From DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

TESTING THE BOUNDARIES FOR EXPECTATION EFFECTS IN HEALTH AND DISEASE

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Stockholm 2022

Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2022

ISBN 978-91-8016-737-6
Cover illustration: Boundaries, illustration by Sebastian Pontén.

TESTING THE BOUNDARIES FOR EXPECTATION EFFECTS IN HEALTH AND DISEASE
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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The thesis will be defended in public at Karolinska Institutet, Solna, 16th of September.

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POPULAR SCIENCE SUMMARY OF THE THESIS

Our expectations affect us in our daily lives, yet we are rarely aware that we have them. Without us consciously knowing, our expectations constantly exacerbate and minimize symptoms in our body. We might think that it is the new diet we just started that has made us less sick, or the polluted air in our neighborhood giving us the headache. Yet, it might just be these expectations that shape these symptoms.

The research area of how expectations shape our health has increased during the last 50 years and with the development of fMRI and PET methods there have been great advances of which neurobiological mechanisms are involved in this process. Expectation effects have been shown to be created in mainly four ways; conditioning, social learning, therapeutic relationship, and verbal/written information. Yet, it is unclear what is minimally required to elicit these effects.

The purpose of this thesis is to investigate three factors traditionally considered important for the formation of expectation effects: conscious awareness, endogenous opioids (the body's own "morphine") and face-to-face therapeutic encounter.

In study I, we investigated if pain processing would be affected by conscious awareness by giving pain while participants were asleep and awake. We found that pain processing, such as the "pain alarm" response, is partly dependent on conscious awareness. In study II, we blocked endogenous opioids pharmacologically by using naltrexone to test if these endorphins were necessary for pain conditioning. Results showed that conditioned responding was not dependent on endogenous opioids. In study III, we tested if placebo analgesic effects (pain reduction) could be created via online communication. We found that placebo analgesic responses were created even when information about a pain-relieving treatment was delivered online. In study IV, we collected raw data from studies that randomized between online and face-to-face psychological treatment to assess whether treatment expectations have comparable effects on treatment outcomes. Our findings suggest that treatment expectations are equally important for online as face-to-face interactions. In sum these results challenge known boundaries for when expectation effects can be created.

ABSTRACT

Expectations affect our physiology and clinical outcomes, however the boundaries for this modulation are poorly understood. The purpose of this thesis is to investigate minimal requirements to elicit expectation effects on health-related outcomes, using experiments and an independent patient data meta-analysis. More specifically, this thesis will build on three aspects that traditionally are considered important for the formation of expectation effects: conscious awareness (Study I), endogenous opioids (Study II) and face-to-face interaction with a health-care representative (Study III, Study IV). I will thus investigate expectation effects from neurobiology up to our interaction with the context around us.

In study I the role of conscious awareness in pain processing was investigated in a non-clinical population (*N*=114) to see if expectations can shape pain even when the participant is not aware of getting noxious stimuli. This was done by assessing whether noxious heat given while asleep would lead to changes in pain ratings in a subsequent test-phase when awake. Two control experiments consisted of only the test-phase. The results showed that participants who had been getting noxious heat while they were sleeping, displayed the same pattern of heightened pain ratings (i.e., pain alarm response) as participants in the control conditions who had not been exposed to the noxious stimuli during sleep. In comparison, the awake condition rated all test-phase stimuli the same. The results emphasize how important expectations are for shaping pain perception.

Study II investigated if endogenous opioids are necessary for placebo-like effects/conditional responding. Healthy participants (*N*=30) were randomized to naltrexone/placebo before a pain-cue conditioning, using pressure pain and functional magnetic resonance imaging (fMRI). Results show comparable conditioned analgesic (pain relieving) and hyperalgesic (pain enhancing) responses in participants with naltrexone or placebo. These findings indicate that full function of the endogenous opioid system during pain conditioning is not necessary for conditional responding.

Study III investigated if placebo effects can be created through online communication. Healthy participants (*N*=30) were randomized to empathetic/neutral communication online where they learnt about a sham analgesic TENS machine (fake pain-relieving machine). After this, a placebo experiment face-to-face was performed, in which the communication was held to a minimum. Results showed that placebo effects were induced during online communication, both in the empathetic and the neutral condition.

In Study IV expectation ratings and how they relate to treatment outcome in online and face-to-face psychological treatment were investigated in an individual patient data meta-analysis. Individual participant data from studies that randomized patients to online versus face-to-face psychological intervention and who administered the Credibility and Expectancy Questionnaire (CEQ) were analyzed. Results shows comparable effects of how expectation ratings predicted clinical outcomes post treatment between online and face-to-face treatments.

These results suggest that pain processing such as pain alarm response is affected by conscious awareness, endogenous opioids are not necessary in all situations to create pain cue conditioning, placebo effects can be created through online communication and expectations seem to be just as important for online treatments as it is for treatments delivered face-to-face. In sum, these results challenge formerly known boundaries for expectation effects.

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I. **Pontén, M.,** Fust, J., D'Onofrio, P., van Dorp, R., Sunnergård, L., Ingre, M., Axelsson, J., Jensen, K. (2019). The pain alarm response-an example of how conscious awareness shapes pain perception. Scientific reports, *9*(1), 1-8.

II. **Pontén, M.,** Fust, J., Kosek, E., Guterstam, J., Jensen, K. (2020). Naltrexone during pain conditioning: A double-blind placebo-controlled experimental trial. Molecular Pain, *16*, 1744806920927625.

III. **Pontén, M.,** Ljótsson, B., Jensen, K. (2019). Shaping placebo analgesic responses on the Internet: a randomized experimental trial. *Pain reports*, *4*(3).

IV. **Pontén, M.,** Jonsjö, M., Vadenmark, V., Moberg, E., Grannas, D., Andersson, G., Andrews, G., Boersma, K., Hedman-Lagerlöf, E., Kleinstaeuber, M., Weise, C., Kaldo, V., Ljótsson, B., Andersson, E., Axelsson, E., Jensen K. Expectancy effects in online versus face-to-face psychological interventions– an individual participant data meta-analysis. (Manuscript)

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

Jensen, K. B., Kirsch, I., **Pontén, M**., Rosén, A., Yang, K., Gollub, R. L., des Portes V, Kaptchuk T, Curie, A. (2017). Certainty of genuine treatment increases drug responses among intellectually disabled patients. Neurology, *88*(20), 1912-1918. PMID: 28424273

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
BOLD	Blood Oxygen Level Dependent
CBT	Cognitive Behavioral Therapy
CEQ	Credibility/Expectancy Questionnaire
CNS	Central Nervous System
dlPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
iCBT	Internet-based Cognitive Behavioral Therapy
IBS	Irritable Bowel Syndrome
IPDMA	Individual Participant Data Meta-Analysis
fMRI	functional Magnetic Resonance Imaging
IASP	International Association for the Study of Pain
mPFC	Medial Prefrontal Cortex
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PAG	Periaqueductal Gray
RVM	Rostral Ventromedial Medulla
PET	Positron Emission Tomography
RCT	Randomized Controlled Trial
TENS	Transcutaneous Electrical Nerve Stimulation
vlPFC	Ventrolateral Prefrontal cortex
WAI	Working Alliance Inventory

1 INTRODUCTION

Imagine doing a smell test and you smell something that you are told is matured parmeggiano cheese. You sniff and sense the salty, bitter scent. Perhaps it makes you think of a bottle of wine that it would pair nicely with, only to later find out that it was the smell of dried vomit. This actually happened in an experiment where participants got the wrong information of different smell samples and represents one of many examples of when expectations shape our perception of our surroundings (1).

However, expectation effects are unlikely to be elicited in all diseases and situations. For example, there is no evidence of cancer tumors being shrunk by our expectations, in contrast to symptoms that accompany cancer such as nausea where there is ample of studies showing expectation effects (2).

Thus, expectation effects seem to be possible in certain situations and in certain symptoms. The question is, what is needed for an expectation effect to be created? This thesis focuses on how our expectations and prior experience can shape health outcomes and the boundaries for such influences to happen. To investigate this, three functions commonly thought of as imperative to create expectation effects were investigated: conscious awareness, endogenous opioids and face-to-face interaction with a clinician (see Figure 1). In this thesis I will focus on how expectations influence pain and psychiatric symptoms.

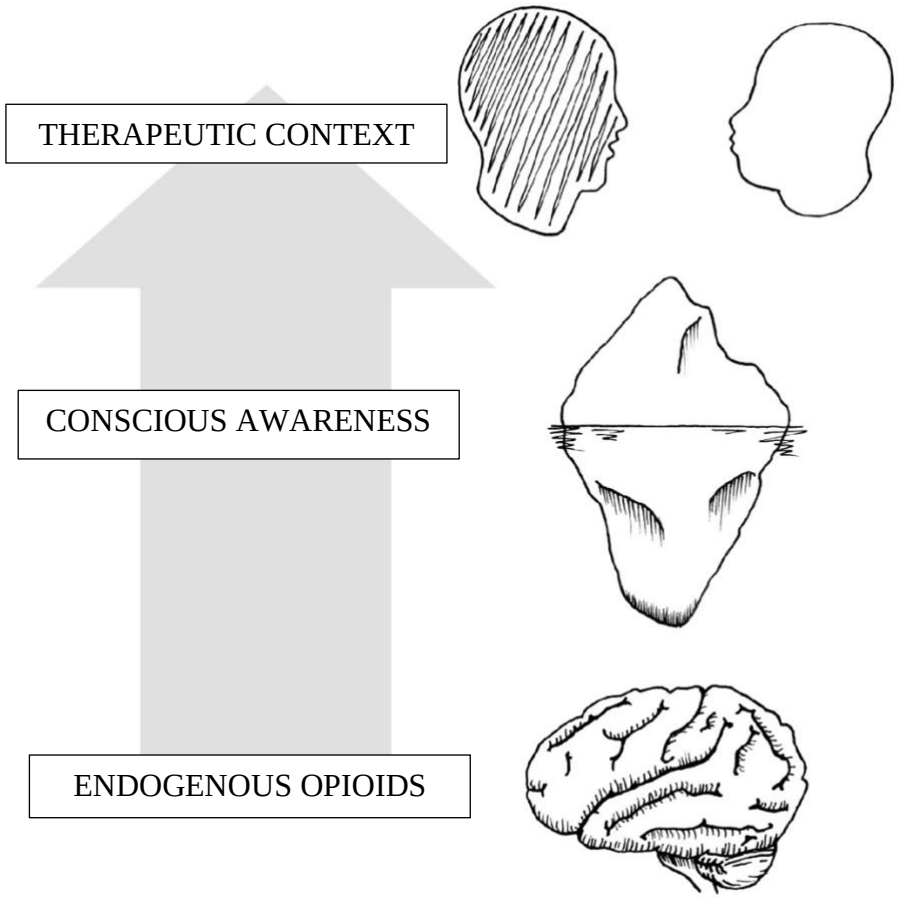


Figure 1. *Schematic illustration of the thesis. On top, therapeutic context illustrated by two persons talking (clinician and patient). Middle, conscious awareness illustrated by an iceberg (from which the larger part lies below the surface). At the bottom, endogenous opioids illustrated by a brain. The arrow illustrates that the thesis investigates expectation effects from basic brain function to the context surrounding a treatment. Illustration by Sebastian Pontén.*

2 LITERATURE REVIEW

2.1 EXPECTATIONS

One morning in a mail terminal in Stokke, south of Oslo, a white envelope burst and released a cloud of white powder similar to that seen in media reports of anthrax (a serious infectious disease). This led to unnerving consequences as employees reported difficulty breathing and burning skin. They quickly evacuated and closed the mail terminal and 44 people went to the hospital. However, when the powder was analyzed, it turned out to be a harmless flour product that someone had mailed. This is an example of how negative expectations can affect bodily symptoms and is sometimes referred to as the *nocebo effect*.

In contrast, positive expectations have been shown to shape how much individuals appreciate a wine. In an experiment, wine tasted better when the participants thought it was more expensive and this was mirrored in the brain where brain regions associated with pleasure were activated (3). This is sometimes referred to as the *placebo effect*, and a more precise definition will be presented in section 2.5 of this thesis.

The influence of expectations on perception and action is a widespread interdisciplinary research field including medicine, neuroscience, social and cognitive psychology and behavioral biology to name a few (4). Expectations play an important role in somatic (5, 6) and psychiatric symptoms (7, 8) with pain being one of the most studied symptom (9) .

2.2 TERMINOLOGY AND DEFINITIONS

There is no clear definition of the term expectations (10, 11) and the heterogeneity in the conceptualization has been highlighted as a considerable drawback in meta-analyses and systematic reviews (6, 12). In this thesis the term expectation refers to "future-directed beliefs that focus on the incidence or non-incidence of a specific event or experience" (13). These can be consciously held cognitions, or implicit (e.g. conditioned learning) (14-16).

I will in this thesis use the concepts *expectation effects* and *placebo effects*. Expectation effects can be seen to include all situations where expectations shape our symptoms, whereas placebo is mostly mentioned where a placebo treatment is involved (inactive treatment). However, a clear distinction between these concepts is yet to be defined as many studies of placebo mechanisms are done without the inclusion of a placebo treatment, why I will sometimes use these concepts interchangeably.

2.3 PLACEBO

A major field of research on expectation effects is studies on placebo effects, which is a genuine psychobiological phenomenon where inert or non-specific treatment components lead to symptom reductions and is an important component of medical practice and clinical research (17). There is evidence of different types of placebo effects ranging from immune responses (18), hormonal secretion (19) and pain responses (20) with different neurobiological mechanisms depending on the specific conditions underlying each placebo effect (21, 22).

The concepts *placebo response* and *placebo effect* are sometimes used as if they mean the same thing. When a new drug is to be developed, the treatment effect is calculated by comparing the changes observed in the drug group (treatment response) and placebo group (placebo response), respectively. The placebo effect, on the other hand, is the difference between the placebo response and the changes that would have been observed without receiving a placebo (natural course). One must therefore subtract the change in an untreated control group and check for spontaneous remission, regression to the mean (when rare or extreme measurements tend to be followed by measurements closer to the mean), the Hawthorne effect (when individuals change their behavior when knowing they are being studied), etc. to calculate the placebo effect (23).

2.3.1 Historical background

Placebo is a word that has changed its meaning over the years. It comes from the latin word placere which means to please. This word was used primarily in a religious context up until the 18th century, for example in a mistranslation of the bible where it said placebo dominus (I shall please the lord). Two hundred years later, a medical doctor called Cullen introduced this word to the medical science. Notes from his lectures in 1772 shows that he claimed to his students that placebo is a useful tool that can lessen the symptoms for patients (24, 25).

The notion, that the *reason* for our improvement or worsening might be different than what we believe, has fascinated people for centuries and has led to new ways to study medicine, e.g., the randomized placebo-controlled trial. The first documented placebo-controlled study can be dated back to 1784. During this time Franz Mesmer, a German physician, introduced a new treatment called animal magnetism. He claimed it was a new “fluid” comparable to gravitation and that it could cure illnesses. Animal magnetism was launched as a miracle cure. However, some concerns were raised about this theory and King Louis XVI appointed thus a selection of scientists and physicians (one of those was the ambassador Benjamin Franklin) to investigate this new treatment. The commissionaires tested the treatment on

several patients by telling them that they were exposed to “mesmerized” objects or untreated objects (i.e., placebo). From these blind trials it was evident that, although the subjects indeed many times were improved, this only happened when the subjects were aware of the “mesmerized” objects being present (26).

2.3.2 The neurobiology of placebo

Advances in neuroimaging techniques such as functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) have contributed to a rapid increase in studies investigating neural mechanisms underlying placebo responses, with pioneer studies published twenty years ago (27-29). Since then, a number of different brain areas have been linked to placebo responses, both for patients and healthy individuals. For example, the prefrontal areas have been linked to placebo responses such as the dorsolateral and ventrolateral prefrontal cortices (dlPFC/ vlPFC) (30, 31) and also mesolimbic reward system (32). Several neurotransmitters have been linked to placebo responses, such as dopamine, opioids and cannabinoids (33). Recently the imaging studies on placebo effects have developed with more complex designs including computational approaches aiming at tapping neural markers for placebo effects (34).

Most studies investigating the neural mechanisms underlying placebo responses have been on placebo analgesia , whereby expectations and prior experience lead to pain relief and have been shown to profoundly shape pain responses (9). Petrovic et al. showed in their paper a shared neuronal network for placebo analgesic responses and opioid analgesic responses (29). This has been followed up by studies showing that placebo analgesic responses are associated with activations in the insula, amygdala, thalamus, anterior cingulate cortex (ACC), the midbrain surrounding the periaqueductal gray and prefrontal cortex (orbitofrontal cortex, ventromedial and dorsolateral cortices)(35, 36). Many of these areas include regions that release opioids and dopamine and have been linked to the descending pain modulatory system (37, 38) as well as the dopaminergic system (39).

It is important to note that placebo analgesia is a phenomenon that is multifaceted with different cerebral mechanisms across studies. For that reason, an individual patient data meta-analysis on placebo analgesia fMRI experiments was made. The results revealed activities in additional brain areas otherwise not captured in the individual studies such as cerebellum, some specific parts of the thalamus and the habenula (40).

2.4 PAIN

In order to study expectations' influence on pain it is important to understand the concept of pain. The following sections will present definitions and common theories of basic pain physiology.

Pain varies highly among individuals and is context dependent. Past experiences, attention and distraction, memories, emotional state, are factors that can both increase or decrease the pain experience (41). Instead of only being a sensory process, pain is suggested to be a combination of sensory discriminatory, cognitive and affective processes that together form the painful experience an individual may have (42).

2.4.1 Definition

Pain is subjective by its definition. According to the International Association for the Study of Pain (IASP) pain is defined as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"(43) This definition includes painful sensations even when no tissue damage is present. This is of importance for the definition of chronic pain states where often no tissue damage is related to the reported painful state.

2.4.2 Pain physiology

Pain signals are subject to modulation where ascending and descending pain pathways in the body interact, making the painful input not linear to the subjective painful experience (41). In healthy pain modulation pain signaling starts in the peripheral nervous system where pain receptors, also called nociceptors, are activated by noxious stimulation (44, 45). The nociceptors have three different axons that are activated by different modalities of painful stimuli. The Aδ-fibers axons are myelinated and can transfer a pain signal fast towards the central nervous system and is associated with sharp pain (46). Recently another A-fiber axon was discovered that was shown to be able to transfer pain signals up to the speed of touch (47). The C-fiber transfer pain signals more slowly and is associated with blunt, burning pain (48). Pain signals are then projected through action potentials to the dorsal horn of the spinal cord. There are three different types of neurons in the spinal cord that project the painful signaling; projection neurons, inhibitory interneurons and excitatory interneurons enabling both up- and down-regulation of pain (49-51). The pain signals are then projected up to thalamus and other cerebral regions of the central nervous system (52).

Many areas in the brain are involved when pain is evoked, labelled sometimes *the pain matrix* or *neuromatrix of pain (53)*. The different areas activated during pain can be divided into a sensory-discriminative (lateral) and an affective-motivational (medial) component (42, 54). The sensory -discriminative component (localization, duration and quality of the stimulation) includes sensimotor areas S1 and S2, thalamus, and posterior insular cortex. The affective-motivational component (emotional aspects and unpleasantness of pain) includes limbic structures and prefrontal areas such as the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), anterior insula and amygdala. In addition, there is a cognitive evaluative component in pain processing, often involved in placebo analgesia. A brain region associated with cognitive evaluation of pain is primarily found in lateral prefrontal cortex (54, 55). Other areas involved in pain processing include the cerebellum, subdivisions of cingulate cortex, and hypothalamus among others (56, 57).

The descending pain modulatory system involves both pain inhibiting and pain facilitating effects on nociceptive processes (58). The descending pain inhibitory processes include the activation of frontal lobes, ACC, insula, amygdala and hypothalamus where descending signals are sent to periaqueductal grey (PAG) (59). The PAG projects to rostral ventromedial medulla (RVM) in the brainstem region where there are both pronociceptive cells (ON-cells) and antinociceptive cells (OFF-cells). Finally, the signaling is projected to the dorsal horn of the spinal cord (41).

The processing of pain in the different brain areas is complex and dynamic. The different regions constantly interact and there are studies investigating the communication between these areas during pain (60). Although the regions in *the pain matrix* have been assumed to be activated during pain it is contested whether these areas together are activated specifically for pain or more generally to salient stimuli (61).

2.4.3 Predictive coding

Many theories have been presented of how the brain creates the human perception of pain. One theory that uses computational models is predictive coding, a theoretical framework that is based in Bayesian theory (62). This framework challenges a more traditional view of the brain where the brain passively receives input from the environment and then processes the input in higher levels of the brain. Instead, the brain regions constantly interact. According to this framework, models (mental representations) are created based on previous experience to which sensory input is then compared to. To have a minimal mismatch (prediction error) between the model and sensory input is important for the adaptation to our environment.

Through prediction-driven learning these models are continuously updated (63), which means that perception may be shaped in order to match what is predicted (9).

2.5 HOW ARE EXPECTATIONS CREATED?

Expectations, i.e. predictions about future outcomes, can be formed implicitly and explicitly and are created by social, verbal and conditioned cues (64). Four well known ways expectations can be elicited are: conditioning, social learning, the therapeutic relationship between patient and clinician and written and verbal information.

2.5.1 Conditioning

Classical conditioning is a basic learning mechanism in which a person learns to predict events by associating an initially neutral stimulus (e.g., a bell) with an unconditioned stimulus (e.g., food) that leads to an automatic response (e.g., salivating). Classical conditioning has been used in many placebo experiments and have been shown to change autonomic responses like hormonal and immune responses (19, 65) as well as pain responses (19, 66, 67). Operant conditioning is a related mechanism in which behaviors are shaped based on its consequences (rewards and punishments) and has recently been suggested to shape placebo analgesia (68, 69).

2.5.2 Observational learning

In addition to classical and operant conditioning, observational learning has been suggested to play an important role in the formation of placebo effects (68). By observing the behavior of another person, placebo effects have been elicited in a similar magnitude as classical conditioning (which includes first-person experience of pain relief) (70).

2.5.3 Therapeutic relationship

Therapeutic relationship is the interaction between a patient and a clinician and has been shown to predict clinical outcomes for a range of medical (71), psychological (72), and placebo treatments (73). The therapeutic relationship has mostly been investigated in observational studies; however there are studies that systematically manipulate the therapeutic alliance (74). These studies have shown that a clinician’s ability to convey warmth and competence is an important contributor to the placebo effect (75, 76).

2.5.4 Written and verbal information

Written and verbal information have been used in many experiments to investigate the conscious expectations of a treatment (64). This is oftentimes referred to as response expectancy (77) where placebo experiments use verbal cues as modulators of expectations. For example, post-operative patients have been shown to get more pain relief in an open administration of morphine as opposed to when it is hidden (78, 79). This was shown in a so called open-hidden experiment where either the medicine was administered openly with the whole treatment context (i.e the nurse letting the patient know he or she will get an injection of the medication) or hidden (i.e the injection of the medicine is controlled by a computer and the patient is completely unaware that a treatment is being given). The results showed that when the injection of morphine is given openly the pain ratings are reduced to around 4 out of 10 in intensity. On the other hand, when the injection was given with hidden administration it was only reduced to around 6 out of 10. This is despite administering the same medication and dosage. This indicates that knowledge about a treatment affects its outcome (78).

2.6 BOUNDARIES OF EXPECTATION EFFECTS

Although there is evidence of expectation effects in many areas, there are limits to when and how disease symptoms and progression can be affected by expectations. Broadly speaking, expectation effects do not alter the pathophysiology of diseases beyond the subjective and self-appraised symptoms connected to the disease. The symptoms that are shaped by expectations are often under the control of the central nervous system (CNS), and typically include pain, itch and psychiatric symptoms (2)

There are different aspects that have been suggested to be essential to form expectation effects, for example intact cognition (conscious awareness), endogenous opioids and the relationship between a practitioner and patient.

2.6.1 Conscious awareness

Conscious awareness is a puzzling phenomenon. On one hand most people agree that they know if they are consciously aware or not, at the same time there is no consensus on a definition and also a disagreement of the mechanisms. Some argue that conscious awareness is purely an internal experience that cannot be researched with methods from neuroscience as they depend on external observations. This thesis will however assume that there are insights to be gained with methods from neuroscience and I will therefore not aim at a simple

single definition or mechanism. Instead, consciousness can preferably be investigated with the notion that there is a combination of multiple complex mechanisms (80).

Consciousness ranges from “alert” to “unconscious” on a continuum. Conscious states last for a relatively longer period such as heightened vigilance, awake, drowsiness, sleep, epileptic seizures and coma (80), where nonlinear transitions between these states are common (81). Conscious events are shorter, characterized by brief conscious awareness, (e.g., appearance of a figure in the visual field) and is the most studied part of consciousness in neuroscience (80).

There has long been a debate whether there needs to be conscious processing of the relations between stimuli and responses to create expectations (16, 82, 83). However, studies on pain conditioning have shown conditioned analgesic and hyperalgesic responses established outside of conscious awareness (84, 85). In these two experiments, the pain cue (a picture of a face) that was going to trigger expectations was shown so fast that the participants could not consciously recall what they just had seen. Even though they had no conscious recollection of the link between cue and pain relief, they rated consistently lower pain after the cue that was meant to trigger expectation for pain relief.

Sleep has been studied extensively regarding conscious awareness, as it is characterized by limited sensitivity to the environment but also selective arousal of certain stimuli. This makes it a suitable experimental environment to further investigate the role of conscious awareness in expectation effects (86). There have been attempts at testing learning during sleep, for example using smells (87) and there is evidence of complex sensory processing during sleep (88) as well as processing of noxious stimuli during sleep that includes cortical activations (89-92). One proposed theory how this can be possible is that during sleep parts of the brain are awake (93), and that there is simply no clear difference between a sleeping and wakeful brain (94).

2.6.2 Endogenous opioids

About forty years ago, Levine and colleagues were able to show by investigating post-operative dental patients and their pain responses that placebo analgesia can be mediated by endogenous opioids. After surgery, patients were administered first a placebo and then naloxone (a drug that reversibly blocks endogenous opioids). Patients who were responders to the placebo (i.e got reduced pain or no increase in pain after the placebo) reported increased pain levels after receiving naloxone. The non-responders (increase in pain after taking

placebo) on the other hand reported similar pain levels on naloxone as on placebo. This was the first evidence of endogenous opioids mediating placebo analgesia, as there was only increase in pain responses after naloxone in placebo-responders(95) . In 1999 Benedetti et al replicated this study, adding more weight to the hypothesis that placebo analgesia is paralleled by a release of endogenous opioids (96). Since then, endogenous opioids have been shown to be important both in clinical and experimental pain (37, 39, 97)

However, at the same time, there are several studies that have found no effect of the naloxone on placebo analgesia (98-100) or just partial blocking (37, 101). Placebo analgesic responses seem thus to be part of a flexible system that involve several mechanisms and neurotransmitters (9). Fields and Levine state that it is important to investigate in what contexts placebo analgesia is blocked by naloxone and when it is not (102).

2.6.3 Face-to-face interaction vs online interaction

Face-to-face interaction is one of our most important ways to communicate with one another and is suggested to be different from computer-mediated communication, (103, 104). Physical distance between individuals has been suggested to reduce empathy (105). In addition, online communication often lacks non-verbal cues, which can lead to misunderstandings (106). However, others argue the opposite, that the absence of these cues can enhance the interpersonal interaction (104). It is therefore unclear how expectation effects will be affected depending on if the interaction is face-to-face or online.

Digital health has recently started to gain more attention in the placebo literature. Smartphones have for example been argued to be exceptionally well equipped to elicit expectation effects due to the way we personalize and trust these devices (107). However, there are few experimental studies that systematically manipulate the therapeutic context and the influence of online interaction on placebo effects.

2.6.3.1 Expectations in face-to-face vs online interventions

Accumulative evidence shows that expectations predict treatment outcomes in face-to-face psychological treatment for a range of disorders (7, 108), and recent analyses of studies in online settings indicate that this might be the case for online interaction too (109, 110). Yet, there has been little research comparing expectations in Internet-delivered and face-to-face settings across disorders.

3 RESEARCH AIMS

The overall aim of the thesis was to explore the minimal requirements to elicit expectation effects on health-related outcomes. Specific aims and hypotheses for each study are presented below:

3.1 STUDY I

The aim of the first study was to investigate how expectations and prior experience shape pain perception in relation to conscious awareness.

3.2 STUDY II

This study aimed to investigate if expectation effects can be elicited although endogenous opioids have been blocked.

3.3 STUDY III

Study III sought to investigate if expectation effects could be induced in an online therapeutic setting.

3.4 STUDY IV

In study IV the aim was to compare expectations on therapeutic outcomes in online and face-to-face psychological treatment.

4 MATERIALS AND METHODS

4.1 METHODOLOGICAL CONSIDERATIONS

I have used a diversity of approaches to investigate boundaries of expectation effects in this thesis, including three experimental studies and one individual patient-data meta-analysis (IPDMA). The experiments included two different pain modalities (pressure/heat), two neuroimaging modalities (EEG/fMRI), and a pharmacological challenge. For details, please see individual manuscripts.

4.2 PARTICIPANTS

We chose to include healthy participants in the ages 18-55 in studies I-III. In Study II we had to find a way to select participants who would be able to take an afternoon nap in a sleep lab and sleep through heat stimulations. Therefore, we interviewed each of the participants to see what their sleep patterns were. We decided to include participants who reported no sleeping problems and had a sleep latency of less than 30 minutes. We also asked if they normally were able to sleep in the afternoon and if they believed they could fall asleep in a sleep lab.

In study IV randomized controlled trials (RCTs) with interventions aimed to treat somatic and psychiatric conditions in adults were included (see Table 1).

Table 1. Inclusion criteria

	Study I	Study II	Study III	Study IV
Age	18–55 years old	20 and 55 years old	18-55 years old	>18 years
Language	Swedish speaking	Swedish speaking	Swedish speaking	Any language
Population/studies	Healthy participants	Healthy participants	Healthy participants	RCTs that compared therapist-guided Internet-delivered therapy and face-to-face therapy Interventions aimed at treatment of psychiatric or somatic disorders

4.3 PROCEDURES

4.3.1 Experimental pain

Two types of pain modalities were used in the studies, heat pain (study I and III) and pressure pain (study II). Heat pain was induced with two comparable devices using a 3 x 3 cm (Medoc Advanced Medical System, Israel) or 2.5 × 5 cm thermode (Somedic Senselab AB, Hörby, Sverige). The thermode was attached to the participants lower leg (study I) or forearm (study III). Each heat stimulus lasted for 4 seconds. Pressure pain was elicited using a pneumatic, automatic, computer-controlled stimulator on participant's left thumb nail via a 1 cm^2 hard rubber probe. The duration of each pressure stimuli was 2.5 seconds.

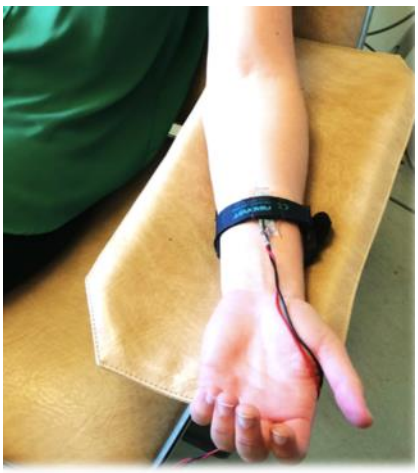
4.3.2 Calibration procedure

Before any experimental testing, a calibration of each participant's pain sensitivity was performed. In study I ascending temperatures were applied to find each participant's

individual temperature that would represent “high pain”, and “low pain” (subjectively rated on an 0-100 Numeric Response Scale ranging (NRS) from “no pain” to “worst imaginable pain”). The chosen “low pain” temperature was always three degrees Celsius below the “high pain” temperature. For example, if 48 degrees Celsius was chosen as a “high pain” temperature, the “low pain” temperature would be 45 °C. In study II the calibration consisted of series of ascending pressure stimuli and participants were asked to subjectively rate the pressure stimulus on a scale ranging from 0-20 (Gracely scale). Each participant´s pain threshold (first pressure rated above 0) and high pain (first pressure rated above 15) was noted. From this range, three pressures were calculated and tested to find each participant´s low pain (5 Gracely) and high pain (15 Gracely). In study III, each participant’s pain threshold (first stimulation rated above 0 NRS) and maximum pain (60 NRS) was found by applying ascending temperatures starting at 38 degrees.

4.3.3 Sham analgesic device

In study III, placebo analgesia was induced by using a sham analgesic device, made to look like a genuine Transcutaneous Electric Nerve Stimulator (TENS). This consisted of an electrode that was connected to a plastic box where a beeping sound and light indicated when it was “ON”. The electrode was applied on the participants’ skin next to the heat probe at the volar forearm. Both the electrode and the plastic box were inactive and could not give any sensation to the forearm.



The sham analgesic device was introduced in the pre-experimental communication online as a device that gives pain relief through a mild electrical current that activates peripheral nerves in the skin resembling a TENS device.

In the experimental room, the device was introduced by the simple statement “This is the analgesic device you have read about on the Internet”. After this, each participant’s high temperature (60 NRS) was administered three times while the sham analgesic device was turned “OFF”, “ON” and then turned “OFF” again. Participants subjectively rated the pain after each stimulation. The difference in pain ratings between when the device was ON and OFF represent the placebo effect. After the placebo experiment, the participants subjectively rated how they perceived the sham analgesic device (see Figure 2).

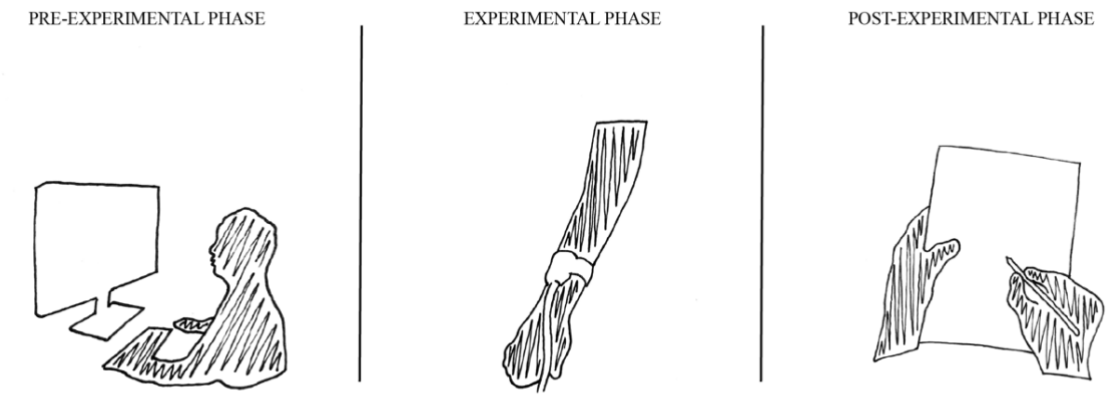


Figure 2. *Schematic overview over the experimental procedure. The pre-experimental phase was 3-4 days before the experiment and consisted of reading and answering questions online. The experimental phase lasted approximately 30 minutes. Post-experimental phase lasted approximately 15 minutes and consisted of questionnaires and debriefing. Illustration by Sebastian Pontén.*

4.3.4 Pre-experimental communication online

In study III, every participant was randomized to either empathetic or neutral communication online. The online communication mimicked clinical online-based treatments where the participants communicate with their therapist through information modules and feedback from the therapist. The participants answered questions about pain experiences and pain relief. Furthermore, the participants read information about the sham analgesic device. The empathetic version was written according to the empathetic checklist (73) which included factors like using the participant's vocabulary, asking open ending questions, reflections, validating emotions and avoiding medical jargon. This was shown along with pictures of the experimenter, the sham analgesic device and heat probe. The neutral version included no photographs and was written according to the neutral checklist. A validation procedure confirmed that the different communication versions were perceived as intended.

4.3.5 EEG

The brain demonstrates different electrical activity during sleep and wakefulness and this can be captured using electroencephalogram (EEG) (111). EEG is a noninvasive electrophysiological monitoring method that records the electrical activity in the brain using electrodes placed on the scalp (112). Sleep consists of two states, Rapid Eye-Movement (REM) sleep and Non-Rapid Eye-Movement (NREM) sleep. The electrical activity in REM sleep is similar to an awake brain whereas NREM sleep is a combination of k-complexes,

spindles and slow waves. NREM is divided in to four stages where the lowest threshold for arousal is in stage I and the highest threshold for arousal is in stage IV (113).

The EEG recordings were tailored for sensitivity to sleep stages and scored by an experienced sleep researcher. The initial plan was to administer noxious heat only in stage II, however, due to participants waking up we also administered heat in stage III and REM-sleep. If the participants woke up, no stimulations were given until the participant had reached stage II sleep again.

4.3.6 How to make participants sleep through pain?

In study I we had to make adjustment to make sure as many participants slept through the stimulations as possible, therefore some adjustments were made during the process. The first six participants were asked to shorten their sleep by at least two hours, where the maximum of hours allowed sleeping the night before was 6 hours. Due to participants waking up during the experiment, the rest of the participants were asked to sleep maximum 5 hours per night for two nights before the experiment.

4.3.7 Pain measures

Two pain scales were used to rate pain intensity, NRS was used in study I and III and Gracely in study II. The NRS is a scale that ranges from 0 (no pain) to 100 (worst imaginable pain) and can be administered both orally and graphically. Gracely scale is a scale on the intensity of pain ranging from 0 to 20. In study I and III the participants were asked to verbally rate their pain. In study II the participants rated the Gracely scale by pressing on a device.

4.3.8 Self-report questionnaires

In study III we created a study-specific questionnaire regarding how they perceived the sham analgesic device (rated on a 0-100 NRS scale) and the online communication (rated 0-100 NRS on how positive it felt). The participants perception of the experimenter was measured using the bond dimension of the Working Alliance Inventory (WAI), a validated scale that intends to measure the relationship between a patient and clinician (114).

4.3.9 fMRI

Functional magnetic resonance imaging (fMRI) is a non-invasive method that measures brain activity by detecting changes in cerebral blood flow and blood oxygenation. When an area in the brain is active it needs more oxygen, which leads to blood flow to these areas to enable oxygen transportation. Oxyhemoglobin (oxygenated blood) and deoxyhemoglobin (not

oxygenated blood) have different magnetic properties. The changes in the cerebral blood flow and blood oxygenation that the fMRI measures are called blood oxygenation level-dependent (BOLD) signal. fMRI has compared to other brain measuring methods such as EEG (electroencephalography) a relatively good spatial resolution but a poor temporal solution.

4.3.10 Individual patient data meta-analysis (IPDMA)

IPDMA is considered to be the gold standard of meta-analyses and involves retrieving individual data from each trial instead of making analyses on aggregated data as in regular meta-analyses. IPDMAs tend to be large international collaborations enabling more reliable and detailed results as well as a potential to answer new research questions otherwise not possible as it offers more detailed and flexible analyses (115). Study IV followed Cochrane recommendations for IPDMAs as well as PRISMA-IPDs guidelines.

4.3.11 Credibility and expectancy questionnaire (CEQ)

Expectancy/Credibility ratings were obtained from the Credibility and Expectancy Questionnaire (CEQ) constructed by Devilly and Borcovec. This is an easy to administer scale that is used in clinical outcome studies to measure rationale credibility and treatment expectations (116). Higher scores reflect higher expectations and credibility of the treatment. This scale has shown to be related to treatment outcome in face-to-face Cognitive Behavioral Therapy (CBT) and guided Internet-based Cognitive Behavioral Therapy (iCBT) for depression and anxiety disorders (109, 117, 118).

4.4 ETHICAL CONSIDERATIONS

IASP ethical guidelines for pain researchers have been carefully followed in this thesis. Prior to participating, all our participants provided written informed consent and all studies were approved by Regional Ethical Review Board in Stockholm - study I: (Dnr 2015/1197-31), study II: Dnr 2012/1062/32 , study III (Dnr 2016/1210-31/1). The researchers made sure that the participants could read and understand the written consent and that they knew that participation was voluntary. Data was handled according to rules and regulations. In study IV the participants were not asked if they wanted their data to be used in this IPDMA study. However, obtaining an additional consent from participants for meta-analyses is rarely practiced. Historically, IPD reviews have been exempt from ethics approval as informed consent have already been obtained by the trial investigators. Nevertheless, we obtained ethics approval (Dnr 202103833) to make sure all aspects of protecting the rights of the participants were sought for.

In order to be able to examine how prior experience and expectations shape pain responses the full aim of the study was not disclosed until after the experiment in studies I, II, III. Not disclosing all information from the beginning is problematic from an ethical view. However, this is the only way to experimentally examine the effects expectations can have on pain responses. Participants are informed of the full aim of the study and all questions are answered after the experiment. Also, the participants were informed of the right to withdraw their data from the study.

An experimental pain design requires the researcher to be conscious of the participants' particular individual needs. This was done by conducting a calibration procedure where the painful stimuli were given in a sequential order. This enables the participant to familiarize with the rating scale and the painful stimulations. In addition, each participant's pain tolerance and pain sensitivity were be noted and used to decide pain levels in the experiment. A predetermined highest rated pain level was used to not administer more pain than necessary for the study. Besides using equipment that are tested to be safe, the participants' safety within the procedures was provided by instructing them how to remove the device that gave the painful stimulations.

In studies I-III participants were subjected to painful stimulations. However, these stimulations were brief and not subjecting participants to risk of injury. The results from this research can in an experimental and clinical context lead to expanded knowledge about mechanisms of pain. In study IV data was sent between the universities, opening for a potential risk that data get misplaced. However, regulations on data sharing were carefully followed. Considering the risks and potential benefit from the studies, the existing infringements of the participants were deemed to be justifiable.

5 SUMMARIES OF STUDIES I-IV

5.1 STUDY I BRIEF DESCRIPTION OF DESIGN AND RESULTS

In this study we investigated if pain can be shaped by expectations while not being consciously aware. We used sleep to obtain an unconscious state.

5.1.1 METHODS

Healthy participants were exposed to noxious heat either when asleep (n=30) or awake (n=24). After this, when participants were awake, a test-phase followed with painful stimulations. Two control experiments consisted of only the test-phase (n=32 and n=28).

5.1.2 RESULTS

Participants who had been sleeping prior to the test-phase, and thus not aware of getting noxious heat, displayed heightened pain ratings (i.e., pain alarm response), as if they had not been exposed to the painful stimuli during sleep. In comparison, the awake condition rated all test-phase stimuli the same. In the two control conditions, who had no prior experience of painful stimulations, the pain alarm response was further pronounced. This illustrates how profoundly important expectations are for shaping the perception of pain.

5.2 STUDY II BRIEF DESCRIPTION OF DESIGN AND RESULTS

In this study we investigated if expectation effects can be elicited although the endogenous opioids have been blocked.

5.2.1 METHODS

A pain-cue conditioning, using pressure pain in combination with naltrexone/placebo administration and functional magnetic resonance imaging (fMRI), was performed in healthy controls. Prior to conditioning, 30 healthy participants were randomized in a double-blind procedure to receive an acute, oral dose of either naltrexone (50 mg) or an inert pill. A pain stimulator was placed on the thumb, and a response-device in the right hand allowed for pain ratings (0 to 20) Gracely scale while in the MRI scanner. The procedure included a conditioning procedure with a learning sequence where two different visual cues were paired with high pain and low pain pressures, followed by a test sequence where identical painful stimulations followed the visual cues. The outcome was calculated using the difference in pain ratings between the high pain cue and low pain cue.

5.2.2 RESULTS

Results showed significant conditioned analgesic and hyperalgesic responses across groups regarding subjective pain ratings ($p < .001$), yet no significant difference between subjects

receiving naltrexone or inert pill (p =.193) was demonstrated. Correlation analysis showed significant correlation between the effect of high and low pain cues during the test sequence and the previously rated difference in high and low pain ratings during the learning sequence (r=575, p =.002). No significant difference in brain activation between groups was shown using functional neuroimaging analyses.

Here we demonstrate comparable conditioned analgesic and hyperalgesic responses in participants with naltrexone or placebo. These findings indicate that full function of the endogenous opioid system during acquisition in pain conditioning is not necessary for conditional responding.

5.3 STUDY III BRIEF DESCRIPTION OF DESIGN AND RESULTS

In this study we investigated expectation effects in an online therapeutic setting.

5.3.1 METHODS

30 healthy participants were randomized in a double-blind fashion into two different pre-experimental online communication versions; one empathetic version and one neutral version (non-validating). After this, a placebo experiment with a sham analgesic device face-to-face with an independent experimenter (blinded as to communication type) was performed.

5.3.2 RESULTS

The participants rated the pain lower when the sham analgesic device was turned on as compared to when it was off (p = .003), demonstrating a significant placebo analgesic effect. Pain testing without prior communication using only the sham analgesic device was proven to not be enough to elicit placebo effects in an additional control experiment. Exploratory analyses revealed that empathetic online condition was associated with more positive ratings and higher compliance regarding online tasks, however there was no significant difference in placebo effect between the neutral and empathetic communication groups. The results in this study indicate that expectation effects can be created even when information about the pain-relieving treatment is delivered online rather than face-to-face.

5.4 STUDY IV BRIEF DESCRIPTION OF DESIGN AND RESULTS

5.4.1 METHODS

Individual participant data from studies that randomized patients to online versus face-to-face behavioral therapy were analyzed in order to determine expectancy effects in online versus face-to-face behavioral therapy. MEDLINE (Ovid) and PsycINFO (Ovid) were used to search for studies that randomized patients to either online or face-to-face behavioral therapy aimed at treatment of psychiatric or somatic disorders and who used the Credibility

and Expectancy Questionnaire (CEQ). Corresponding authors of matched studies were contacted for individual participant data.

5.4.2 RESULTS

7045 screened studies resulted in 62 full-text articles, out of which six provided individual participant data (n=491). Expectation ratings predicted clinical outcomes post treatment, however there was no difference in the prediction slope between online or face-to-face therapy. Hence, online treatment appears to be susceptible to expectation effects similarly as face-to-face therapy.

6 DISCUSSION

Expectations have been shown to affect many health outcomes, but not all. The power of the mind is unlikely to shape all our bodily symptoms. Learning where this boundary goes is important for understanding how the body works, but also for the development of treatments.

All four studies in this thesis investigated boundaries of how expectation effects on health outcomes can be created. The main findings point to the direction that expectations play an important role for basic pain reactions, even when endogenous opioids are blocked and even in therapeutic encounters online.

6.1 LEARNING FROM NOXIOUS STIMULI DEPENDENT ON CONSCIOUS AWARENESS

In study I we wanted to explore if expectations can shape pain perception even if a person is consciously unaware. To test these boundaries, we used sleep as a method to obtain an unconscious state. This allowed selective arousal for the brain to process noxious stimulation but also limited sensitivity that enabled the participants to sleep through the stimulations. One group of participants got repetitions of noxious stimulations when asleep and one group got the stimulations while being awake. After that a test-phase followed with a new series of noxious stimulations where all participants were awake and rated their pain. We found that participants that had been asleep during repeated noxious stimulation displayed a pain alarm response in the test-phase, as if they had not been exposed to noxious stimulations. Two control experiments confirmed that when naïve to pain, a pain alarm response is present. This suggest that basic habituation-like learning from noxious stimulations is (at least to a large extent) dependent on conscious awareness.

In parallel to our findings, a study found that conscious awareness is necessary for serial dependence in perception. In that study the authors investigated if visual stimuli need to be consciously perceived to affect subsequent ratings. Results indicate that perception of a stimulus is not only dependent on the stimulus that is being processed, but also the expectations based on previous experience. These are also called perceptual priors (119) and are likely affected by conscious awareness. Even though pain and vision are different perceptual modalities, both studies illustrate the impact of conscious awareness on effects such as serial dependence.

Yet, previous research has shown that pain can be modulated nonconsciously in some instances (84, 85, 120). In several studies by Jensen et al., conditioning with pain and

subliminal cues (nonconscious) that signal high or low pain were used. Both learning and activation of analgesic and hyperalgesic pain responses could be achieved nonconsciously. The results have been corroborated in a study that activated previously conditioned analgesic and hyperalgesic pain responses with subliminal cues (121) and partly corroborated in a study using other cues than faces (122). However, the participants in these experiments were awake during the pain stimulations and the nonconscious component represented by rapid visual cues that hindered conscious recognition. Sleep seems thus to be a conscious state that hinders learning from pain stimuli in a more profound way than subliminal cues. To what extent higher-order processing might be present unconsciously is thus open for debate.

6.2 EVIDENCE OF EXPECTATION EFFECTS WHEN ENDOGENOUS OPIOIDS ARE BLOCKED

In study II we showed that conditional responding is not dependent on endogenous opioids. This despite that there are studies where placebo analgesic responses have successfully been blocked (95, 96)

There are different explanation models as to why some placebo analgesic responses are naloxone insensitive. Amanzio et al. emphasized in their paper that placebo analgesia based on verbal suggestions is mediated by endogenous opioids but that pharmacological conditioning (taking a drug and then replacing it with placebo) is mediated by different neurotransmitters depending on the drug (96). For example, the pharmacological conditioning using NSAID (Non-steroid- anti-inflammatory drug, an analgesic drug that is not an opioid) was insensitive to naloxone and involved the endocannabinoid system (96, 123).

In addition, there has been a discussion whether lack of effect of naloxone on placebo analgesia can be partly explained by differences between study populations. In a study on patients with Irritable Bowel Syndrome (IBS) and placebo analgesia, the authors suggest that clinical improvement in the patients is not likely mediated by endogenous opioids as naloxone did not affect the treatment outcome (98).

Another discussion concerns the experimental context. Placebo analgesia acquired in a stimulus context (placebo learning using cues that signal changed stimulus intensities, e.g., lower heat, instead of treatment cues) has a shorter extinction phase and activates different brain areas compared to treatment context (placebo learning using cues that signal treatment effects on a symptom) (35, 124) indicating that this is a factor to consider.

6.3 EVIDENCE OF EXPECTATION EFFECTS IN ONLINE TREATMENTS

In study III we showed that an online medium is enough to create expectations about a sham analgesic treatment. In the subsequent face-to-face placebo experiment significant placebo effects were elicited, even though communication was held to a minimum and all information about the sham analgesic device was delivered online. A control experiment where no information was given either online or face-to-face about the sham analgesic device led to no placebo responses.

Even though our fundamental social training since infancy is based on face-to-face interaction, we seem to be able to form similar expectation effects online. Social interactions are increasingly conducted online and we seem to engage in similar processes as in face-to-face interaction such as information sharing, turn-taking and rapport building. In addition, placebo analgesia was seen to be induced with a pre-recorded video similarly to live face-to face observation (125). Thus, there is a possibility that there are comparable expectation effects in online vs face-to-face treatments. This is in line with the results we found in study III and IV where we showed comparable effects between face-to-face and online.

Patients' ratings of treatment expectancy have historically mostly been seen as a nuisance in psychotherapy research. Expectancy questionnaires have been included in the studies only to demonstrate comparable/dissimilar expectancies in the therapy and in the control condition (108). In study IV we wanted to look more closely at these questions and see how they relate to treatment outcome. We found an association between ratings of treatment expectations and treatment outcome. This corroborates previous findings in two meta-analyses (n=8016, n=12722) that showed a significant association of pre-treatment expectations with treatment outcome for various conditions and treatments (weighted effect size r=.12 and r=.18)(7, 108). These were all face-to-face treatments and this thesis suggest that similar effects of expectations on treatment outcome can be seen in online treatment.

6.4 STUDY LIMITATIONS

The limitations for studies I-IV are discussed in the respective articles, here I have added the limitations which are not included or elaborated on there.

6.4.1 Selection bias

In study I-III solely healthy participants were recruited. That means that they had no history of medical or psychiatric illness and no ongoing medication for any chronic illness or

psychiatric illness. In addition, the recruitment for participants was made on an academic study website. This might affect how well the study can be generalized to other populations as the most common users of these platforms are younger participants with higher education.

It is very common to study expectation effects on healthy participants. The advantage is that it allows the experiment to be well controlled, yet the disadvantage is that it might be a threat to the external validity (126). Therefore, it is important to perform these experiments in patient populations in the future.

6.4.2 Response bias

Response bias is the tendency for participants to report symptoms in a way they feel is warranted or socially accepted. This might lead to an overestimation of the expectation effect. Although neuroimaging technologies such as functional magnetic resonance (fMRI) and positron emission tomography (PET) cannot distinguish what is really *felt* (and also have its own disadvantages that affect the validity and reliability) some argue that fMRI and PET studies might aid at least somewhat in determining whether expectation effects are independent from response bias, as they can show difference in brain activations during stimulations compared to during assessments (126). Yet, as with all research on subjective ratings, there really is no way to objectively assess subjective symptoms.

7 CONCLUSIONS

The results in this thesis suggest that pain processing such as pain alarm response is affected by conscious awareness, endogenous opioids are not necessary in all situations to create pain cue conditioning, placebo effects can be created through online communication and treatment expectations seem to be just as important for online as it is for face-to-face interaction. In sum, we challenge previously known boundaries for when expectation effects can be created. This calls for more research on expectation effects in clinical research as these are an important factor in clinical treatment.

8 POINTS OF PERSPECTIVE

There are several possible avenues for further research that arise from the presented studies in this thesis. Pain treatments and experimental studies on pain can benefit from knowing that a pain alarm response (initial heightened pain rating) exists, and instead incorporate a design that minimizes the influence of pain alarm response on pain ratings. The role of consciousness could be further explored by assessing how conscious awareness affects pain alarm response when participants have different states of consciousness, such as drowsiness and unconsciousness. In addition, it would be interesting to study how important intact cognition is for the formation of expectation effects by employing an experimental design on patients with cognitive disabilities. This would be of scientific interest but also potentially lead to developments in treatments for people with cognitive disabilities such as Intellectual disability and Alzheimers' disease.

The role of opioids in pain modulation is contested and our study is one of many studies that have failed to show a link between the pain relief and endogenous opioids. This has implications for popular science and health care as there has long been the prevailing notion that placebo analgesia is dependent on endogenous opioids. Perhaps a new view is emerging and maybe it rather is a case of fine tuning the experience of pain (127). Future studies would benefit from applying the experimental methods previously used for healthy participants on patients e.g (37).

The results in this thesis could have implications for how Internet-delivered treatments are designed. As expectations seem to play just as an important role in online treatment as in face-to-face treatment it is important to investigate how to harness and optimize these effects in online treatment. The World Health Organization (WHO) considers eHealth as one of the most rapidly growing types of health care today and the full potential of these treatments will not be realized unless we learn more about the expectation effects in these treatments.

Possible avenues that can increase the knowledge is to perform studies that manipulate expectations and therapeutic alliance in online treatments for patients. Here different aspects of the digital health can be explored to see how they contribute to expectation effects. For example, the design of the app, the information provided, beliefs about digital health interventions or technology in general could all be investigated (as suggested by Torous et al. (107)). A possible experimental design could be utilizing open notes. This is where the notes from the health provider are made available to the patient and has been launched in

many regions in Sweden. This medium has been suggested to have the potential of creating placebo and nocebo effects (128).

A project close to my heart is to explore expectation effects in psychiatric populations. This has long been understudied mostly for practical reasons. The most common placebo and nocebo experiment uses pain, as it offers brief and reliable pain modulations compared to other symptoms such as mood that has complex temporal dynamics and cannot be turned “on “ or “off” in response to stimuli. One advantage of studying expectation effects in psychiatric populations is that many treatments are now delivered over the Internet. Internet-delivered CBT is particularly suited as it is well controlled as compliance and adherence are monitored. In addition, variability between therapists can be held to a minimum as therapeutic drifts easily are checked for. By mapping how much patients' expectations contribute to the psychological treatment effect it has the potential of being both theoretical important but also leading to therapeutic improvements of Internet-delivered CBT.

I would finally be interested in investigating other constructs than expectations, such as hope and desire (129) as expectations has been shown to not be a good predictor in populations with chronic conditions with treatment failures in their medical history (130).

9 ACKNOWLEDGEMENTS

These 4+ years have been a very special in my life. I have enjoyed this time greatly, much thanks to the wonderful people on these acknowledgment pages.

Karin Jensen, my supervisor, words cannot express how immensely grateful I am for you believing in me, guiding me and helping me through these years. Thank you for your invaluable patience and feedback. I appreciate all our discussions and for making it fun to go to work. Thank you for introducing me to your fellow colleagues in Boston and for the opportunities to travel and discuss science with people across the world. **Eva Kosek,** I am so grateful you wanted to take the time to be my co-supervisor and for sharing your deep knowledge on science of pain. **Eric Westman**, my co-supervisor, thank you for your encouragement and for our fun and productive discussions.

My mentor **Töres Theorell**, thank you for sharing your experience about how this "world works" and for our musical encounters. Thank you for introducing me to all the musical friends during my stay in Boston.

All members of The Pain Neuroimaging Lab, thank you for showing me how fun and inspiring a workplace can be. **Maria Lalouni**, thank you for being my PTP-supervisor, colleague and friend. It is always fun to work with you, where the most challenging data collections or monotonous tasks are a joy to do together. Your productivity is impressive and it's a privilege to have been able to work so closely with you during these years. **Jens Fust**, for your commendable patience with all my questions during these years. I feel humbled to have worked with you, your humor and knowledge has made work a fun place to be at. **Martin Jonsjö,** I'm very happy I started making Varan-tv jokes with you in the ski lift at the ski-conference many years ago. Thank you for being my PTP-supervisor, my colleague, my friend and for teaching me about the good things in life. **Granit Kastrati,** thank you for your exceptional generosity in helping me with my brain imaging questions. **Filip Gedin,** thank you for your positivity, our discussions about life and for reminding me to get coffee breaks during the day. **William Thompson,** thank you for generously sharing your expertise. You have a way of explaining the difficult things understandably and has enabled me to get in touch with so much more in this research world, **Sebastian Blomé,** your positive energy makes it a joy to work with you! **Gustaf Håkansson,** I've very much enjoyed our inspiring discussions in the corridor.

Thank you **Angelica Sandström, Silvia Lanton, Isabel Ellerbrock, Jeanette Tour, and Frida Bayard** for nice lunches and travels together.

Participants volunteering in the studies, thank you for having patience with all the questions and pain testing. Without you, nothing of this would be possible.

Thank you to everyone at Behavior Medicine. A special thanks to **Mike Kemani** for your humor and knowledge, I have greatly enjoyed our scientific discussions, **Linda Holmström** for welcoming me to Beteendemedicin, **Lotta Gentili,** J**enny Rickardsson**, **Jenny Åström**, **Björn Lilieqvist**, **Rikard Nilsson**, thank you for letting me join your warm and friendly atmosphere, thank you fellow PTP-students **Linda Sunnergård, Julia Lönnborg, Emma Kettis.**

Thank **John Axelsson** and **Paolo D'Onofrio** for great support during the exceptionally challenging data collection in the sleep study.

Thank you to all personnel at KI that has made these studies possible to make. A special thanks to **Mimmi Wernman** for your support and laughs and **Jonathan Berrebi** for your help and lunches together. Thank you **Rouslan Sitnikov** and **Amir Shafazands** at the MRI center for your help and impressive patience with all my questions. You made MRI center a fun place to go to.

Mats Lekander, thank you for showing that music, art and science are branches of the same tree. I have very much enjoyed organizing the culture days at KI with you. And thank you **Sandra Tamm**, **Leo Kowalski** and **Vera Kerstens** for great music making together with a pinch of scientific discussions.

Erik Andersson, I don't think I know anyone that can give positive feedback as well as you do, thank you for your encouragement and for pushing me to do my best. Thank you **Brjánn Ljóttsson, Erik Hedman-Lagerlöf, Maria Hedman-Lagerlöf** and **Erland Axelsson** for great scientific collaboration and laughs.

Kristoffer Månsson, **Joar Guterstam** and **Tomas Furmark** thank for laughs and for great discussions about placebo and psychological treatment.

Thank you to the members of The Program in Placebo Studies and the Therapeutic Encounter hosted at Beth Israel Deaconess Medical Center/Harvard Medical School and a special thanks to **Ted Kaptchuk** for generously welcoming me to your group during my

stay, **Sarah Ballou** for being my supervisor, **Charlotte Blease** for fun collaborations and discussions about placebo and life, **Irving Kirsch** and **John Kelley** for inspiring talks. Thank you **Marco Loggia, Vitaly Napadow** and the rest of your teams labs at Martinos Center for letting me see your inspiring work. Thank you **Lisa Wong** for amazing music making and for introducing me to science of music and medicine.

Thank you **Lene Vase** and your team and a special thanks to **Susan Tomczak Matthiesen, Sigrid Juhl Lunde** for being great companions on placebo-conferences.

All my dear friends thank you. A special thanks to **Wilhelmina** for making the commute to work so much more endurable. Thank you **Sanna, Sara, Björn** and **Stefan** for ”räkhjälm”-lunches and for being a great support. Thank you **Caroline** and **Leo** for listening to my science ramblings and proof-reading my texts.

Thank you, **Carina**, I’m so happy we have these scientific projects together. You are a true inspiration.

Late grandpa **Urban** and late grandma **Gunvor**, thank you for showing me that kindness should be at the heart of curiosity and ambition.

Mamma and **pappa,** I am so very thankful for your love and knowing you believe in me, it is a soothing feeling to know support is always close. **Emeli, Jonathan and Sebastian**, I am truly grateful and proud of being your sister, thank you for believing in me. And thank you Sebastian for helping you sister with the fantastic illustrations for this thesis.

Hanna and **Nils**, my dream team, I am deeply grateful for you every day.

3

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