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PLACEBO EFFECTS IN HEALTH AND DISEASE - HOW EXPECTATIONS SHAPE TREATMENT OUTCOMES

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Placebo effects in health and disease - How expectations shape treatment outcomes
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

The context in which a medical treatment is administrated influences treatment outcomes. As of today, the health care system has little knowledge about the non-specific components that contribute to the positive effect of a given therapy, often referred to as the placebo component, and how this may be harnessed in order to maximize treatment effects. The overreaching aim of this doctoral thesis is to investigate the impact of non-specific treatment components on clinical outcomes, in particular the role of expectations. More specifically, this thesis focuses on two clinically relevant, yet poorly investigated, topics: 1) Are placebo effects dependent on higher order cognitions? This was investigated among patients with intellectual disability (ID) and in an experimental setting in healthy individuals. 2) Are placebo effects affected by the duration of a chronic disease? In order to study this, outcomes from a randomized controlled trial (RCT) among fibromyalgia (FM) patients were analyzed.

Study I investigated the influence of non-conscious expectations on placebo analgesia, using an implicit priming task called Scrambled Sentence Test (SST). Healthy participants were randomized to receive positive or neutral expectations via the SST, followed by a placebo manipulation with a sham analgesic device. Results demonstrated no effect of implicit priming on placebo analgesia, yet the study indicates that placebo analgesia is largely explained by prior experience of pain relief, and that the social interaction with a trustworthy clinician may have competed with the possible effect of implicit priming.

Study II examined the relationship between placebo analgesia and the time (months, years) a person has been exposed to chronic disease, by assessing placebo responses in a pharmacological trial in patients with FM. Results revealed that FM duration was associated with baseline pain levels as well as placebo analgesia. These results point to the importance of early FM interventions, as the chance to harness endogenous pain regulation and to avoid chronification may be higher early in the disease course.

Study III investigated how treatment expectations may shape outcomes in pharmacological clinical trials among patients with ID. The placebo component in ID clinical trials was examined by performing a meta-analysis comparing drug responses in open-label trials (with 100% certainty of getting the real drug) with drug responses in placebo-controlled trials (with 50% chance of getting the real drug). The results demonstrated placebo effects among patients with ID, as the effect of the real drug in open-label context was associated with better treatment outcomes than the same drug in a placebo-controlled context. Our study validates the notion that patients with ID are influenced by contextual factors in clinical trials in spite of severe cognitive deficits.

LIST OF SCIENTIFIC PAPERS

I. **Rosén A**, Yi J, Kirsch I, Kaptchuk T, Ingvar M, Jensen K. Effects of subtle cognitive manipulations on placebo analgesia – an implicit priming study. *Accepted in The European Journal of Pain (2016)*

II. Kosek E, **Rosén A**, Carville S, Choy E, Gracely RH, Vitton O, Marcus H, Petzke F, Ingvar M, Jensen K. The effect of pain chronification on placebo analgesia: Lower placebo responses after long-term exposure to fibromyalgia pain. *In revision*

III. Jensen K, Kirsch I, Pontén M, **Rosén A**, Yang K, Gollub R, Portes V, Kaptchuk T, Curie A. Certainty of genuine treatment increases drug responses among intellectually disabled patients. *Under review*

CONTENTS

LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ACR	American College of Rheumatology
BDI	Beck's Depression Inventory
CSQ	Coping Strategies Questionnaire
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth edition
EPQ12	Eysenck Personality Questionnaire
FM	Fibromyalgia
FIQ	Fibromyalgia Impact Questionnaire
IASP	International Association for the Study of Pain
ID	Intellectual Disability
IQ	Intelligence Quotient
n	Number of participants or patients in sample
NRS	Numerical Rating Scale
fMRI	Functional Magnetic Resonance Imaging
PET	Positron Emission Tomography
PGIC	Patient Global Impression of Change
RCT	Randomized Controlled Study
SF-36	Short-Form 36
SPSS	Statistical Package for the Social Sciences
SST	Scrambled Sentence Test
STAI-T	Spielberger Trait Anxiety Inventory
VAS	Visual Analogue Scale

1 INTRODUCTION

Most medical treatments can be divided into a specific treatment component (e.g. a pharmacological substance or a surgical intervention) and a non-specific component that includes the context surrounding the delivery of treatment, such as the interaction between a patient and a clinician treatment expectations (Colloca, Lopiano, Lanotte, & Benedetti, 2004), see figure 1. In daily clinical work, clinicians practice the art of medicine with the assumption that the context surrounding the treatment plays an important role for the treatment outcomes. Yet, clinical research has mainly focused on the specific components of an active treatment. As a result, the health care system has limited knowledge of how non-specific components of a therapy, often referred to as the placebo component, may be used in clinical praxis in order to maximize treatment effects. Generally, the non-specific contributions of a medical context can be difficult to investigate because of its complex nature. However, increased scientific investigations of the placebo component of existing treatments, in experimental as well as clinical settings, would be of profound value, irrespective of patient population. Overall, this thesis strives to increase knowledge about the non-specific components of medical treatment, in particular through studying the role of treatment expectations. As a scene for this, two clinically relevant, yet poorly investigated, questions were chosen: 1) Are placebo effects dependent on higher order cognitions? Here, we investigated placebo effects among patients with intellectual disability (ID) and in an experimental setting among healthy individuals; and 2) Are placebo effects dependent on the duration of a chronic disease? To address this question, we studied placebo outcomes among patients with varying exposure to fibromyalgia (FM) pain.

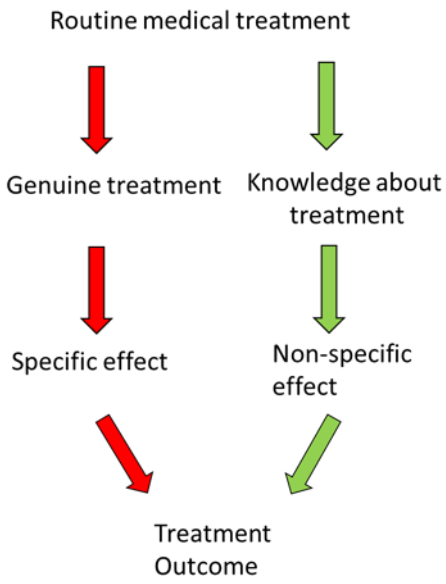


Figure 1. *Schematic illustration of the effects of specific and non-specific components on treatment outcome. Adaptation from a model by: Colloca et al. 2004, The Lancet Neurology.*

1.1 THE CONCEPT OF PLACEBO

1.1.1 Terminology and definitions

In order to study the placebo component of a treatment, there is a need to clarify the terminology related to the concept. This is a challenge since there is a large quantity of different terms related to placebo effects, and different terms are used depending on the scientific context

(Choliz & Capafons, 2012). The aim of the following section is to define the placebo concept as clearly as possible and to present the chosen terminology for this thesis. Overall, the term placebo can be used as follows (Finniss, Kaptchuk, Miller, & Benedetti, 2010) (Koshi & Short, 2007):

I) Placebo as something you give, for example a sugar pill

For many years, placebo has mainly been associated with the use of an inert substance or inert procedure in the placebo control group of a Randomized Controlled Trial (RCT). In the RCT setting, the role of the placebo is to disentangle the specific effects of a genuine medical treatment, from the non-specific effects surrounding the treatment. In this setting, the placebo effect is generally something unwanted that investigators wish to minimize (Enck, Bingel, Schedlowski, & Rief, 2013). A different, more controversial use of the placebo, is the prescription of inert substances (or physiologically active substances) in the clinic, in order to promote positive expectations or to please the patient. For that reason there is a division between "pure placebos" (inert treatments with no pharmacological effect, e.g. sugar pills) and "impure placebos" (physiologically active treatments with no effect on the condition being treated e.g. vitamins, antibiotics, massage) (Meissner, Hofner, Fassler, & Linde, 2012; Tilburt, Emanuel, Kaptchuk, Curlin, & Miller, 2008).

II) Placebo as a response following administration of a placebo treatment

Today, it is well established that there are clinical improvements also in the placebo group of clinical trials; so-called placebo responses (Kirsch, 2009; Linde, Niemann, Schneider, & Meissner, 2010; Peerdeman et al., 2016). This response relies on the patient believing in the efficacy of the treatment and therefore the psychosocial context around the patient is often emphasized when defining a placebo response (Benedetti & Amanzio, 2013). In comparison to the placebo treatment itself (I), such as a sugar pill, the placebo response (II) has been the focus of placebo research as it includes the factors that surround the administration of the sugar pill and attributes meaning to the treatment (Moerman, 2002).

III) Placebo as a response that follows any treatment

All medical treatments, not only placebo treatment, are surrounded by a psychosocial context that interacts with and affects treatment outcomes. In this sense, a placebo effect does not require a placebo treatment (Kirsch, 2013), as the specific treatment (e.g. morphine pills) and the placebo component of the treatment administration (e.g. induction of positive expectations) may be additive. The outcome of genuine treatment can thus be improved by enhancing the

placebo component, for example by fostering positive patient-clinician relationships, and thereby achieve better clinical results (Kelley, Kraft-Todd, Schapira, Kossowsky, & Riess, 2014).

Irrespective of treatment given (genuine or placebo), one complicating circumstance when estimating the non-specific contribution to a treatment response is that the treatment response may reflect the influence of several other variables, such as natural history of a disease, regression towards the mean and response bias (J. Howick et al., 2013; Kirsch, 2013). This leads to the distinction between placebo effect and placebo response (a schematic illustration of this can be found in figure 2). In a recent summary (Kirsch, 2013), the terms are defined as follows.

Placebo response: is the outcome that follows after administration of a placebo including the changes that would be observed even without the administration of a placebo. These changes might reflect the natural history of the disease, regression toward the mean and other methodological bias.

Placebo effect: is the outcome after subtracting the changes that would be observed even without the administration of placebo.

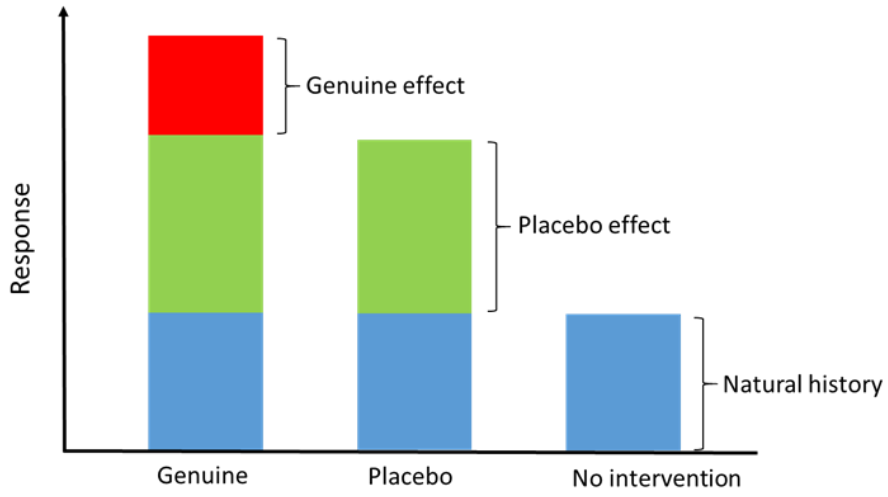


Figure 2. *Schematic illustration of the contribution of non-specific treatment components in an imaginary treatment setting. Each bar (x-axis) represents the total treatment response (y-axis) for each group. The blue section represents the e.g. natural history and the green section represents the non-specific effects of treatment. The specific effect attributable to a genuine treatment represents only a part (red section) of the complete treatment response which also includes the placebo effect due to non-specific components as well as natural history of improvement (J. Howick et al., 2013).*

The simplest way to describe placebo-controlled clinical trials assumes that drug and placebo effects are additive, such that the drug effect is the difference between the response to the drug and the response to the placebo. Yet, in spite of vast evidence for an additive model, there are also indications of more complex, non-additive, drug-placebo interactions. For example, positive information about asthma treatment increased treatment responses in the placebo arm, but not the drug arm, of a large asthma study with more than 600 patients (Wise et al 2009).

The non-specific factors of a treatment may also induce negative expectations of a treatment. This effect is called nocebo and may result in negative treatment outcomes. Nocebo is generally something highly unwanted except for experimental interventions where the nocebo may be interesting per se (Enck, Benedetti, & Schedlowski, 2008).

Although there is a large amount of literature discussing the concept of placebo, there is no consensual agreement about its definition (Jeremy Howick, 2016). In this thesis, a modified placebo definition by Vase et al. will be used (Vase, Riley, & Price, 2002): "*The placebo response is the reduction in a symptom as a result of factors related to treatment expectations (conscious and non-conscious) and/or a subject's/patient's perception of the therapeutic intervention"*. This modified definition opens up for a broad view of what is included in the psychosocial environment that may contribute to the placebo effect. Some researchers have changed the term placebo into "context", to avoid the reduction of a placebo as something used in RCTs or used as an inert treatment (Blasi, Harkness, Ernst, Georgiou, & Kleijnen, 2001). In this thesis, the terms contextual, non-specific and psychosocial context will be used interchangeable to describe factors contributing to placebo effects.

1.1.2 The power of mind

The connection between mind and body has for a long time fascinated and challenged medical science (de Craen, Kaptchuk, Tijssen, & Kleijnen, 1999), and was discussed already in the 1600s by René Descartes. Placebo effects constitute one of the most prominent examples of so called "mind-body interactions", as patients' expectations about treatment ("mind") may activate what we normally consider autonomous physiological reactions ("body") that affect treatment outcomes. The power of mind can be illustrated by the following mental picture: "Imagine that you are in a wonderful garden full of lemon trees. You pick one lemon and hold it in your hand. The scent is magnificent and you start pealing the lemon. You then taste the lemon by chewing slowly on a small juicy peace, how does it taste and what do you feel?" Maybe you experienced increased salivation by simply thinking about the lemon, maybe you did not. However, this is one way of demonstrating how our

thoughts (“mind”) affect autonomous physiological processes (“body”), exemplified by salivation in this case.

1.1.3 The history of placebo

1.1.3.1 Early historical background

Placebo effects have been present throughout the medical history, since most early medical treatments were likely totally ineffective. Pre-scientific medicine often treated patients with different forms of remedies, including “Usnea” (the moss from the skull of a victim of a violent death) and other procedures such as cutting, bleeding, and heating (Czerniak & Davidson, 2012). Today, pre-scientific medicine is generally deemed ineffective and sometimes bizarre. Yet, at the time, these treatments were believed to have specific healing effects, and not just “pleasing” the patient.

The word placebo was first used in the 14th century as a translation of a Bible psalm from the Latin “Placebo Domine” to “I will please the lord” (de Craen, Kaptchuk, Tijssen, & Kleijnen, 1999). Placebo was until the late 18th century above all used in a religious context and the translation from a religious to a medical term is due to the work of a British physician, William Cullen. In the year of 1772, Cullen presented a series of lectures, where he introduced the “placebo” as a useful tool for both patients and therapists. He regarded a placebo treatment as one given to please, and stated that placebo may indeed reduce symptoms (Kerr, Milne, & Kaptchuk, 2008).

1.1.3.2 The first placebo-controlled experiment in medicine

Already back in 1784, the first known placebo-controlled experiment was performed to evaluate the healing mechanisms of “mesmerism” (Kaptchuk, Kerr, & Zanger, 2009). Mesmerism was based on the beliefs that humans had certain fluid channels that could be targeted with a mesmerism object (charged with “animal magnetism”) and thereby cure bodily symptoms. Initially, the rituals of mesmerism showed profound results, however this was during the enlightenment era and scientists raised criticism towards the method. As a response, an experiment exposing participants to either “genuine” mesmerism objects or “fake” objects was conducted. In these trials, large number of participants responded to both objects, and it was concluded that mesmerism had no true effect, and that the effects likely were due to participants´ beliefs (Kaptchuk et al., 2009).

1.1.3.3 Placebo in medical science

In 1955, Beecher and colleagues published a groundbreaking paper, titled "The Powerful Placebo", that introduced the concept of placebo to the general medical community. Instead of treating the placebo arm of placebo-controlled clinical trials as a nuisance factor, this paper directed the interest towards the placebo group, by describing placebo responses from 15 different clinical trials. The results were pooled and the estimated power of the placebo effect (quantified as the amount of patients that were relieved by the placebo) was approximately 35% (Beecher, 1955). Although this paper has been criticized for its methodological flaws (Kienle & Kiene, 1997), it was the first attempt to quantify the placebo effect, and contributed significantly to further scientific interest in placebo effects per se.

The first known study designed to investigate the placebo response and placebo responders was conducted by Lasagna and colleagues in 1954 (Lasagna, Mosteller, Von Felsinger, & Beecher, 1954). The study investigated the effects of subcutaneous injections of morphine or placebo on postoperative pain. The participants in the placebo group were divided into responders and non-responders and the results suggested that only 14% of patients consistently responded to placebo. Also, the study concluded that there was no difference between responders and non-responders regarding age, gender and intelligence. Most importantly, the study by Lasagna and colleagues discussed the complexity of placebo controls in clinical trials and provided a hypothesis to explain placebo effects. So far, there had been no studies investigating the mechanisms behind placebo effects. Therefore the work in 1978 by Levine and colleagues (Levine, Gordon, & Fields, 1978), was a significant step towards understanding of the mechanisms behind placebo analgesia. In their study, Levine et al. hypothesized that placebo analgesia could be mediated by endogenous opioids. Their data demonstrated that placebo analgesia in post-operative dental pain was reduced by administration of an opioid antagonist (naloxone). This was the start for many studies to follow, confirming the involvement of endogenous opioids in placebo analgesia.

1.2 THE SCIENCE OF PLACEBO

1.2.1 Factors contributing to placebo effects

Several psychological mechanisms are suggested to contribute to placebo effects. The two most commonly described mechanisms include conditioning of positive treatment responses (associative learning) (Finniss 2010) and expectancy through verbal suggestion of positive treatment outcomes (Colagiuri & Smith, 2012; Cormier, Lavigne, Choiniere, & Rainville,

2016). It is believed that both mechanisms lead to an increase of treatment expectations, even if one is implicit (conditioning) and the other is explicit (verbal suggestion). The role of treatment expectancy in understanding placebo effects will be further discussed in the next section. Factors such as desire to get well (Vase, Robinson, Verne, & Price, 2003) and hope to recover (Vase et al., 2002) have been found to affect placebo outcomes. Also, the treatment context is known to have an influence, such as the characteristics of the placebo given (Kong et al., 2013; Meissner et al., 2013; Waber, Shiv, Carmon, & Ariely, 2008) and the patient-clinician relationship (Kaptchuk et al., 2008; Kelley et al., 2014). In spite of a large literature pointing to the contribution of different contextual factors, it is difficult to isolate their specific contribution to the placebo effect. Moreover, placebo researchers avoid talking about one placebo effect, as there are several routes to activation of placebo effects (e.g. verbal suggestion, conditioning), several neurobiological mechanisms involved (e.g. dopamine release, endogenous release of opioids) and their unique interaction with contextual factors (Kirsch, 2013).

1.2.2 Expectations

An expectation is a prediction based on reasoning and/or learning from experience, and in placebo studies verbal suggestion is often employed to enhance a patient's expectation about a treatment and thereby promote placebo effects (Peerdeman et al., 2016). In line with this, there are numerous studies linking high pre-treatment expectations about a certain treatment (not only placebo treatment) to positive treatment outcomes, both in experimental and clinical contexts (Colagiuri & Smith, 2012; Cormier et al., 2016; Mondloch, Cole, & Frank, 2001; Vase, Petersen, Riley, & Price, 2009). So far, most published work has focused on the influence of patients' expectations on treatment outcomes. However, clinicians' expectations about a patient's chances to benefit from a certain treatment may also affect outcomes (Gracely, Dubner, Deeter, & Wolskee, 1985; Witt, Martins, Willich, & Schutzler, 2012), and furthermore, it is possible that the interaction between the expectations of the patient and clinician should be considered (Barth, Schafroth, & Witt, 2016).

1.2.3 Measuring and manipulating expectations

Common methods when studying the effect of treatment expectations on clinical outcomes include assessments of pre-treatment expectations and manipulation of expectations through verbal suggestions (Bishop, Yardley, & Lewith, 2007; Peerdeman et al., 2016). An illustrative example of the relationship between pre-treatment expectations and treatment outcomes can be found in a pooled analysis of four RCTs (n=864), with the aim to investigate the effect of

acupuncture treatment for different chronic pain conditions. The results showed significant associations between positive treatment expectations (measured at baseline and after 3 sessions) and positive treatment outcomes (at treatment completion and 6 month follow-up); emphasizing the importance of fostering positive treatment expectations prior to an acupuncture intervention. In order to estimate the effects of different expectancy manipulations, Peerdeman and colleagues recently conducted a comprehensive meta-analysis of the effects of treatment expectations on pain outcomes (Peerdeman et al., 2016). The meta-analysis suggest that interventions aimed at boosting positive expectations have a positive effect on subjective ratings of pain, in particular verbal suggestions about pain analgesia. Yet, evidence is not conclusive. As opposed to previously mentioned studies there are studies indicating that positive treatment expectations are not necessarily associated with positive outcome. For example, Sherman et al. (Sherman et al., 2010) found no associations between expectations and outcomes in an acupuncture trial in patients with chronic back pain. Inconclusive data was also found in a pharmacological trial of amitriptyline for pain, where expectations about treatment outcomes correlated with analgesia in the real treatment group, but not in the placebo group (Turner, Jensen, Warms, & Cardenas, 2002).

1.2.4 The neurobiology of placebo effects

Today, there are many studies demonstrating that placebo effects are not only represented by subjective reports, but also display corresponding changes in neurobiological systems (Wager & Atlas, 2015). Studies using placebo treatment in various different medical conditions have elucidated pathways through which non-specific treatment factors activate neurobiological responses (e.g. endogenous regulation of endocrine and immune systems) resulting in health promoting effects (Albring et al., 2012; Benedetti & Amanzio, 2013). So far, three main neurotransmitters have been closely linked to placebo effects: opioids, dopamine and cannabinoids (Jubb & Bensing, 2013). Most mechanistic placebo studies have been performed on placebo analgesia, which has been associated with the release of different endorphins, in particular endogenous opioids (Tracey, 2010). Similarly, placebo effects in other clinical domains are associated with activation of other neurotransmitter systems. For example, in Parkinson's disease there is release of endogenous dopamine during placebo treatment (Lidstone et al., 2010) and in anxiety and depression placebo responses are associated with increased activity in neural networks related to emotional regulation (Enck et al., 2013).

1.3 PAIN

Pain is the most common reason for seeking health care, and is the cause of major suffering in the general population. Pain is defined as a subjective experience by the International Association for the Study of Pain (IASP 1990 definition), and suggests that pain involves several dimensions, including a sensory-discriminatory, affective-motivational and cognitive-evaluative component (Melzack & Casey, 1968). In this thesis, two different studies investigate placebo analgesia; one experimental study in healthy controls, and one in patients with chronic pain. As both studies include pain as a primary outcome, the following section will present some basic pain physiology.

1.3.1 Pain perception

The subjective perception of pain results from the integration between peripheral nociceptive input and contextual, emotional, pathological, genetic, and cognitive factors (Tracey & Mantyh, 2007). Thus, the experience of pain is not linear to the nociceptive input, and the response to the same stimulus can differ substantially between individuals (Tracey & Mantyh, 2007). Pain is by definition a subjective experience, as illustrated in the definition from the IASP: *"pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* (Merskey & Bogduk, 1994). This definition is specifically important for understanding chronic pain conditions, where there is often presence of high intensity pain in absence of any known tissue damage or other nociceptive input (Treede et al., 2015).

1.3.2 Pain modulation

Pain modulation can take place at several levels of the neural axis, and involves up- or down-regulation of pain signals. In a simplified illustration of pain signaling, afferent pain transmission starts from any part of the body via activation of pain receptors, known as nociceptors. The afferent signal projects to the dorsal horn of the spinal cord where the signal is relayed to secondary afferent neurons to be projected up to different regions of the brain (Cortelli, Giannini, Favoni, Cevoli, & Pierangeli, 2013). There is no primary pain area in the brain, instead the nociceptive signals are projected to several regions (Jensen et al., 2016), that together are sometimes called "the pain matrix" (Melzack, 1999). In addition to brain areas that process ascending nociceptive signals, there is also a descending pain inhibitory cerebral network, which regulates the ascending pain signals and therefore affects the perception of pain (Ossipov, Dussor, & Porreca, 2010). The pain inhibitory system is always part of the normal pain response and involves opioid-, serotonergic- and noradrenergic pathways (Staud, 2013).

Placebo analgesia is a prominent example of how psychological processes may activate the descending pain inhibitory pathways in the brain (Eippert, Bingel, et al., 2009).

1.3.3 Acute and chronic pain

Acute pain is an adaptive reaction to a noxious stimulus, as this sensation alerts us to possible injury. In acute pain, there is often a relationship between the degree of noxious input (e.g. an injury) and the amount of pain. Yet, in chronic pain, the painful sensation becomes permanent even in the absence of any tissue damage, which means that pain has become dysfunctional. By definition, pain that lasts or recurs for more than 3 to 6 months is considered chronic, and can be related to a number of different medical conditions but there may also be no clear cause (Merskey & Bogduk, 1994; Treede et al., 2015). Mechanisms of chronic pain involve disturbances of central pain processing, such as pain amplification and impaired inhibition of pain (Clauw, 2015). Today, there are limited treatment options for treatment of chronic pain, which causes physical and psychological suffering. For example, patients report significantly reduced health-related quality of life and psychological well-being (Lynch et al., 2008).

1.3.4 Placebo analgesia mechanisms

Since the first study in 1978 (Levine et al., 1978) showing that placebo analgesia could be mediated by endogenous opioids, there have been several studies continuing the work by identifying neurobiological mechanisms for placebo analgesic effects (Tracey, 2010). Brain imagining techniques such as functional Magnetic Resonance Imaging (fMRI), which measures brain activity by detecting Blood Oxygenation Level Dependent signals (BOLD), and Positron Emission Tomography (PET), which measures brain activity (or sometimes neurotransmitter binding potential) by detecting metabolic processes, have provided a powerful way to assess specific brain areas correlating with placebo analgesia (Atlas & Wager, 2014). In 2002, Petrovic et al. published the first PET study showing a shared neuronal network of placebo and opioid analgesia (Petrovic, Kalso, Petersson, & Ingvar, 2002). After this finding, a growing amount of neuroimaging studies have demonstrated that placebo analgesia depends on activation of brain regions capable of releasing endogenous opioids and dopamine. The brain regions involved in generating placebo effects include cortical and subcortical areas, such as the Anterior Cingulate Cortex (ACC), insula, thalamus and amygdala (Atlas & Wager, 2014; Tracey, 2010). Several of these key regions have also been linked to descending pain modulatory systems including the endogenous opioid system (Eippert, Bingel, et al., 2009; Zubieta et al., 2005) and dopaminergic system (Scott et al., 2008). In addition to the above cerebral mechanisms, pain-related activity in the spinal cord has also been reduced by placebo

(Eippert, Finsterbusch, Bingel, & Buchel, 2009). This spinal activation provides evidence for placebo influence on the afferent nociceptive signals, thus, before signals reach cortical processing (Eippert, Bingel, et al., 2009). In sum, placebo analgesia has historically been seen as an effect of e.g. altered perception or response bias. However, now there is comprehensive evidence that placebo responses involve changes of underlying disease mechanisms.

1.4 FIBROMYALGIA

FM is a common chronic pain disorder. The estimated prevalence in the general population ranges from approximately 2-5% (Jones et al., 2015) with a female dominance (80%) (Yunus, 2001). Currently, there are two sets of diagnostic criteria for FM proposed by the American College of Rheumatology (ACR). One published in 1990, which requires chronic widespread pain and pain at palpation of a certain number of pre-defined tender points (Wolfe et al., 1990), and one published 2010 which excludes the palpation of tender points and includes a set of questions about "non-pain symptoms" typically related to FM (Wolfe et al., 2010). The changes from the 1990 to the 2010 criteria came about as an effort to make the criteria more useful in a primary care setting. In Study II of this thesis, the ACR 1990 criteria were used. FM is a multi-symptomatic pain syndrome and includes chronic, migrating, widespread musculoskeletal pain typically accompanied by other symptoms such as fatigue, disturbed sleep and cognitive problems (R. M. Bennett, 2009; Glass, 2009). In line with vast evidence from FM research, FM is considered a centralized pain disorder, which means that pain can occur in absence of damage or inflammation of peripheral tissues (Clauw, 2015). Often FM is regarded as the extreme end of a continuum of centrally mediated pain syndromes, in which pain amplification and an inability to activate endogenous pain inhibition are possible causes of pain (Clauw, 2007). This state is often referred to as "disinhibition" and could possible explain the unique presence of high intensity pain at a large number of body sites seen FM. Once centralization of pain occurs, the response to regular treatments for nociceptive pain (i.e. nonsteroidal anti-inflammatory drugs and opioids) is decreased (Clauw, 2015).

1.4.1 Treatments for fibromyalgia

There is no clear standardization of treatments for patients with FM. However, as FM is a multi-symptomatic syndrome, multimodal and interdisciplinary treatments are recommended (Clauw, 2015). These modalities commonly include a combination of non-pharmacological therapies (exercise, cognitive behavioral therapy, educative support) and pharmacological treatments (i.e. antidepressants with documented effect on FM and anti-epileptics) (Clauw, 2015; Hauser, Thieme, & Turk, 2010). In Study II of this thesis, the FM intervention group

received treatment with the antidepressant milnacipran, which is a selective norepinephrine serotonin reuptake inhibitor (SNRI) (Bernstein, Albrecht, & Marcus, 2013). However, as Study II is exclusively investigating the outcomes in the placebo arm of the clinical trial, milnacipran treatment is not discussed in more detail.

1.5 PRIMING

1.5.1 The concept of priming

Human behavior is often assumed to be linked to conscious decisions, with the impression that we are free to choose between different possible options of action in order to pursue desired outcomes (Wegner, 2003). However, there is a growing literature showing that people pursue goals without conscious awareness, and that our actions are initiated by non-conscious processes long before we become aware of our intention to act (Custers & Aarts, 2010). Priming is described as a non-conscious (implicit) memory effect and is theorized to work through activations within associative networks in the brain (Tulving & Schacter, 1990). This means that exposure to one stimulus (prime) influences our responses to other stimuli, if they are associated in our memory. The activation of such implicit associations can thus influence our behavior, even if we are not aware of the connection between the prime and the measured behavior (or the memory associations causing the priming effect) (Bargh, Chen, & Burrows, 1996; Tulving & Schacter, 1990).

1.5.2 Semantic priming

One common approach to induce non-conscious memory associations is through semantic priming. There are two common ways of presenting a semantic prime, either subliminally, where people are not consciously aware of the prime as it is presented to short to be consciously perceived, or supraliminally where people are consciously aware of the prime but not aware of its assumed influence on the experimental task (Bargh & Chartrand, 2000). Supraliminal priming typically includes a task where participants read sentences or single words (primes) aimed at influencing a specific behavior (subjects unaware of the relationship prime – measured behavior) (Bargh et al., 1996; Richter et al., 2014). One simplified way of illustrating semantic priming is to imagine that you have just read a list of words related to a certain concept, and then is asked to fill out the blanks in an incomplete word at the end of the list. In this scenario you may be more prone to finish the incomplete word with something associated with the concept of the list of words, even if you are instructed to choose any word of your choice. In

the example below, a priming effect would mean that the left blank formed the word “pear” and the right blank would form the word “pier”.

APPLE	BOAT
ORANGE	SHIP
BANANA	ANCHOR
P_ _ R	P_ _ R

1.5.3 Priming manipulations

Some classical experiments have demonstrated how semantic priming may affect behavior. In a seminal study from 1996 (Bargh et al., 1996), subjects were primed with words related to the stereotype of elderly people (example: Florida, forgetful, wrinkle), using a Scrambled Sentence Test (SST). While the words did not explicitly mention speed or slowness, those who were primed with the words related to the elderly walked more slowly upon exiting the testing booth than those who were primed with neutral words. Similar effects were found with rude and polite stimuli: those primed with rude words were more likely to interrupt an investigator than those primed with neutral words, and those primed with polite words were the least likely to interrupt. Priming effects have received a lot of attention in the field of behavioral sciences, yet, it is important to note that the robustness of priming results are questioned and there are several failed attempts to replicate the findings (Doyen, Klein, Pichon, & Cleeremans, 2012); see Methodological considerations and the Limitations section.

Studies investigating the effect of semantic priming on pain perception are scarce (Meerman, Verkuil, & Brosschot, 2011; Richter et al., 2014). In particular, there are no studies investigating how semantic priming may influence pain by targeting subjects’ expectations about pain relief. As placebo analgesia is closely related to positive treatment expectations (Tracey, 2010), it is possible that semantic priming with words related to positive expectations in general could influence placebo effects.

1.6 INTELLECTUAL DISABILITY

ID is a chronic disability characterized by significant limitations in intellectual functioning (mental capacities such as reasoning, problem-solving, abstract thinking, learning from experience) and significant limitations in adaptive behavior (everyday tasks such as social and practical skills) (Cooper, 2014; Vissers, Gilissen, & Veltman, 2016). ID has several causes (i.e. brain injury, psychiatric conditions) but can also be caused by genetic factors. Two of the most common genetic causes of ID are Down syndrome and Fragile X syndrome (Picker & Walsh,

2013). ID is confirmed by both clinical assessment and standardized testing of intelligence (IQ scores of 70 or below), and requires a significant impairment of general mental abilities and functioning needed for everyday life (DSM-V) (R. Cooper, 2014). Until recently, treatments for ID have mainly focused on treating secondary symptoms caused by the disorder, such as attention deficits and anxiety, and on minimizing complications related to comorbidities like epilepsy (Curie et al., 2016). However, lately new pharmacological treatments targeting the underlying genetic defect are becoming a reality for a subset of patients with genetic forms of ID. It is possible that these therapeutic opportunities may lead to enhanced cognitive functioning among patients with ID (Picker & Walsh, 2013).

1.6.1 Placebo in ID

Many RCTs have investigated different pharmacological treatments for patients with genetically determined ID, yet, little attention has been directed toward the placebo group. This means that there is limited knowledge about ID patients' ability to improve as a response to placebo treatment. In response to this, a recently published meta-analysis specifically investigated the treatment effects in the placebo control group in RCTs that focus on core ID symptoms (Curie et al., 2015). The results revealed that patients with ID had a significant overall placebo response from pre- to post treatment, both for subjective outcomes (a third-person evaluation of the patient's improvement) and objective outcomes (direct evaluation of the patient's abilities). The authors of the meta-analysis proposed several mechanisms that may contribute to placebo effects in ID, including expectancy, implicit learning and placebo by proxy induced by clinicians and family members.

2 ETHICAL CONSIDERATIONS

The World Medical Association has developed the Declaration of Helsinki, containing ethical statements for medical research involving human subjects (World Med, 2013). In this thesis, all statements of the Declaration of Helsinki that apply to our studies have carefully considered, however, there are still ethical topics that deserve additional discussion as placebo research raises some specific issues regarding deception. Placebo is often associated with deception and incomplete disclosure, implicating that patients must be unaware of getting a placebo treatment in order to receive a placebo response (Annoni & Miller, 2016). There are some obvious ethical dilemmas associated with deception and incomplete disclosure, as it violates the ethical principles of respect for patient autonomy and informed consent (Kaptchuk et al., 2010). For example, participants might not have chosen to participate if fully informed about all details of the study. One way of addressing these ethical concerns is to debrief the participants about the

deception/incomplete disclosure at the end of the study (Miller, Gluck, & Wendler, 2008), and also give participants the chance to withdraw their data if they disapprove with the deceptive aspect of the study.

In Study I we did not inform the participants that they were receiving sham analgesic treatment (deception). The participants were also not aware of the true purpose of the priming task used in the study (incomplete disclosure). However, directly after the experiment all participants were debriefed by explaining the deception and the rationale for the study and were also offered an opportunity to withdraw their data. Even though participants were carefully debriefed at the end of the study, it is possible that the deception resulted in some psychological discomfort. However, no participant in the experiment withdrew their data or expressed any disapproval.

In clinical studies, the use of deception would be of greater concern than in experimental studies, as using a placebo treatment without patients knowledge would compromise the patient-clinician relationship, undermine trust in health care and potentially harm the patient (Kaptchuk et al., 2010). In line with laws and regulations, all FM patients included in Study II were aware of the purpose of the study and that they could receive either genuine treatment (milnacipran) or a placebo treatment (sugar pill). Moreover, after the study the patients were debriefed about their treatment allocation.

Study III was a meta-analysis with the aim to investigate placebo responses in patients with ID. As patients with ID are considered a vulnerable patient population, unable to understand the information given about the study, informed consent is often given by close relatives to the patient (World Med, 2013). As Study III is a meta-analysis of data already collected, we did not have to directly handle the ethical dilemma of obtaining informed consent from vulnerable individuals. Furthermore, Study III had a favorable risk-benefit ratio as the results may lead to improved treatment for ID patients.

Study I and II were approved by the Regional Ethical Review Board in Stockholm (Study I, approval date 2014-06-11, Dnr. 2014/932-31/2 and Study II, approval date 2005-03-30, Dnr 2005/279-31/1). Study III did not require an ethical approval since it was a meta-analysis and did not include any active interventions on humans.

3 GENERAL AND SPECIFIC AIMS

The broad general aim of this thesis was to investigate the role of non-specific treatment components on treatment outcomes, both in healthy participants and in clinical populations. More specifically, the aim was to address three previously understudied aspects of placebo responses. The specific aims of each study are presented below:

3.1 STUDY I

The aim of Study I was to evaluate if placebo analgesia can be influenced by non-conscious expectations induced by semantic priming. We hypothesized that exposure to positive priming would result in a more positive mindset that would transfer to greater placebo responses, compared to neutral priming.

3.2 STUDY II

The aim of Study II was to evaluate if placebo responses are dependent on the duration of a chronic disease. This was investigated among patients with FM, with different exposure to FM pain (months, years). We hypothesized that longer duration of FM was associated with lower placebo responses as expectations (and/or pain modulatory systems) may have been impaired over time.

3.3 STUDY III

The aim of Study III was to investigate the role of treatment expectations on treatment outcomes among patients with ID. We hypothesized that the treatment response to the same drugs would be higher in trials with 100% certainty of getting the real drug (open-label drug trials) compared to trials with 50% likelihood of receiving the real drug (placebo-controlled drug trials).

4 METHODOLOGICAL CONSIDERATIONS

This section will present the methodological considerations relating to the three studies included in this thesis: a randomized experimental study in healthy participants with a double-blind design (Study I), a RCT in FM patients with a double-blind design in a clinical setting (Study II) and a meta-analysis of results from RCTs in an ID population (Study III). For more detailed methods see the individual manuscripts in the addendum of this thesis.

4.1 PARTICIPANTS

In Study I, healthy participants were recruited via advertisements on university message boards and through an academic study website (http//www.studentkaninen.se). In Study II patients with FM were recruited from primary care as part of a pharmacological multicenter study including three sites; one in England, Sweden and Germany, respectively. In Study III, patients with ID were included as a part of already performed RCTs or open-label clinical trials. Descriptive data for the participants in all three studies are shown in table 1.

Table 1. *Descriptive data for the study cohorts of Study I-III. FM= Fibromyalgia; ID=Intellectual Disability; n=numbers of participants; OL=open-label trial; RCT= Randomized Controlled Trial; VAS=Visual Analogue Scale.*

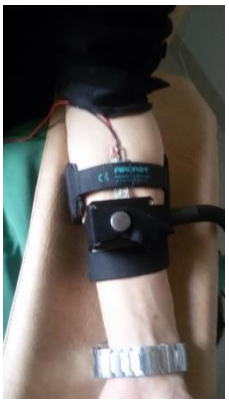
	Study I	**Study II**	**Study III**
Participants	Healthy	FM	ID
n (male/female)	36 (15/21)	37 (n.a./37)	OL 261 (170/91) RCT 1548 (1006/542)
Age (years) mean and ranges	25 (18-48)	45 (24-55)	OL 24 (2-53) RCT 18 (0-53)
Inclusion criteria for participants	Age 18-55 years Generally healthy	Age 18-55 years Female Fulfilling ACR 1990 criteria ≥ 40 mm VAS weekly pain	Any age Genetically determined ID

Advertisements on academic study web sites (Study I) might affect the external validity (i.e. to whom the results of this research can be applied) as these web sites commonly attract younger participants from higher education. However, in Study I there was a reasonably variance in age (see Table 3.1.) and education (67% of participants had a university education and 33% high school education), suggesting that the results may be translated to a broader population. Initially, we were concerned that participants with an education in medicine or psychology

would be suspicious about the experimental study set up, as the experiment included a "medical procedure" with a fake sham device. However, there was no participant (irrespective of education) revealing the true rationale of the experiment, indicating that our choice not to exclude this group was correct. Recruiting patients for clinical RCTs often includes greater challenges than recruitment for experimental studies. In Study II, the diagnostic criteria for FM had to be confirmed, all therapies that might interfere with the study treatment (milnacipran) were discontinued and there were many more exclusion criteria that related to the properties and side effects of the study treatment. This is a limitation, as the included FM sample might not be representative for the general FM population. RCTs often require a "balancing act" between the internal validity of a study (i.e. research designed so that there are few alternative explanations for changes in the dependent variable other than the effects of the independent variables) and the external validity (i.e. is this result applicable to the FM population). In addition, Study II was designed as a mechanistic study, aiming for understanding the mechanisms responsible for the drug effect, and therefore strict inclusion criteria were of major importance. Finally in Study III we decided to limit our meta-analysis to studies including patients with genetic causes for ID, manifested from early development, instead of including studies in patients with ID of any etiology. This was done in order ensure that ID was present from birth, as opposed to ID acquired late in life, where patients had a normal cognitive development before disease onset. If different etiologies had been mixed in the analysis, this may have confounded the results in an unpredictable way and impaired the interpretability.

4.2 PROCEDURES

4.2.1 Experimental pain



In Study I, experimental heat pain was induced by delivering painful stimuli on the forearm using a 3x3 cm heat probe (Medoc Advanced Medical System, Israel). Each heat stimulus lasted for 4 seconds. A calibration of each participant's pain sensitivity was performed before the onset of any experimental testing. The calibration started at 40 degrees Celsius (°C), with an increase by one degree per trial up to participants' subjective pain rating of 60 on a 0-100 numeric response scale (NRS) ranging from 0=no pain to 100=worst possible pain, or a maximum of 49 (°C).

In Study I, placebo analgesia was induced with a sham analgesic device. An electrode for the skin was placed on the volar forearm (next to the heat device) and connected to a couple of electronic boxes that could be turned "on" with a beeping sound. Both the electrode and the electronic boxes were inactive, as they did not have the capacity to induce any sensation to the skin. The sham analgesic device was introduced by saying *"This is a machine used in our laboratory to lower the sensation of pain. By placing this electrode close to the heat probe, the analgesic device applies a high frequency electrical current which affect nerve fibers and will therefore decrease pain"*. After the placebo experiment, participants rated the analgesic device as both credible and having the ability to give effective pain relief.

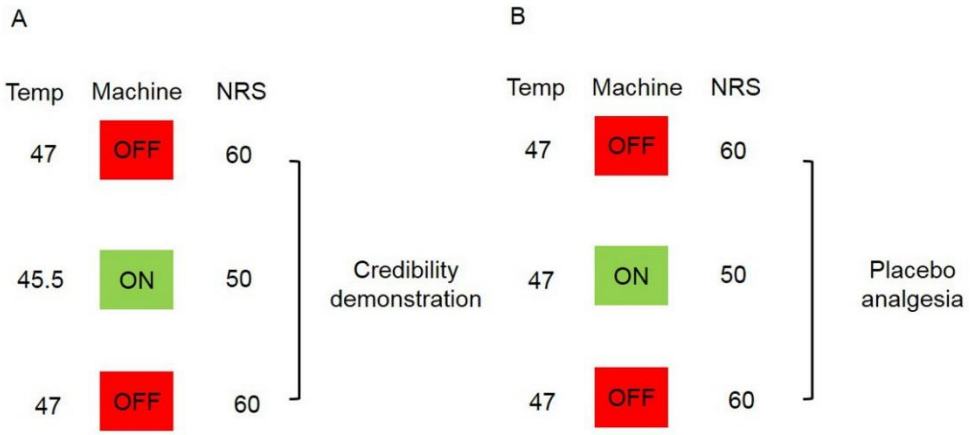


Figure 3. *Schematic overview of the sham device procedure. A) Before the priming task, a credibility demonstration of the sham device was performed, where participants' high pain temperature was administered (while the experimenter indicated that the analgesic device was "off"), and then the temperature was surreptitiously lowered by 1.5℃ (while indicating that the analgesic device was "on"), lastly, the high pain temperature was administered again (while indicating that the analgesic device was "off"). B) The test of placebo analgesia was performed after the priming task. The participants' high pain temperature was administered three times; first when indicating that the analgesic device was "off" (baseline), then when indicating that the machine was "on" (placebo analgesia), and one last time while indicating that the machine was "off" (baseline).*

Pressure pain was used to induce experimental pain in Study II, and pressure pain sensitivity was the primary outcome to assess changes in pain processing following the intervention. Pressure pain stimuli were applied to the thumbnail using an automated, pneumatic, computer-controlled stimulator with a plastic piston that applied pressure via 1 cm2 rubber probe (Jensen

et al., 2009). This apparatus allowed for an individual calibration of a pressure intensity corresponding to each individual's 50 mm rating on a 100 mm Visual Analogue Scale (VAS) ranging from 0=no pain to 100= worst possible pain. Each patient's pressure that corresponded to 50 mm VAS was referred to as P50 in the study.

In Study II, the patients received an oral placebo treatment. The appearance of the placebo pill was identical to the genuine pharmacological pill (milnacipran). In comparison to other placebo treatments, for example sham acupuncture or a sham analgesic device (as in Study I), a placebo pill has the strength of enabling a robust double-blinded design (since sugar pills and genuine pills look identical). Nevertheless, unblinding can still occur in pharmacological clinical trials due to apparent physiological effects of genuine pharmacological treatments (including side-effects). In Study II no data was collected regarding patients' beliefs about receiving genuine or placebo treatment.

4.2.2 Priming with Scrambled Sentence Test (SST)

In Study I, the method chosen for inducing non-conscious expectations was through priming with SST. SST is a commonly used supraliminal priming technique were the participant is exposed to clearly visible words in a pen-and-paper language task (J. Bargh & Chartrand, 2000), aimed at evoking specific associations. This means that the participants were aware of the words in the SST task, but not aware of the underlying purpose (i.e. to activate associations to positive treatment expectations). Participants were simply told that they would perform a language task, without further specifications. The participants were randomized to either perform an SST aiming at activating associations to positive expectations, such as "things getting better", or randomized to a neutral SST with similar sentences but without the positive associations (see table 2.) The SST entails creation of sentences from a string of 6 scrambled words (in total 15 sentences). The instructions for the SST task were: "The words in the following sentences have been scrambled. Can you change the order of the 6 words, remove one word, and thereby make the sentences grammatically correct? If yes, spell out the grammatically correct sentence consisting of 5 words in the box to the right. If no, leave the box blank".

Table 2. *The sentences included in the SST (N.B. this is a translation from Swedish which might affect the meaning of the English sentences).*

Positive	**Neutral**
you take will new a record	very skin shower turned wet my
pillows warm comfortable bed sheets give	environment same food travel vacation recurring
exercise relaxation we on now healthy	mine ground coming containing box tools
oak many massive years sturdy building	lunchbox again eats she food from
working day sleep deep much effective	hours repeating frequently awake sleep work
get you praise today will fine	in-house gets done mopping everything
now flows success in career smoothly	some oak massive years building old
shining in-house clean gets when mopping	we now high jumping practicing new
mine ground coming box containing joy	take new will you pasta one
long environment travel beautiful vacation food	with eat the up fried breakfast
up tasty eat chocolate with it	the job now year career ongoing
she again enjoys the food good	new colors turn one many paintings
cream soft got my very skin	sheets give low pillows bed old
his used shining he future time	time future he jumped used his
turn beautiful pretty colors one painting	you today perfume will get picky

4.2.3 Awareness check of SST

After the experiment, an awareness check of the prime was performed with the following questions "could you detect any themes or specific purposes of the language test? Participants could answer "yes" or "no", and if yes, the participants were asked to specify their response. None of the participants reported the correct theme or purpose of the priming concept. This validates that the goal of the SST procedure was not consciously perceived by the participants, which is a perquisite for a proper priming experiment.

4.2.4 Validation of SST

As there were no previous attempts to enhance placebo effects by means of priming, the SST was validated in an independent group of participants (n=36). All 30 sentences (15 positive and 15 neutral) were mixed in one questionnaire. The participants were asked to rate to what degree they perceived each sentence to induce positive expectations. The 15 positive SST sentences were rated significantly more "positive" than the 15 "neutral" sentences, indicating that the sentences were at least consciously deemed differently regarding expectations (see Study 1). However, this may not have been the case during the priming experiment itself, when the participants were unaware of the purpose of SST (i.e. not explicitly asked to rate degree of positive expectations).

4.3 DATA COLLECTION

4.3.1 Pain measures

In Study I, the NRS was used to rate heat pain intensity. The NRS ranged from 0 (no pain) to 100 (worst imaginable pain). The NRS can be administrated both as a graphically and orally delivered scale. As the participants in the experiment had pain devices on their forearm, we chose to verbally ask them to rate their perceived heat pain intensity by giving a number between 0-100.

In Study II the VAS was used to rate pain intensity, which is probably the most commonly used scale in both clinical and experimental settings. The VAS is presented as a 100 mm line, anchored by verbal descriptors "no pain" on the left and "worst imaginable pain" on the right. The patients were asked to put a mark on a 100 mm line to indicate their perceived pain intensity. Both the NRS and the VAS are deemed reliable and appropriate for use in clinical practice and scientific research (Williamson & Hoggart, 2005).

4.3.2 Self-report questionnaires

In order to capture a more complex picture of symptoms and traits, different self-report questionnaires were used in Study I and II. In Study I the participants answered two different questionnaires after the experimental procedure: the Eysenck Personality Questionnaire (EPQ12) including 12 items (yes/no answers) used to assess trait neuroticism (Eysenck, Eysenck, & Barrett, 1985), and a study specific questionnaire including questions about i) awareness and difficulty of the priming procedure ii) credibility of the sham device and iii) credibility of the treating experimenter.

In Study II, several questionnaires were used both at baseline and after intervention, the Short Form 36 (SF36) which measures different domains of health status (Ware & Sherbourne, 1992), the Beck Depression Inventory (BDI) which is commonly used to assess depressive symtoms (baseline only) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), the Coping Strategies Questionnaire (CSQ) where the subscale of catastrophizing thoughts about pain was used (Burckhardt & Bjelle, 1994) and the Spielberger Trait Anxiety Inventory (STAI-T) for measuring trait anxiety (Spielberger, 2010). Also, the Fibromyalgia Impact Questionnaire (FIQ), which measures the impact that FM has on patients' daily life and physical functioning, was used (R. Bennett, 2005). In order to assess the spatial spread of patients' pain across the body, FM patients were asked to complete a pain drawing, which is a schematic drawing of a

person where the patients mark with a pencil where they feel pain, and the number of painful areas are calculated.

4.3.3 Measure of clinical improvement

The Patient Global Impression of Change (PGIC) is a 7 point scale measuring the patient's subjective report of clinical improvement in relation to a given treatment. The scale ranges from 1 (very much improved), to 7 (very much worse). The PGIC ratings were used to classify the patients in Study II as either "treatment responders" (defined as any type of improvement) and "non-responders" (defined as patients having no change at all, or worsening of symtoms). PGIC is previously validated among patients with FM and represents a clinically relevant tool for assessing disease management (Rampakakis et al., 2015).

There are several possible ways one could classify patients as responders or non-responders. Yet, when analyzing all different treatment outcomes (FIQ, Pain drawing and pain measures) in relation to PGIC, the patients who were classified as responders (according to PGIC) were significantly improved in almost all outcomes in contrast to the non-responders who were not improved in any outcome, thus validating the use of PGIC to classify responders.

4.3.4 Expectancy measures

In Study I the participants answered the expectancy question "Based on what you just felt, to what extent do you think this machine may reduce this type of heat-pain on a scale between 0-100, where 0=no pain relief and 100=complete pain relief", as an explicit account of the effectiveness of the machine. This question was added because we were interested in participants' belief in the sham device and how this may affect the placebo analgesic response.

4.4 PILOT STUDY

One important aspect of understanding nocebo mechanisms is the possibility to control negative side effects in clinical practice (Enck et al., 2013). However, experimental paradigms to investigate nocebo mechanisms are less well established. Therefore, we designed and piloted a nocebo study which was intended as Study I in the present thesis. We hypothesized that the inclusion of general negative expectations with SST would be associated with an increased nocebo response. During the process of including the first 13 participants in the nocebo pilot experiment, no nocebo responses were observed. This means that the participants did not receive more pain from the "pain intensifying electrode". One reason for the lack of a general nocebo response could be that the experimenter (the author of this thesis) is an educated

physiotherapist with long experience of patient-clinician interactions, and thereby is trained to decrease pain and create a positive treatment environment. To be an effective nocebo experimenter one may need to provide a less supporting environment. Therefore, the lack of nocebo responses could have been affected by the inability to create a non-supporting context. Because of this challenge and possible confounder, we decided to change setting to a placebo design with priming related to positive expectations. After inclusion of two participants in the new design we noted an adequate placebo response and therefore adjusted the protocol for a placebo design in the final experiment (Figure 4).

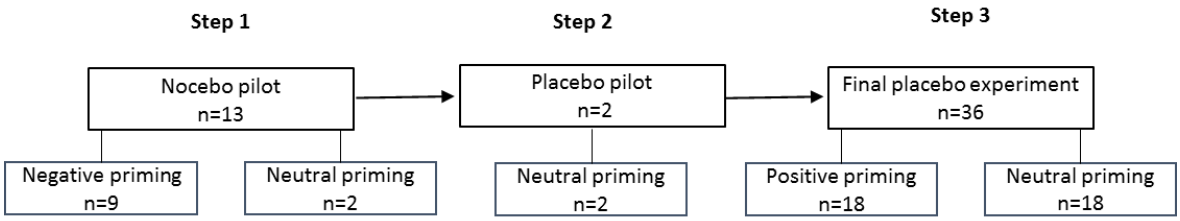


Figure 4. *Schematic picture of the steps towards the final placebo design including the number (n) of participants.*

4.5 META-ANALYSIS

In Study III, a meta-analysis was performed as the method to present a combined result for placebo effects in RCTs and open-label trials in patients with genetically determined ID. Explained in general terms, a meta-analysis averages the results of effect sizes from many studies (both negative and positive results) on a single topic. In Study III, treatment response were defined as the difference in outcome measures from pre to post treatment within each treatment arm of an RCT. Data management, and calculation of effect sizes, i.e. bias-corrected standardized mean differences (Hedges' *g*), were performed using the Comprehensive Meta-Analysis software version 3.0 (www.meta-analysis.com). Since considerable heterogeneity was expected, all analyses were performed with random-effects rather than a fixed-effects model and effect sizes were reported as Hedges' *g*, which is a variation of Cohen's d that corrects for biases due to small sample sizes (Cooper, Hedges, & Valentine, 2009).

5 SUMMARIES OF STUDIES I-III

5.1 STUDY I, BRIEF DESCRIPTION OF DESIGN AND RESULTS

In this study, a double-blind randomized experimental design was used to test if implicit priming with SST could alter placebo analgesic responses. The intervention was a one-visit type of study conducted in a hospital environment, where the randomization and experiment were performed on the same day, with no follow-up. Participants (n=36) were first included, and then randomized to either a neutral (n=18) or positive (n=18) priming condition. Both the participants and the experimenter were blind as to the priming content (positive/neutral).

The results showed that a sham analgesic device could successfully induce placebo effects, were the participants' pain ratings were significantly lower when the sham analgesic device was turned "on" compared to "off". However, there was no difference in placebo effects between participants receiving the positive or neutral priming procedure. Interestingly, women were more inclined to report high explicit expectancy of analgesia (by answering the question: to what extent do you think this machine may reduce this type of heat-pain on a scale between 0-100?) compared to men, in spite of similar reports of reduced pain when the effectiveness of the machine was tested. Furthermore, there was a positive correlation between explicit expectancy of the efficacy of the device and placebo outcome among women, but not among men.

Overall, the study showed positive correlations between participants' prior experience of pain relief (induced before priming) and placebo analgesia. There was also a correlation between high trait neuroticism and greater placebo analgesia. In the present study, participants reported feeling very safe and confident in the treating experimenter, indicating that the interaction with a trustworthy clinician may have overridden a possible effect of priming on placebo analgesia.

5.2 STUDY II, BRIEF DESCRIPTION OF DESIGN AND RESULTS

The aim of this study was to investigate the placebo responses in FM patients in relation to time since onset of widespread pain. We hypothesized that patients with long exposure to FM pain would have lower placebo responses. Patients took part in a 12-week pharmacological multi-center study, using a double-blind randomized placebo controlled design. The placebo arm (n=37) of this trial was analyzed by dividing patients into placebo responders (n=15) or non-responders (n=22), based on patients' subjective report of clinical improvement. Pain measurements and most questionnaires (see method section) were performed at baseline (before randomization) and at study end (after 12 weeks).

At baseline, placebo responders had lower ratings of depression and less catastrophizing thoughts compared to non-responders. Still, this difference did not affect the primary outcome of the study. Placebo responders improved in almost all outcomes (FIQ, average weekly pain (VAS), pain drawing). Conversely, placebo non-responders did not improve in any outcome.

Across groups (responders and non-responders) there was no overall correlation between FM duration and the primary outcome measure; defined as the mean change in pressure pain sensitivity (P50) from baseline to after intervention. However, there was a correlation between FM duration and mean change in P50 among placebo responders, indicating that shorter FM duration was related to larger placebo-induced reduction in pressure pain sensitivity. This correlation was not found among placebo non-responders.

There was an overall relationship between FM duration and pain variability (difference between maximum-minimum weekly pain), indicating that a longer duration of pain leads to a more constant weekly pain. When performing separate correlations for placebo responders and non-responders, the negative correlation between FM duration and pain variability was seen among non-responders, but not among placebo responders.

5.3 STUDY III, BRIEF DESCRIPTION OF DESIGN AND RESULTS

Study III was a meta-analysis of pharmacological clinical trials, assessing the role of treatment expectations and placebo responses in patients with ID. To address this, the study compared the drug responses in open-label trials versus placebo-controlled trials, as they represent 50% versus 100% certainty of receiving the genuine drug (low versus high expectations).

The different drug categories were matched between open-label and placebo-controlled studies for a comparable meta-analysis. In the final statistical comparison 24 studies were used (12 open-label, 12 placebo-controlled). The treatment response was defined as the difference in outcome measures from pre to post treatment within each treatment arm.

The matched results showed higher effect sizes (better treatment outcome of the drug) in studies with 100% likelihood of getting the genuine drug (open label) compared to the drug arm (and the placebo arm) in placebo-controlled studies. There was no correlation between the effect sizes and the duration of the different clinical trials, indicating that long and short trials had comparable treatment results.

6 GENERAL DISCUSSION

All three studies in this thesis investigate aspects of non-specific treatment components on treatment outcomes. The main findings point to the important role of expectations as a mediating factor for positive treatment outcomes of placebo processes, both in healthy individuals and in clinical populations. The results point to the significance of non-specific treatment effects in patients with chronic conditions, such as FM and ID. Hence his thesis highlights the importance of the psychosocial context in obtaining placebo effects, both for individuals with and without cognitive deficits. The subsequent sections present an extended discussion on the reported findings in this thesis, aiming to integrate the present findings with already existing knowledge, but also to discuss limitations and suggest some future research.

6.1 LACK OF PRIMING EFFECT ON PLACEBO ANALGESIA

One theme of this thesis was to investigate if placebo effects are possible to display without higher order cognition. In Study I we investigated this issue by using implicit priming of positive expectations, a method where explicit memory functions are not involved (Tulving & Schacter, 1990). The results from Study I showed that a sham analgesic device could successfully induce placebo effects, however there was no difference between the positive and neutral priming in placebo analgesia. Contrary to our study, previous studies of negative priming and pain sensitivity have demonstrated effects on reduced pain tolerance (Meerman et al., 2011) and increased pain sensitivity (Richter et al., 2014). However, these studies included words with negative valence, such as health complaints or suggestions of increased pain, enabling a direct link to pain reduction via suggestions about pain. As we wished to assess implicit effects of priming on placebo analgesia, instead of direct suggestions, our study used words associated with positive expectations instead of words suggesting pain reductions.

One methodological strength of Study I is the double-blind design (patients and clinicians). However, this may be one explanation for not receiving an effect, as other priming studies have not been double-blind (Bargh et al., 1996). In a previous priming study, Doyen et al. (Doyen et al., 2012) found that priming of walking speed had opposite effects on participants depending on the information given to the priming experimenter. Applied on our study, this means that if the experimenter had known which priming group the participants belonged to the experimenters may unintentionally have influenced placebo outcomes. The present results thus question the validity of the results obtained from non double-blind priming studies.

6.2 PATIENT CLINICIAN INTERACTIONS

In Study I, participants reported very high confidence and trust in the treating experimenter, indicating that the placebo experiment was performed in a "positive" context. It is possible that this interaction may have overridden any subtle effects of the semantic priming. A recent meta-analysis suggests that the patient-clinician relationship is a key component for successful treatment, across several medical disciplines and treatment modalities (Kelley et al., 2014). Moreover, studies indicate improved treatment effects in response to positive communication including, for example, warm, empathic, trustful and engaged interactions (Blasi et al., 2001; Kaptchuk et al., 2008; Kelley et al., 2014; Suarez-Almazor et al., 2010). Furthermore, in a study of antidepressant treatment by McKay and co-workers (McKay, Imel, & Wampold, 2006), results demonstrated that the individual psychiatrists contributed to larger variance in treatment outcomes than the difference between drug and placebo. These results propose that one or more uncontrolled therapist factors may better predict of treatment outcomes, than the specific features of the intervention.

The psychosocial interactions described above could be labeled as "direct", where patients and therapists exchange information in an explicit manner, both orally and via written text. However, in Study III, it is likely that the patient-clinician interaction had more of an implicit effect, where subtle social cues may influence placebo responses indirectly via "placebo by proxy". A placebo by proxy effect occurs when a patient's treatment outcome is affected by the behavior and expectations by other people (e.g. therapists, relatives, friends) interacting with the patient during treatment (Grelotti & Kaptchuk, 2011). This phenomena is well known in studies relating to young children, and there is evidence that parents expectancies and behavior affect treatment outcomes in a way that cannot be explained by the child's knowledge or expectations of treatment outcomes (i.e. direct placebo effect) (Whalley & Hyland, 2013). The results in Study III showed that greater certainty (i.e. greater treatment expectations) of genuine treatment increased drug responses among patients with ID. As patients with ID have severe cognitive deficits, as for example the ability to create expectation and learning by prior experiences, their ability to receive placebo responses should be considered low. We therefore suggest that the enhanced drug responses found in Study III may be described as an "expectancy by proxy" effect of clinical outcomes, reflecting the 100% certainty of getting the real drug through the expectations of surrounding parents, caretakers and clinicians. These results challenge the existing theories about placebo effects (Wager & Atlas, 2015), implying a need for higher order cognitive functions in order to receive a placebo response.

6.3 PLACEBO RESPONDERS

Since the first known study investigating the personality traits of a placebo responder (Lasagna et al., 1954), the ability to predict who will be a placebo responder has continued to be of great interest to researchers. In spite of the large interest, there has been no conclusive evidence for the existence of a typical placebo responder (Horing, Weimer, Muth, & Enck, 2014). However, some studies have linked psychological traits such as dispositional optimism (Geers, Wellman, Fowler, Helfer, & France, 2010), empathy (Hunter, Siess, & Colloca, 2014) and fear of pain (Lyby, Aslaksen, & Flaten, 2011) to placebo responsiveness. In this thesis we found some individual characteristics that were associated with placebo outcomes. In Study I, high trait neuroticism was associated with greater placebo analgesia. In line with this finding, one of the earliest investigations of predicting a placebo responder profile, comparing responders to non-responders, found that responders were more anxious, self-centered and had more somatic symptoms (Lasagna et al., 1954). The same was found in a study where high neuroticism correlated with high response to placebo injections in patients with discogenic low back pain (Wasan, Kaptchuk, Davar, & Jamison, 2006). Nevertheless, neuroticism has been investigated as a possible predictor of placebo outcomes before without showing any conclusive effects (Kelley et al., 2009; Pecina et al., 2013).

The interaction between personality traits and environmental factors was investigated in a placebo acupuncture study (Kelley et al., 2009) where the patient-clinician relationship was manipulated (emphatic vs. neutral therapist). In this study, the authors found that female gender and personality traits (extraversion, agreeableness and openness to experience) influenced placebo responses. However, this was true only in the treatment group with warm and empathetic patient-clinician interactions (Kelley et al., 2009), and not in the limited condition. In line with this study, it is likely that a more neutral or "unsafe" experimental environment applied to our study (Study I) may have rendered different results, so that high trait neuroticism would not correlate with placebo analgesia. A neurotic personality may be defined as anxious and insecure, and is sometimes referred to as "emotionally unstable". It is possible that a neurotic personality in turn influence the behavior of the therapist, so that he/she acts more calm and confident, in contrast to the interaction with a more "stable" personality where reduction of anxiety is not needed. Hence, a safe environment may be required in order to succeed with a deliberate manipulation of expectations in participants with a high level of emotional instability.

In Study II we found lower ratings of depression and less catastrophizing thought among placebo responders compared to non-responders. One possible explanation for this result is that

patients with less negative affect at baseline may have been more likely to shape positive treatment expectations, and be open to new experiences. Our results correspond with studies by Geers and colleagues, showing association between positive placebo analgesic responses and dispositional optimism (Geers et al., 2010).

Gender differences in placebo outcomes are occasionally reported but the results are inconclusive and often dependent on different interaction effects (Aslaksen, Bystad, Vambheim, & Flaten, 2011; Horing et al., 2014). In Study I, we found no overall difference between female and male participants in placebo analgesia. However, there was a positive correlation between explicit expectancy (reported belief in sham analgesic device) and placebo effects for female but not male participants. When speculating about the reason for this difference, it is possible that male participants showed a tendency to give lower ratings when explicitly asked about the effectiveness of the sham device, compared to the actual pain relief reported during pain testing. Studies have suggested that traditional gender roles influence verbalization of pain (Robinson & Wise, 2003; Sanford, Kersh, Thorn, Rich, & Ward, 2002) and it possible that male participants may have underreported their belief in the effectiveness of the sham device, as a result of psychosocial factors as giving ratings to a person with opposite gender.

Altogether, since the contextual factors of each treatment setting vary greatly, and there is a constant interplay between the patient's personality traits and various external factors, it is likely that one will not be able to characterize a placebo responder that responds to all placebo treatments irrespective of context. Instead of trying to identify who responds best to placebo, the author of this thesis suggest that it might be would be more fruitful to focus on creating a health care setting for maximizing generalized placebo effects irrespective of patients' characteristics.

6.4 THE IMPACT OF FM DURATION ON PLACEBO ANALGESIA

Study II is, to the best of the author´s knowledge, the first study to show that the response to placebo treatment is reduced as a function of FM duration. Placebo analgesia rests on the activation of the pain inhibitory network in the brain and endogenous release of opioids (Wager & Atlas, 2015), and since FM is related to dysfunctional pain modulation (with impaired function of the pain inhibitory network), it could be a challenge for FM patients to activate placebo analgesia. However, there are two comprehensive meta-analyses of placebo responses in FM clinical trials (Hauser, Bartram-Wunn, Bartram, Reinecke, & Tolle, 2011; Hauser, Sarzi-Puttini, Tolle, & Wolfe, 2012), confirming the presence of placebo responses in FM, even if

the results were not analyzed in relation to FM duration. In analogy, Parkinson's patients are defined by deficit in dopamine function, yet, they release endogenous dopamine in response to a placebo when expecting a dose of L-dopa (de la Fuente-Fernandez et al., 2001; Lidstone et al., 2010). Several studies have shown evidence for structural brain changes in response to chronic pain exposure (Apkarian et al., 2004; Kuchinad et al., 2007; Lutz et al., 2008; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009). Moreover, it has been shown that duration with FM (independent from chronological age) has negative effect on brain grey matter volume, including pain inhibitory regions (Jensen et al., 2013), indicating that time would possible be a key variable when assessing FM treatment mechanisms.

Several studies have shown that ratings of expectations and emotional state may significantly contribute to placebo analgesia (Petersen et al., 2014; Wager & Atlas, 2015; Vase et al., 2003). Hence, the decreased placebo response over time may be partially be explained by factors as positive expectations, motivation and hope, as these factors are likely to change over time with FM. In the case of FM, there are still reports of doubt and inadequate recognition of FM as a true medical condition, which may have a negative effect on patients' hope and motivation if exposed to such attitudes within the health care system over time. Moreover, it may take time for FM patients to receive a diagnosis and proper treatment (McCarberg, 2012), and during this time the hope to find adequate relief may diminish. In line with this, a study by Vase and colleagues pointed to the importance of time for placebo analgesia in relation to expectancy and emotions (Wager & Atlas, 2015; Vase, Robinson, Verne, & Price, 2005). They found that placebo analgesia increases over time in patients with irritable bowel syndrome, if it corresponds to increased expectations of pain relief and decreased negative emotions. This result may indicate a sort of opposite effect to the self-reinforcing placebo effect, where patients' positive treatment history may be a potential reinforcement for placebo responses. This was validated in an experimental treatment model where a positive and negative treatment history was created two days prior to the placebo experiment (Kessner, Wiech, Forkmann, Ploner, & Bingel, 2013). Altogether, there may be two interacting mechanisms for explaining the association between time with FM and decreased placebo effects; firstly a path involving disease related neurobiological mechanisms (e.g. impaired function of the pain inhibitory system) and secondly a path involving mechanisms best described in psychological terms (e.g. lowered expectations, hope, and motivation).

6.5 CLINICAL RELEVANCE OF PLACEBO RESPONSE

There is little knowledge about placebo effects in chronic pain conditions (Peerdeman et al., 2016; Petersen et al., 2014). Most placebo pain studies stems from experimental pain settings in samples of healthy participants. A common placebo setting is to give a painful stimulation with, for example, heat pain, pressure pain or electrical pain combined with a placebo manipulation (e.g. sugar pill, placebo cream, sham acupuncture). Yet, it is problematic to compare experimental short-term pain with a chronic pain situation. Primarily because the chronic pain patient is likely to have a different mindset, shaped by the patient's treatment experiences, in combination with differences in pain regulation due to specific disease mechanisms. An outstanding question is how knowledge about placebo effects among patients with chronic disease can be transferred to the clinic. The significant question about placebos to be answered is "is this a meaningful effect for the patient?"

In Study I we found a mean placebo pain reduction of 9 points, measured with a verbal NRS ranging from 0 to 100. However, as this placebo outcome represents results from healthy participants in an experimental pain study, it may be difficult to transfer the result to a clinically relevant environment. In Study II, the patients in the placebo group had lowered their average weekly pain levels from 68 mm VAS before the intervention to 40 mm VAS after the 12 week intervention period (mean change 18 mm VAS). There are different suggestions for determining clinically important differences in pain levels based on VAS ratings; ranging from 10-30 mm (Gallagher, Liebman, & Bijur, 2001; Lee, Hobden, Stiell, & Wells, 2003). In agreement with these suggestions, the reduction in weekly pain is considered to be clinically meaningful. Interestingly, the patients lowered their average weekly pain to 40 mm VAS which was the inclusion criteria cut-off for entering the study. In addition, the placebo responders in Study II received a reduction of 30% in FIQ total score from before to after the intervention, and the minimal clinically important difference for FIQ is proposed to be a 14% change in the FIQ total score (R. M. Bennett, Bushmakin, Cappelleri, Zlateva, & Sadosky, 2009). Altogether, it seems likely that patients in Study II, received a not only statistical difference in placebo outcomes but also a clinically relevant placebo response.

In Study III, the effect sizes in open label and RCTs were analyzed from pre to post treatment. The combined effect size in the open label group was g=0.776 and g=0.390 in the RCT drug group, giving a mean difference between groups of g=0.386. The magnitude of Hedges' g may be interpreted as small (0.2), medium (0.5), and large (0.8) (H. M. Cooper et al., 2009), indicating a small to medium effect size of being 100% certain to receive the drug (open label) compared to 50% certain to receive the drug (drug group in RCT). However, these categories

are to be handled as rules of thumb (Kraemer & Kupfer, 2006) and should be interpreted with caution as different magnitudes of change may be of varying importance depending on the contexts (e.g. severity of disease) (Kraemer & Kupfer, 2006). Consequently, any definite conclusions about clinical significance can not be drawn, based on the observed effect size in the present study.

7 STUDY LIMITATIONS

7.1 EXPECTANCY MEASURES

Treatment expectancy is of particular interest in this thesis, but could not always be directly measured.

In Study II no expectancy measures were collected as the study wasn't initially designed to investigate the impact of expectations or the placebo group per se. Two clinically relevant questions could have been answered if we had included a measure of patients' baseline treatment expectations: 1) Are baseline treatment expectations affected by duration with chronic pain? And 2) Are placebo responses affected by baseline treatment expectations? Moreover, measuring the clinicians' own treatment expectations, and beliefs about which treatment group patients' were allocated to, may have captured the impact of clinicians' expectations on placebo responses.

In line with the possible influence of the clinicians' beliefs about placebo outcomes in Study II, it could also have been interesting to measure the experimenters guesses of priming allocation (positive or neutral) in Study I. If the guesses of the experimenter had been collected and correlated to placebo outcomes, this could have revealed a potential influence of the experimenter's expectations on the participant.

In study III, data regarding treatment expectations was not reported in the articles. Instead, treatment expectations were described as the difference in certainty of receiving the real drug in placebo-controlled trials and open-label trials, as they represent 50% versus 100% certainty of receiving an active drug. However, this expectancy measure is an estimation that does not reflect the true individual expectancy of patients and care takers.

7.2 BLINDING

Another limitation that may have affected placebo outcomes is the varying ability to blind patients as to which treatment they received. Proper blinding to treatment allocation is widely

accepted as an important methodological feature to protect the internal validity of RCTs (Kolahi, Bang, & Park, 2009; Moher et al., 2012). Study II had a double blind design and included an oral placebo pill, which is considered standard to achieve a robust blinded design. Nevertheless, the study did not include any reports of the success of blinding. The patients' perception of treatment allocation may have affected the treatment outcomes. Therefore, we could have asked the patients to guess their treatment assignment and also the degree of certainty, as a way to control the impact of expectations on placebo outcomes (Bang, Ni, & Davis, 2004). In Study III we did not have any information about the blinding success for the included placebo-controlled trials, even if this may have implicitly affected the treatment outcomes through parents', teachers' or caregivers' beliefs about treatment allocation.

7.3 NATURAL HISTORY

One limitation of Study II is the lack of a natural history control group. This group is needed in order to distinguish a "true" placebo effect from changes due to general factors such spontaneous remission and regression towards the mean (Kirsch, 2013). Thus, a natural history control group is used to investigate the change in symptoms (i.e. pain intensity) that occurs even without any treatment. However, as FM is a chronic condition and long-term follow ups of FM patients indicate small chances of recovery (Bengtsson, Bäckman, Lindblom, & Skogh, 1994; Fors, Landmark, & Bakke, 2012), it is possible that there is nothing like spontaneous remission in FM. Still, we can not exclude the effect of regression towards the mean, which is a general statistical phenomenon which can make natural variation in repeated data look like a real change (Kirsch, 2013).

7.4 PRIMING

In Study I our experimental manipulation (positive versus neutral priming) may not have been strong enough to affect placebo analgesia. There are several different priming modalities used in behavioral science. For example in a study by Williams and colleagues (Williams & Bargh, 2008), the authors found that embodied priming, by holding a hot or cold beverage before an interview, could modify the perception of the interviewer to include more warm or cold descriptions of that person's personality. If we had used a different type of priming, other than semantic priming, it may have had a stronger effect on placebo analgesia (e.g. priming with pictures, embodied stimuli).

7.5 SAMPLE SIZE

One limitation of Study II is the small sample size. Study II used the placebo data from a previously performed RCT, designed to investigate the effects of milnacipran on FM pain. Therefore, a power calculation was initially made for finding differences between milnacipran and placebo, and the study was thus not optimized to find differences within the placebo group. Therefore, the results should be interpreted with caution and there is a need to replicate the findings of a connection between the duration of FM and placebo responses. Even though this is a shortcoming, this is an explorative study indicating the importance of taking duration of a chronic disorder into considerations in clinical studies.

The small sample size also restricts the type of statistical analyses that can be performed. In a larger study, multiple regression analyses could have provided more information about the contribution of several different factors to placebo responses. In Study I regression analyses were performed in spite of a relatively small number of participants, yet, the regressions included only one predictor (and adjustment for baseline pain) which required less demands on the number of subjects.

8 CONCLUSIONS

Priming is one of many potential ways to influence behavior, yet, this thesis suggests that placebo analgesia is predominantly influenced by prior experience of pain relief and the interaction with a trustworthy clinician. Study I could not confirm a connection between priming with SST and placebo analgesia. However, it is possible that treatment outcomes in the clinic are affected by different types of non-conscious cognitive processes, based on earlier studies demonstrating that treatment outcomes can be triggered by non-conscious cues (Jensen et al., 2014; Jensen et al., 2012).

This thesis suggests that placebo responses are progressively smaller in FM patients with the longer duration they have suffered from chonic pain. This points towards the importance of early FM diagnosis and treatment interventions to increase benefits from the non-specific treatment components that constitute one part of health care administration. In addition, this thesis suggests that the duration with chronic pain should be taken into consideration when interpreting results from FM clinical trials, and possibly for other chronic pain conditions too.

Finally, this thesis shows that patients with ID are influenced by the certainty of receiving the genuine medication in clinical trials. This result provides evidence that patients with ID are

influenced by contextual factors associated with genuine placebo effects, despite cognitive deficits.

9 FUTURE RESEARCH

There is little knowledge about the impact of chronic disease duration in both genuine and placebo treatment outcomes. Therefore, it would be clinically relevant to further investigate this issue with the aim to increase treatment response and improve the wellbeing of patients. To capture the complexity of physiological and psychological changes over time, research should include both quantitative and qualitative approaches. One example could be to interview patients with chronic disease to explore their experiences of treatment expectations, motivation and hope and how these may have changed over time.

In addition, it would be of great interest to focus on the possible contribution of the individual clinicians on treatment outcomes. Rather than controlling for the effect of clinicians in clinical RCTs, it would be interesting to investigate the impact of clinician per se either with or without manipulation of the clinicians' behavior. This approach would likely be clinically relevant and may give an opportunity to define clinician characteristics that may predict a positive treatment outcome. As each patient is an individual with her own characteristics and needs, it is the responsibility of health care to meet all different individuals in the best possible way. Health care can hardly shape their clients, but rather do its best to optimize the quality of the delivery of care and approach for each individual patient. One way of doing this is to employ knowledge gained from the scientific investigation of non-specific treatment factors. The present thesis is an attempt to increase such knowledge with the aim to develop principles of care that maximizes non-specific treatment responses for the good of the individual across different ailments and sufferings.

10 SVENSK POPULÄRVETENSKAPLIG SAMMANFATTNING

Man kan säga att varje behandlingstillfälle i sjukvården består av två delar som kan ha effekt på patientens tillfrisknande. Den första delen är den specifika behandlingen, som exempelvis en smärtlindrande medicin. Den andra delen är den ospecifika behandlingseffekten, som utgörs framför allt av kommunikationen med behandlaren, där kunskap om den aktuella behandlingen samt förväntningar, hopp och motivation skapas. Den förbättring som sker på grund av positiva förväntningar om ett behandlingsutfall kallas för en placeboeffekt. Placeboeffekten är således ett skeende där våra tankar och tidigare erfarenheter påverkar kroppens funktioner. Detta sker genom ett intimt samspel mellan de biologiska processer som utgör våra tankar och de som reglerar kroppsliga symptom.

Syftet med den här avhandlingen var att undersöka två saker: Om tiden med kronisk smärta påverkar placeboeffekter och om begränsade kognitiva förutsättningar påverkar placebo, bland annat genom att undersöka ifall individer med nedsatt förmåga till minne och inlärning (kognitiva funktioner) kan få placeboeffekter.

I första studien undersöktes ifall omedvetna förväntningar som framkallats genom priming kan påverka placebosmärtlindring. Priming kan beskrivas som en effekt där något vi ser, läser eller hör omedvetet kan väcka associationer som påverkar våra senare beteenden. I ett experiment slumpade vi individer till att utföra två olika typer av priming (utformat som ett språktest), ett som relaterade till positiva förväntningar (saker kommer bli bättre) och ett som relaterade till neutrala förväntningar. Efter primingen utfördes ett smärt-test där en helt inaktiv smärtlindrande ”placeboapparat” användes. Resultatet visade att deltagarna fick bra smärtlindring av ”placeboapparaten”, men det blev ingen skillnad om man tidigare hade blivit primad med positiva eller neutrala förväntningar.

I den andra studien undersöktes om tiden (månader, år) med kronisk smärta vid fibromyalgi påverkar placebosmärtlindring. Patienter som ingått i en läkemedelsstudie och där behandlats med sockerpiller (placebo) analyserades i denna studie. Efter behandlingen såg vi att längre tid med kronisk smärta gav mindre placebosmärtlindring.

I den tredje studien undersöktes ifall förväntningar på en behandling kan påverka behandlingsutfall hos patienter med genetiskt orsakad intellektuell funktionsnedsättning. Eftersom man trott att placeboeffekten är beroende av att man kan lära sig av erfarenheter och skapa förväntningar om framtiden, har det hållits för troligt att patienter med intellektuell

funktionsnedsättning inte kan erhålla placeboeffekter. Denna studie visar dock att studier med högre behandlingsförväntningar ledde till bättre behandlingsutfall än studier med lägre behandlingsförväntningar hos patienter med intellektuell funktionsnedsättning. Detta innebär att patienter med intellektuell funktionsnedsättning kan erhålla placeboeffekter. Vi tror att dessa placeboeffekter kan bero på att förväntningarna från omgivningen, såsom familj och behandlare, påverkar patienten.

Sammanfattningsvis visar resultaten i denna avhandling på att placeboeffekter minskar ju längre tid en patient haft sin långvariga smärta. Vidare visar denna avhandling att patienter med intellektuell funktionsnedsättning kan erhålla placeboeffekter, trots nedsatt förmåga till minne och inlärning.

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