogether. Prior research indicate the involvement of negative emotions in this response (Benedetti et al., 2006; Bingel et al., 2011). For instance Bingel et al. (2011) observed opposite effects of positive and negative treatment expectancies on sgACC, an area implicated in descending pain modulation. During positive expectations activity in this area increased, while it decreased during negative expectations. Further, the nocebo response was predicted by increased activity in medial prefrontal cortex, MCC and the hippocampus. These areas are implicated in the exacerbation of pain by negative emotions. In addition, they also observed increased anxiety when negative treatment expectancies were induced, suggesting that negative emotions were an important factor in the response. Thus, the observed increase in stress and blood pressure in the nocebo groups in our study are in line with prior research and suggests an involvement of descending facilitatory modulation of pain by negative emotions somewhere along the pain processing network.

We investigated the hypothesis that negative treatment expectancies increase stress and that this is mediating the increased pain in the nocebo groups. Blood pressure was measured prior to the pretest, after the administration of cream and verbal suggestions, and after the posttest. The results showed that positive and negative treatment expectations had opposite effects on subjective stress and blood pressure. Suggestions of analgesia decreased stress and blood pressure while suggestions of hyperalgesia increased them. Further, stress and blood pressure mediated the effect of both positive and negative treatment expectations on pain. This is consistent with earlier studies showing that nocebo hyperalgesia is related to anxiety and a negative emotional state (Benedetti et al., 2006; Bingel et al., 2011) and studies showing that placebo analgesia is mediated by reduced stress (Aslaksen et al., 2011; Aslaksen & Flaten, 2008).

Consistent with previous research on the relation between blood pressure and pain, we observed that higher levels of systolic blood pressure were related to decreased pain (al'Absi & Petersen, 2003). However, hyperalgesic and analgesic suggestions had opposing effects on blood pressure. Suggestions of analgesia decreased blood pressure and this decrease mediated decreased pain. Suggestions of hyperalgesia increased blood pressure and this increase mediated decreased pain, i.e. larger increases in blood pressure after hyperalgesic information was associated with less pain in the posttest. These results are hard to interpret, but they at least suggest that stress and blood pressure are independent modulators of pain. While negative expectancies increased stress, blood pressure and pain, only the increase in subjective stress mediated an increase in pain. Thus, the increased blood pressure after negative expectancies cannot account for the nocebo hyperalgesic effect. Given that high systolic blood pressure is associated with decreased pain, these results suggests that increased blood pressure might dampen the nocebo hyperalgesic response. This hypothesis could be tested by somehow manipulating blood pressure levels after induction of negative treatment expectancies.

The results from report II were less clear. The results showed that there was no CPM in the no info group. Therefore, we cannot be certain that CPM was present, and consequently that expectations modulated the CPM effect. Still, our observations are in fact congruent with the observations done in two other reports manipulating expectancies towards CPM. Goffaux et al. (2007) found that CPM reduced pain, somatosensory evoked potentials and spinal nociceptive withdrawal reflex after analgesic suggestions, but that this effect was blocked after hyperalgesic suggestions. Inspection of their data show that about four of the subjects in the hyperalgesia group exhibited an effect of CPM, while the 6 remaining subjects exhibited no change or increased pain. Goffaux et al. (2009) found that expectancies of analgesia induced CPM responses in females with fibromyalgia, while expectancies of hyperalgesia resulted in a nocebo hyperalgesic response during CPM. Taking all these observations into consideration, indicate that expectations of increased pain can abolish the analgesic effect of CPM.

The observed sex difference in nocebo response observed in report II was not replicated in report III. Although females showed a similar response in report II and III, males showed a nocebo hyperalgesic response only in report III. Suggestions of hyperalgesia reversed the analgesic effect of EMLA similarly in males and females, while CPM was only reversed in females in report II. However, it should be noted that only 7 of 22 subjects in the

nocebo EMLA group were males. These sex differences must be treated with caution. The sample sizes in the groups were too small to draw any firm conclusions. Further, we did not control for menstrual cycle, a factor that could influence pain sensitivity (Mogil, 2012). Thus, these results should be replicated with better controlled studies before any possible explanations are provided.

Pain report is subject to social influences and it cannot be ruled out completely that the treatments changed the subject's pain report without changing nociceptive processing and the perception of pain. In report II and III we included physiological measures that are modulated by pain but are not specific for pain. Generally, the physiological measures correlated well with subjective reports, both of stress and pain. It is therefore unlikely that our results could be entirely explained by reporting bias. In future studies it would be better to include more specific measures of nociceptive processing, for instance fMRI, nociceptive reflexes or ERPs. In report I we controlled for reporting bias by including laser evoked potentials as an electrophysiological correlate of pain. The pattern of results for the N2 LEP data were similar to the pain report data. We observed no placebo effect, and no interaction between drug and treatment expectancies. There was also a marginally significant effect of drug on N2 potentials indicating that the drug effect on pain was reflected in reduced cortical responses to A-delta fiber activity triggered by the laser stimulus. There were no effects on the P2 data. If caffeine reduced pain by reducing nociceptive input to the cortex, we would expect a drug effect on both the N2 and P2 components. However, the level of arousal modulate N2 and P2 amplitudes to laser stimuli (Beydoun, Morrow, Shen, & Casey, 1993). Beydoun et al. (1993) observed that during drowsiness, both N2 and P2 amplitudes were reduced compared to wakefulness, with a larger effect on the P2 amplitude. Since caffeine enhanced arousal in our experiment, this could have occluded a drug effect on the N2 and P2 component, with a larger impact on the P2 component.

We also observed correlation between posttest-pretest difference scores on pain and both N2 and P2 amplitudes in the placebo and active placebo conditions. Since the latency of N2 and P2 components were in the range 200-350 ms, and the normal reaction time to laser stimuli is longer than this (Plaghki & Mouraux, 2003; Sikandar, Ronga, Iannetti, & Dickenson, 2013), it is reasonable to suppose that N2 and P2 amplitudes are not modulated by decisions on how to report. Thus, the reduction in pain in the active placebo condition was at least not entirely due to response bias, but reflected changes in cortical processing of the laser

stimulus. Why the correlations were only present in the placebo and active placebo condition is unclear.

Overall Conclusions

The present observations and interpretations encourages the following conclusions that should be put to further empirical testing:

i) Drugs can enhance the placebo analgesic response. The effect of a drug can serve as an internal stimulus that provide feedback and either enhance or disrupt the drug effect, depending on the content of verbal suggestions given upon drug administration. This should be further investigated by including trial by trial measures of expected pain levels, pain report, measures of emotional reactions and physiological indexes of both pain and emotional responding. Measures of individual sensitivity to internal cues could also be considered to investigate individual differences.

ii) Negative treatment expectancies can block the effect of analgesic treatments. This nocebo hyperalgesic effect is partly mediated by the increased stress induced by negative expectancies.

iii) Caffeine reduce pain, but this effect is modulated by treatment expectancies.

These results have important implications for the design and interpretation of clinical trials and for clinical practice. In the randomized double blind clinical trial, which is the gold standard for testing drug efficacy, it is assumed that the placebo response is identical in the active drug group and the placebo group. Hence, the drug effect can be measured by subtracting the response in the placebo arm from the drug arm. However, these results show that the drug effect, either its side effects or its effects on the symptom, can provide feedback that enhance the placebo response in the drug group. Thus, the assumption of additivity of placebo response and drug response might not always hold.

The results of the studies reported here supports the notion that expectancies will continuously be updated based on experiential evidence. Thus, patients receiving treatments for their symptoms might search for confirmations that the treatment was effective. Correct expectations might increase confidence that the treatment is working and this might enhance the treatment effect. Incorrect expectations might in the worst case block the drug effect or increase the symptoms. Thus, giving patients the proper information is important.

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