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Harnessing placebo effects by targeting expectancies

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Harnessing placebo effects by targeting expectancies

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Acute physical symptoms provide important warnings of injury or illness and are as such highly functional. Usually, these symptoms quickly disappear, but a substantial proportion persists [172]. Particularly chronic pain, a symptom of numerous medical conditions including rheumatoid arthritis, migraine, and irritable bowel syndrome, is common [215]. Chronic itch and fatigue are other examples of symptoms that occur in several conditions (e.g., skin diseases and chronic fatigue syndrome, respectively) with a high prevalence [199,315]. Experiencing physical symptoms, especially when they are chronic, can have a major negative impact on an individual's daily functioning and quality of life, and is associated with high societal costs (including medical expenses and lost productivity) [41,199,304,315]. Despite great effort over time, the etiology, course, and treatment of physical symptoms remain insufficiently understood. Consequently, patients frequently do not experience adequate relief through medical care [41]. Important factors that can influence treatment outcomes are non-specific or context factors, such as doctor-patient interactions and patients' expectations about the treatment [24,75]. These factors are generally understood to shape placebo effects [24]. As such, the study of placebo effects offers the possibility to investigate their influence on the outcomes of treatment for physical symptoms.

Placebo and placebo-like effects

Placebo effects are the improvements following the administration of a placebo (i.e., an inert treatment such as a sugar pill or a saline injection) that are typically ascribed to a person's expectations about the effects of the placebo [24,57,59]. The potency of placebo effects is convincingly demonstrated in a rapidly growing body of research [24,298]. Pain is by far the most studied outcome in placebo research, and placebo analgesia can be seen as a prototype of placebo effects. Repeatedly, people have been found to report less pain after receiving a placebo that they have been led to believe is a potent painkiller [298,299]. Most evidence for placebo effects stems from experimental research in which the effects of placebos on experimentally evoked pain (e.g., using a cold pressor test or electrical stimulation) are assessed in samples of healthy participants [298,299]. Research in clinical populations is more limited, but does suggest that also patients who experience acute or chronic clinical pain (e.g., surgery pain or chronic low back pain) can benefit from placebos [52,112].

Placebo-like effects are related effects that take place when no placebo is given and that can be ascribed to expectancies [24]. They occur whenever patients receive an active treatment and can also occur when, for example, expectancies of health

improvement are induced merely by suggestion. The most striking examples of placebo-like effects stem from comparisons of administering a treatment in full view of a patient by a clinician versus treatment administration outside of the patient's awareness (e.g., infusion of drug regulated via a machine). Studies using this open-hidden design demonstrate that the analgesic effects of active treatments such as morphine are significantly reduced when a patient is not aware of its administration [5,15,30,226,259]. Furthermore, the effects of analgesics and other active treatments can be enhanced by providing positive, rather than neutral, suggestions about their effectiveness [11,148].

Even though the vast majority of research into placebo and placebo-like effects has focused on pain, these effects are understood to be universal [24]. Research into other physical symptoms is more limited, but does show that, among others, Parkinson symptoms like tremor [182], gastrointestinal symptoms like nausea [281], and symptoms like itch and fatigue are also susceptible to placebo and placebo-like effects [47,79,83]. To enhance our understanding of the underlying mechanisms of placebo and placebo-like effects on physical symptoms, and to facilitate harnessing placebo and placebo-like effects in clinical practice, further research into both pain and other symptoms is essential.

Expectancies, the core mechanism of placebo and placebo-like effects

The putative core psychological mechanism of placebo and placebo-like effects is expectancy [24,135,158,159]. Expectancies entail cognitions about future experiences, events, and behavior. Expectancies have been found to be important predictors of treatment outcomes such as pain relief in numerous prospective studies [114,206,210]. One of the most influential theories in placebo research, response expectancy theory, moreover postulates that expectations of responses to a treatment (e.g., pain relief) can modulate the actual treatment outcomes, regardless of the presence of active treatment ingredients [158,159]. The effects of these response expectancies (i.e., expectations of nonvolitional responses) on physical symptoms may result from, among others, changes in behavior (e.g., due to taking analgesic medication or exercise) [158,159]. Importantly, the basic principle of response expectancy theory states that response expectancies can also have a direct, unmediated, effect on nonvolitional responses like pain [158,159]. That is, the mere expectation of pain relief, e.g., because of receiving a treatment or due to the natural course of the symptom, can cause actual pain relief. As such, response expectancies can act as a self-fulfilling prophecy. Notably,

although expectancies are often considered to be conscious, or at least consciously accessible [158,159], also non-conscious expectancies can affect outcomes [280]. When the mediating role of expectancies in placebo and placebo-like effects was studied, expectations of pain (i.e., response expectancies) were shown to indeed modify placebo analgesic effects, and to predict changes in the intensity and unpleasantness of both experimental and clinical pain [15,52,160,208,237,262]. Montgomery and Kirsch [208], for example, found, in one of the first studies in which expected pain levels were manipulated and measured, that expectancy accounted for 49% of the variance in ratings of post-manipulation evoked pain. Response expectancies can thus shape experiences. This implies that targeting response expectancies might be an effective way of harnessing placebo and placebo-like effects.

In addition to response expectancies, other kinds of expectancies, such as stimulus and self-efficacy expectancies, have been described in the literature [17,38,184,217,244]. For example, someone might expect to undergo a painless procedure (i.e., stimulus expectancy), or someone might have high expectations about his/her ability to tolerate pain (i.e., self-efficacy expectancy). These different kinds of expectancies may influence pain in unique ways. Furthermore, expectancies are incorporated in several multifaceted concepts, including optimism and neuroticism [253,257]. The literature on all these expectancy concepts is diverse and widespread, leaving it unclear how they are related and what their interactive influence is on the experience of pain and other symptoms. A further exploration would enhance theoretical knowledge and facilitate effectively targeting expectancies. Additionally, knowledge on how expectancies are formed, is essential for determining how placebo and placebo-like effects can be maximized in clinical practice.

How expectancies are learned

Expectancies are generally thought to be formed via the main learning processes laid down in the dominant psychological theories of learning: verbal suggestion (i.e., instructional learning), conditioning (i.e., learning from direct, personal experiences), and observation of others (i.e., observational learning) [59,159]. Research on placebo and placebo-like effects has mostly focused on verbal suggestion and conditioning as methods for inducing expectancies. In addition, we propose that imagined experiences may also be able to shape expectancies.

Verbal suggestion

Verbal suggestions in placebo research can be described as instructions regarding the expected or intended outcomes of a placebo or active treatment. These instructions are generally communicated orally (e.g., by a doctor during a consult). An example is "The agent that you have just received is known to powerfully reduce pain in some patients" [235,301]. Similarly brief and more elaborate suggestions about placebos have been found to elicit effects that are comparable in nature, and sometimes in size, to the effects of the active treatment to which they are equated [27,31,47,182,225,262,299]. Verbal suggestions can also directly refer to the experience of sensations itself, without reference to a treatment. Verbal suggestions are by far the most frequently studied method of inducing expectancies and the evidence supporting their role in placebo and placebo-like effects is robust [299].

Conditioning

Classical conditioning induces expectancies that certain stimuli or experiences will be followed by other stimuli or experiences [38,244]. Classical conditioning paradigms typically entail the pairing of a biologically relevant stimulus (unconditioned stimulus; US), which elicits a certain response (unconditioned response; UR), with an originally neutral stimulus (conditioned stimulus; CS). In experimental research on the mechanisms of placebo effects, this could be the pairing of reduced experimental pain stimulation (US), which reduces pain (UR), with taking a placebo pill (CS). Upon repeated pairing, taking the placebo alone can elicit pain relief. Laboratory research supports the importance of this form of associative learning for placebo effects, especially when reinforced by a verbal suggestion about the relation between the placebo (CS) and pain relief (UR) [4,31,60,93,143,160,167,208]. In clinical trials, conditioning processes are illustrated by larger effects when a placebo is provided following an effective treatment, than when it follows an ineffective treatment (e.g., another placebo or an active medication at a sub therapeutic dose) [6,178]. Conditioning effects regularly occur in clinical practice as a consequence of previous experiences with a treatment, for example, headache relief directly upon taking a well-known analgesic, even before the active ingredients can take effect.

Mental imagery

In addition to these learning processes, expectancies may also be formed by mental imagery of an outcome. Imagery entails a mono- or multisensory cognitive representation of an experience or event in the absence of environmental input [116,171]. These representations are crucial for thinking about the past, present, and future [171].

Imagery has received little attention in placebo research, but several other lines of research suggest that imagery of a future or desired outcome or experience may be able to induce placebo-like effects. For example, research has shown that imagining a best possible future self (e.g., visualizing that one's private and work life are optimal) can augment general positive expectancies (i.e., optimism) [202,224] and congruently reduce pain and medical care utilization [119,157]. Furthermore, imagery interventions that include images of pain relief have been found to provide pain relief in both experimental and clinical research [22,74,86,174]. These findings suggest that imagery of future physical health or symptom relief might be able to affect future pain and other physical symptoms via expectancies. However, because mediation by expectancies has generally not been assessed directly, further investigation is warranted.

Comparisons and combinations of expectation inductions

Taken together, verbal suggestion and conditioning, and possibly also mental imagery appear to be effective methods for inducing expectancies and thereby influencing pain and other physical symptoms. The comparative effects are largely unclear. In addition, the combination of expectation inductions, each tapping into different learning processes (e.g., conditioning reinforced by verbal suggestion, or imagery along with verbal suggestion) may be most advantageous [4,20]. Research investigating the possible additive and interactive effects of addressing multiple learning processes is limited however. To harness placebo effects optimally, further study into the comparative and combined effects of different expectation inductions is required.

Physiological mechanisms of placebo and placebo-like effects

Research demonstrating placebo and placebo-like effects on physical symptoms has focused predominantly on subjective experiences, as assessed using self-report scales such as visual analogue and numerical rating scales. A rapidly growing body of research indicates, however, that placebo and placebo-like effects go beyond effects on subjective experiences. Effects on subjective experiences have repeatedly been found to coincide with corresponding physiological responses, including changes in brain processes, and in the autonomic nervous and endocrine systems [14,256].

Research has mostly focused on brain processes associated with placebo and placebo-like effects on pain. This has provided reliable evidence for the involvement of brain areas that are known to be engaged in pain processing and expectancy [14].

Likewise, mental imagery of sensations such as pain largely involves the same neural processes as actually experiencing these sensations [86,201].

Given the role of the autonomic nervous system in experiencing physical symptoms like pain [110,175,186,285], research into autonomic responses during placebo and placebo-like effects is of interest. A reduction of heart rate during placebo analgesia has been observed in both experimental and clinical settings [28,230]. Also mental imagery has been found to engage the autonomic nervous system, as indicated by altered heart rate and skin conductance levels [171]. As the evidence is still limited, further research is required to obtain more robust support for the involvement of the autonomic nervous system in placebo and placebo-like effects to various symptoms.

The endocrine system may also be involved. Particularly the stress hormone cortisol may play a role, given the stressful nature of physical symptoms [63,110]. Evidence is currently lacking however, with several studies finding no evidence that placebo analgesic effects are associated with altered cortisol levels [90,146,261]. In some studies, this might be due to methodological limitations, such as insufficient consideration of the circadian rhythm [163,249], necessitating further research to determine the involvement of cortisol in placebo and placebo-like effects.

Treatment characteristics

To unravel the mechanisms of placebo and placebo-like effects on subjective and physiological responses, research has predominantly focused on the different learning processes of expectancies described above. However, also treatment characteristics like the route of medication administration, brand, price, and color of a pill have been associated with differential placebo effects [36,71,84,308]. Most notably, more invasive routes of medication administration (such as injections) are commonly believed to have enhanced placebo and placebo-like effects [150,177,265] and several studies have confirmed this [18,71,323]. For example, in a meta-analysis of the placebo control conditions of clinical trials for migraine treatment, placebo injections were found to provide better headache relief than placebo pills [71]. Other studies did however not fully support the idea of enhanced placebo analgesic effects for more invasive routes [18,87,192,203,265,294]. Most compellingly, a systematic review of clinical trials that included two or more placebo treatment groups, did not find consistent differences between the effects of more versus less invasive placebo treatments [87]. Thus, the factors underlying differential placebo effects for different routes of medication administration are likely to be more complex than commonly believed. Which additional

factors are at play remains to be explored, but may include other characteristics of the routes of administration, such as side effects and ease of use. Further research into the underlying expectancies may provide a better understanding.

Individual differences

Interindividual variability in placebo and placebo-like effects is commonly observed [135,236]. This suggests that differences in individual characteristics (e.g., personality, demographic, and health characteristics) may moderate the effects [75]. Investigating these individual characteristics may enable the prediction of placebo and placebo-like effects and the tailoring of expectation inductions. Previous research has mostly focused on personality characteristics that pertain to dispositional expectancies, such as optimism (characterized by generalized positive expectancies) and neuroticism (characterized by generalized negative expectancies, and other negative emotions and cognitions). More optimistic people have been found to report a larger reduction in pain after a placebo than more pessimistic people [96,100,209], but this association could not always be replicated for placebo and placebo-like effects on pain and other symptoms [120,136]. Research findings regarding neuroticism, as well as other personality characteristics, are equivocal [67,135,295]. Also research into the moderation of placebo and placebo-like effects by demographic and health characteristics is inconclusive [135,311]. Considering these inconsistent findings, it is still unclear which individual characteristics predict placebo and placebo-like effects.

Aim and outline thesis

Placebo and placebo-like effects are now well established, particularly for pain. Research into the mechanisms of placebo effects has paved the way towards the investigation of expectancies as an important determinant of pain and other physical symptoms. A deeper understanding of placebo and placebo-like effects and the role of expectancies herein is crucial for both researchers and clinicians in order to harness placebo effects and thereby maximize treatment outcomes. Currently, knowledge of the comparative and combined effects of different expectation inductions is still very limited. Also, generalizability of placebo and placebo-like effects from the lab to clinical populations and to symptoms other than pain is yet insufficiently clear.

The main aim of the current thesis is to address ways of harnessing placebo effects for relieving pain and other physical symptoms by targeting expectancies. Most importantly, the individual, comparative, and combined effectiveness of expectation inductions (i.e., verbal suggestion, conditioning, and mental imagery) is studied, whereby we measure the effects on both self-reported and physiological outcomes in both healthy and clinical samples. Furthermore, the role of treatment and individual characteristics in placebo and placebo-like effects on pain and other physical symptoms is investigated.

Chapter 2 provides a brief integrative review of the influence of expectancies on pain. We discuss the central role of expectancies in the dominant psychological learning theories, as well as the literature on the influence of different kinds of expectancies (i.e., response, stimulus, and self-efficacy expectancies) and multifaceted expectancy constructs (e.g., optimism and neuroticism) on the experience of pain.

Chapter 3 investigates the evidence for the effects of expectation interventions on patients' pain relief in a meta-analysis. We investigate three methods of inducing expectancies (i.e., verbal suggestion, conditioning, and mental imagery) that are promising for optimizing the effectiveness of analgesic treatments in samples of patients experiencing experimental or clinical (acute procedural or chronic) pain. We explore several possible moderating factors, including the type of pain and route of medication administration. Also, the effects on expectancies and related outcomes are explored.

Chapter 4 reports on an experiment assessing the individual and combined effects of different expectation inductions and their generic effects on pain, itch, and fatigue as indicators of physical sensitivity. Specifically, we assess the effects of both a verbal suggestion of reduced physical sensitivity due to a placebo pill and mental imagery of a best possible health on experimentally evoked pain, itch, and fatigue, using self-report and physiological measures. Additionally, moderation by several individual characteristics is explored.

Chapter 5 describes two experiments in which the effects of mental imagery of reduced pain (i.e., response imagery), on experimentally evoked pain are studied. Hereby we assess whether mental imagery of a response can induce placebo-like effects on pain, using both self-reported and physiological measures. We also investigate the possible additive effects of a verbal suggestion. Furthermore, mediation by response expectancies, as well as moderation by individual characteristics are explored.

Chapter 6 presents the results of an online survey in a large sample representative of the Dutch population to investigate the influence of treatment characteristics on expectancies. We directly compare expectations about the effectiveness of medication administered via different routes of administration (oral, injection, and topical) for

relieving pain and itch. In addition, expectations about other characteristics of the routes and individual characteristics are explored as possible correlates of expected effectiveness.

Chapter 7 concludes the present thesis by giving a general overview and discussion of the results, while focusing on the main research aims and the implications of the current findings for research and clinical practice.

CHAPTER 2

AN INTEGRATIVE REVIEW OF THE INFLUENCE OF EXPECTANCIES ON PAIN

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Abstract

Expectancies can shape pain experiences. Attention for the influence of expectancies on pain has increased particularly due to research on placebo effects, of which expectancy is believed to be the core mechanism. In the current review, we provide a brief overview of the literature on the influence of expectancies on pain. We first discuss the central role of expectancy in the major psychological learning theories. Based on these theories, different kinds of expectancies can be distinguished. Pain experiences are influenced particularly by response expectancies directly pertaining to the pain experience itself, but can also be affected by self-efficacy expectancies regarding one's ability to cope with pain, and possibly by stimulus expectancies regarding external events. These different kinds of expectancies might interact with each other, and related emotions and cognitions, as reflected by various multifaceted constructs in which expectancies are incorporated. Optimism and pain catastrophizing, in particular, but also hope, trust, worry, and neuroticism have been found to be associated with pain outcomes. We conclude with recommendations for further advancing research on the influence of expectancies on pain and for harnessing expectancy effects in clinical practice.

Introduction

Pain is an unpleasant experience, in which not only sensory input but also psychological factors such as cognitions and emotions are at play. One important cognitive factor that can shape pain experiences is expectancies (i.e., cognitions regarding the probability of future experiences, events, and behavior) [114,206,240]. The influence of expectancies on pain gained scientific interest especially due to research on placebo effects. A sham treatment such as a sugar pill or saline injection may relieve pain due to the mere expectation that a treatment will be helpful (i.e., placebo effect), or worsen pain when harmful treatment effects are expected (i.e., nocebo effect) [24,135,158,159]. Similarly, expectancies about treatment outcomes can enhance or reduce the analgesic effects of active treatments [e.g., 11,148]. Besides expectancies about the effects of treatment on pain, people can hold other kinds of expectancies. For example, someone might have high expectations about his/her ability to tolerate pain, and this might actually result in higher pain tolerance [17,184]. Different expectancies are likely to interact with each other, and with related emotions and cognitions. An understanding of the influence of expectancies on the experience of pain is crucial for both clinicians and researchers who treat or study pain, in order to obtain a comprehensive picture of the factors that determine pain and to optimize analgesic interventions via expectation interventions.

In the current review, we provide a brief overview of the literature on the influence of expectancies on pain. First, we discuss the major psychological learning theories concerning expectancies. Based on these theories, different kinds of expectancies are distinguished, and we evaluate the influence of each of these on pain. Subsequently, we discuss multifaceted constructs (e.g., optimism, trust, and worry) in which expectancies are incorporated, and explore the evidence for their associations with pain. We conclude with recommendations for further research on the influence of expectancies on pain and for harnessing expectancy effects in clinical practice.

Expectancies in psychological learning theories

Expectancies are seen as important determinants of behavior, events, and experiences in many psychological theories of learning. Here we describe the most influential learning theories chronologically to gain an understanding of the conceptualization of expectancies.

One of the oldest and most systematically studied learning phenomena in psychology is conditioning. Classical conditioning is generally described as learning that

results from pairing an initially neutral stimulus or event with a biologically relevant stimulus or event [244]. In operant (or instrumental) conditioning, an association is made between a particular behavior and its consequence (e.g., reward or punishment) [38]. According to most contemporary learning theorists, what is learned from these contingencies is outcome expectancies (although conditioning can also be automatic, i.e., not mediated cognitively) [38,161,217,244,280]. These expectancies indicate the perceived likelihood of a stimulus (e.g., receiving food) as the outcome of another stimulus or event (e.g., flashing of a light; in case of classical conditioning), or as the outcome of a specific behavior (e.g., pulling a lever; in case of operant conditioning) [38,161,217,244]. These outcome expectancies are seen as important determinants of behavior. Since most of the expected outcomes described in conditioning research were external stimuli or events, these expectancies have been more specifically referred to as stimulus expectancies, to distinguish them from expectancies of other kinds of outcomes (specifically response expectancies regarding internal experiences, see below) [158,159]. In relation to pain, stimulus expectancies could for example entail expectations of the timing of a painful event, or of receiving a prescription for an analgesic on consulting a doctor.

Social learning theories were developed to address learning in interpersonal contexts and suggested that learning takes place not only via direct experiences (i.e., conditioning), but also via observation of others (i.e., observational learning), and verbal instructions (i.e., instructional learning) [17,158]. Moreover, these theories postulate that not only outcome expectancies, but also other cognitions influence behavior. In the first major social learning theory, Rotter stated that the crucial determinant of behavior is the expected outcome of that behavior, in concert with the value a person places on that outcome [251]. This theory had a major impact and has been further developed by many researchers. One of the most influential extensions is Bandura's self-efficacy theory [17]. Bandura theorized that behavior is determined not only by expected outcomes, but also by expectancies regarding the ability to perform the behavior, i.e., self-efficacy expectancies. For example, someone with high self-efficacy expectations of tolerating pain might engage in physical activities despite pain (e.g., lifting heavy bags despite lower-back pain).

The theories described above focus mainly on expectancies of external outcomes and behavior [17,38,251], expectancies of automatic, nonvolitional responses – i.e., internal experiences such as emotions, and physical sensations such as pain – were largely overlooked. This was addressed by Kirsch in response expectancy theory [158,159]. The hypothesis underlying response expectancy theory is that the expectation of one's own automatic response to a certain behavior or situation (i.e., response expectancy, a

form of outcome expectancy) not only influences behavior, but also directly influences one's actual nonvolitional response, and is as such directly self-confirming [158,159]. These response expectancies, are thought to be acquired through conditioning, instructional learning, and observational learning [158,159]. An example of response expectancy is a patient's expectation of pain relief upon taking an analgesic.

Based on these learning theories, in line with Kirsch's conceptualization [158,159], we distinguish different kinds of expectancies: 1) outcome expectancies, which can be further subdivided into a) stimulus expectancies, i.e., expectancies regarding external stimuli or events and b) response expectancies, i.e., expectancies regarding internal nonvolitional experiences; and 2) self-efficacy expectancies, i.e., expectancies regarding the ability to perform behavior. Several other, largely overlapping, typologies of expectancies have been proposed in the literature [e.g., 13,284], but since stimulus, response, and self-efficacy expectancies have the strongest theoretical foundation and empirical support, we focus only on these three kinds of expectancies in the current review.

The influence of different kinds of expectancies on pain

The different kinds of expectancies may influence pain in unique ways. Response expectancies probably exert the strongest and most direct influence on pain, since they can directly pertain to pain experiences. It is these kinds of expectancies that are generally believed to be the core mechanism of placebo and nocebo effects and that are consequently thought to greatly contribute to the efficacy of active treatments [24,135,159]. When placebo or nocebo effects are induced, pain expectations are modified, and these response expectations predict changes in the intensity and unpleasantness of both experimental and clinical pain [15,56,160,221,262]. Stimulus expectancies may exert an indirect influence on pain experiences, e.g., by affecting behavior, but could possibly also influence pain directly. Stimulus expectancies have received little scientific attention in the context of pain. There are indications that induced expectations regarding the timing of a painful event can reduce pain unpleasantness but not pain intensity [234], but further research is needed. Self-efficacy expectancies have received much more scientific interest. They have consistently been found to predict pain coping efforts and pain tolerance [e.g., 145,184]. Furthermore, self-efficacy expectancies have been found to be robust correlates of chronic pain severity [141], and inducing self-efficacy can reduce experienced pain [e.g., 297].

Thus, empirical research supports the independent effects of response, stimulus, and self-efficacy expectancies on pain. These different kinds of expectancies may also interact with each other. For example, when inducing self-efficacy expectancies, response expectancies may also be enhanced [e.g., 297], and effects of outcome expectancies may be mitigated if one has low self-efficacy expectancies, e.g., when one expects that a physical exercise will reduce neck pain, but also expects that one is not able to perform the exercise [e.g., 17]. A schematic overview of the influence of the different kinds of expectancies on pain is depicted in Figure 2.1.

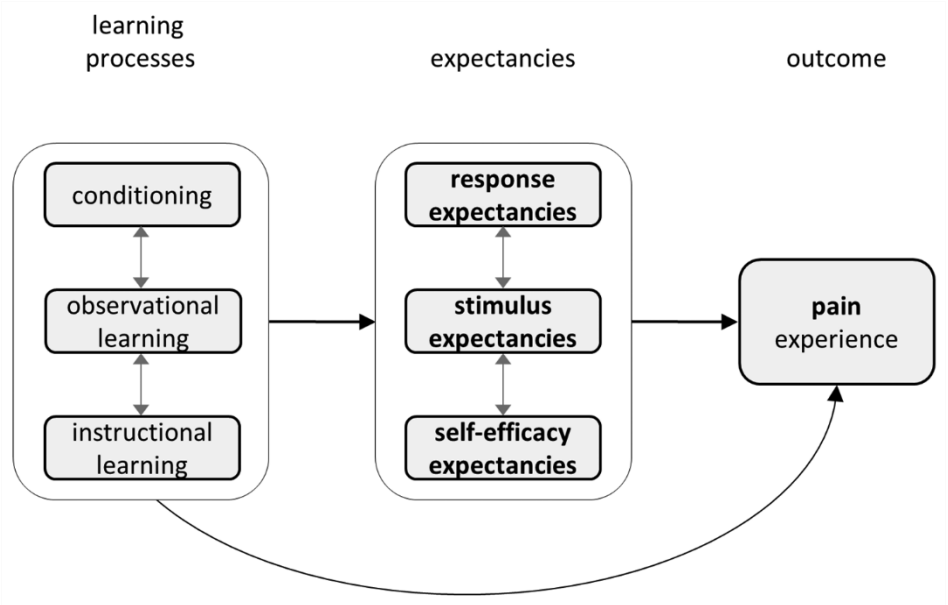

Figure 2.1. Schematic depiction of the influence of expectancies on pain, including the learning processes that influence these expectancies

Note. Probable mediators and/or moderators are behavior, emotions, and cognitions. All elements in the model may also feed back to preceding elements.

Multifaceted expectancy constructs and their influence on pain

The co-occurrence of different kinds of expectancies with related emotions and cognitions is captured in multifaceted constructs, in which expectancies are

incorporated. Here we provide an overview of the most common multifaceted expectancy constructs and their associations with pain.

Optimism and hope are perhaps the most commonly considered multifaceted expectancy constructs. Optimism entails generalized positive expectancies of both stimulus and response type outcomes and is generally seen as a dispositional characteristic, although it can also vary depending on specific situations [257]. High levels of optimism are reliably associated with better health, including less severe acute and chronic pain [106,240]. The experimental induction of optimism can reduce pain sensitivity and pain interference [40,119]. Furthermore, optimism has been found to be associated with larger placebo analgesic effects [96,100,209] [but see e.g., 120]. Hope is a related concept that is described as goal-directed thinking based on constructs that resemble outcome and self-efficacy expectancies (i.e., agency and pathway thinking, respectively) as well as motivational constructs [275]. Hope can pertain to specific situations or goals, but people also vary in their general tendency to be hopeful [273]. Several studies indicate that more hope is associated with using more pain-coping strategies, with higher pain tolerance, and with lower pain intensity [242,273,274]. In addition, a hope-based intervention has been found to increase pain tolerance, though it did not affect pain intensity or pain threshold [32].

At an interpersonal level, trust is a multifaceted expectancy construct that is especially relevant in a medical context in which one has to entrust care of one's health to another person [118]. In the majority of definitions of trust, trusting is seen as entailing expectations that someone, e.g., the physician, will act in a benevolent manner, and that one can rely on this person and his/her intentions [118,218,252]. Trust takes on an emotional quality that extends beyond mere estimations of the likelihood of another person's behaviors [118]. Trust has been found to be associated with health behaviors such as adherence to treatment recommendations [118]. In addition, trust in the physician has been associated with higher tolerance for treatment-induced pain [50].

Other constructs in which expectancies play a role and that can affect pain are constructs related to negative expectancies and the related emotions of fear and anxiety, such as worrying, pain catastrophizing, and neuroticism. Worrying is a repetitive thinking style that concerns a negative future [39]. A person's expectation that the event worried about will happen appears to be an important component of worrying [46,194]. Furthermore, worrying has been suggested to heighten vigilance to threat, such as pain [3,39]. Worrying about pain and worry intensity have been associated with higher pain levels and more frequent pain complaints, respectively [69,306]. One interventional study, for example, found that a worry postponement intervention reduced somatic health complaints, including pain [42]. The related construct of pain catastrophizing has

frequently been a focus in pain research. Individuals who catastrophize often have negative response expectancies (e.g., that the pain may not go away), feel helpless about controlling their pain (i.e., low self-efficacy expectancies), are anxious, and worry and/or ruminate about their pain [238,282]. Pain catastrophizing is thus a comprehensive construct that involves different kinds of negative expectancies and related cognitions and emotions. Pain catastrophizing has consistently been linked to higher acute and chronic pain intensity, pain-related disability, and distress [e.g., 238,314]. The manipulation of pain catastrophizing has been found to affect experimental and chronic pain (both intensity and unpleasantness), though the findings are not fully consistent [164,267,283]. A last related construct is neuroticism. People high on neuroticism tend to be preoccupied with things that might go wrong (i.e., they tend to have negative expectancies, particularly negative outcome expectancies), to be easily frightened, and to feel despondent [253]. Higher levels of neuroticism have been found to predict pain [302,317]. Neuroticism has also been associated with placebo responses, but the results are equivocal [67,220,295].

Implications of current findings

In the current review we set out to provide a brief overview of the literature on the influence of expectancies on pain. We found that different kinds of expectancies can be distinguished, which illustrates the complexity of the construct of expectancy. Nonetheless, it is clear that expectancies have an important influence on pain. Pain is influenced particularly by response expectancies that directly pertain to the pain experience itself. In addition, pain can be affected by self-efficacy expectancies regarding one's ability to cope with pain and possibly also by stimulus expectancies regarding external events. The co-occurrence of various expectancies, and related emotions and cognitions is captured by multifaceted constructs in which expectancies are incorporated. Optimism and pain catastrophizing, in particular, but also hope, trust, worry, and neuroticism have been found to be associated with pain.

To truly grasp the influence of expectancies on pain and to harness these effects, we recommend to refine existing theoretical models of expectancies by also addressing the interplay between different kinds of expectancies. Studies testing the predictions following from these models, should then assess multiple kinds of expectancies and expectancy constructs to determine their independent and interactive influence on pain. In this research the expectancy constructs of interest should be carefully determined, and clearly operationalized and reported. Since no single study can assess

all kinds of expectancies, meta-analytic research can ultimately be used to make overarching inferences about the relative, and possible additive and interactive effects of the various kinds of expectancies on pain.

When addressing the effects of expectancies on pain in research and clinical practice, several additional considerations are of importance. First, it is important to take into account the strength and valence of the expectancy, as well as the intensity, nature, and duration of pain [17,158,159,221]. For example, negative expectancies may exert larger effects on pain than positive expectancies [21], and acute pain is more sensitive to expectation interventions than chronic pain [221]. Second, research has generally focused on short-term effects in artificial laboratory situations. Although there are indications that expectancies can have an enduring clinical impact [e.g., 247], further research into long-term effects is required. Third, expectancies are generally hypothesized and observed to have congruent effects on experiences: one experiences what one expects [114,206,221,240]. However, in the case of a large discrepancy between what is expected and what is observed, expectancies may actually have detrimental effects, resulting in disappointment and experiences that contrast rather than mirror prior expectancies [97,271,284,318]. Importantly, if there is a large discrepancy between the expected and the actual outcome, the current experience may have a larger impact on learning (and thus on future expectancies and experiences), than if the actual experiences are in line with what was expected [245]. Thus, physicians should be wary of inducing either overly positive or overly negative expectancies regarding analgesic treatment outcomes in their patients.

Clinical applications of expectation interventions are very promising for optimizing analgesic treatment effects. Several interventions tap into the learning processes that have been described in the learning theories (i.e., conditioning, observational, and instructional learning). Instructional learning via positive verbal suggestions of analgesic treatment outcomes, in particular, has been found to effectively reduce pain in clinical samples [221]. This demonstrates the significance of the information a physician provides when administering an analgesic treatment. A physician can address conditioning processes by assessing previous treatment experiences. If a treatment has previously been experienced as effective, current treatment outcomes could be enhanced by using the same route of treatment administration, while a switch (e.g., from topical to oral administration) may be beneficial if a patient's previous experiences have been negative [131]. Beneficial social learning may be facilitated via, for example, meetings with fellow or former patients or online video tutorials [139]. Furthermore, interventions evoking indirect experiences of pain reduction via mental imagery appear promising for inducing analgesia [219]. Experimental research suggests that the combination of multiple

strategies, tapping into multiple learning processes (e.g., both conditioning and instructional learning), may be most beneficial [e.g., 4,219].

Conclusion

The theoretical and empirical literature indicates that expectancies are an important determinant of pain, and that expectation interventions can effectively reduce pain. Future research requires the simultaneous study of different expectancy constructs in experimental and long-term interventional research, to further enhance our understanding of expectancies and their potential for optimizing analgesic interventions.

CHAPTER 3

RELIEVING PATIENTS' PAIN WITH EXPECTATION INTERVENTIONS: A META-ANALYSIS

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Abstract

Patients' expectations are important predictors of the outcome of analgesic treatments, as demonstrated predominantly in research on placebo effects. Three commonly investigated interventions that have been found to induce expectations (verbal suggestion, conditioning, and mental imagery) entail promising, brief, and easy-to-implement adjunctive procedures for optimizing the effectiveness of analgesic treatments. However, evidence for their efficacy stems mostly from research on experimentally evoked pain in healthy samples, and these findings might not be directly transferable to clinical populations. The current meta-analysis investigated the effects of these expectation inductions on patients' pain relief. Five bibliographic databases were systematically searched for studies that assessed the effects of brief verbal suggestion, conditioning, or imagery interventions on pain in clinical populations, with patients experiencing experimental, acute procedural, or chronic pain, compared with no treatment or control treatment. Of the 15,955 studies retrieved, 30 met the inclusion criteria, of which 27 provided sufficient data for quantitative analyses. Overall a medium-sized effect of the interventions on patients' pain relief was observed (Hedges' g = 0.61, I^2 = 73%), with varying effects of verbal suggestion (k = 18, g = 0.75), conditioning (always paired with verbal suggestion, k = 3, g = 0.65), and imagery (k = 6, g = 0.27). Subset analyses indicated medium to large effects on experimental and acute procedural pain, and small effects on chronic pain. In conclusion, patients' pain can be relieved with expectation interventions; particularly, verbal suggestion for acute procedural pain was found to be effective.

Introduction

Expectations are important predictors of the outcome of analgesic treatments [62,113,206,276]. As posed in response expectancy theory [158,159], expectations of pain relief can directly elicit and/or enhance actual pain relief. The importance of expectations has particularly become clear in research on placebo effects, of which expectancy is believed to be a core mechanism [23,158,159,236]. Placebos, such as sugar pills and saline injections, have repeatedly been found to provide pain relief, with effects at both subjective [298,299] and neurobiological levels [14,256]. These and other findings suggest that interventions that induce expectations of pain relief, i.e., analgesic expectation inductions, are promising for optimizing the effectiveness of standard analgesic treatments in clinical practice. However, evidence for the efficacy of expectation inductions stems mostly from laboratory research using experimental pain in samples of healthy participants, whereas research in clinical samples (e.g., patients with chronic back pain or postoperative pain) is limited. Although experimentally evoked pain in healthy samples is generally considered a good model for clinical pain, these findings might not be directly transferable to clinical populations. On the one hand, patients with pain, especially chronic pain, have a more extensive and complex history of pain and, often unsuccessful, pain treatment. This might make them more resistant to expectation interventions [95,156]. On the other hand, patients are likely to have a higher desire for pain relief, possibly making them more sensitive to expectation interventions [99,144,237,300].

Three common, brief, and easy-to-implement interventions that have been found to induce and/or enhance expectations are promising for implementation in clinical practice: verbal suggestion, conditioning, and imagery. Verbal suggestion entails instructions regarding treatment outcomes given by, for example, a health care provider. Verbal suggestions such as saying that a placebo or active treatment is an effective analgesic, can induce expectations of pain relief and produce corresponding experiences of pain relief [15,262,266]. Conditioning entails the pairing of a neutral stimulus with an unconditioned stimulus that triggers a certain response. For example, pairing a placebo treatment with reduced pain stimulation can produce expected and experienced pain relief when merely receiving the placebo treatment [4,60,160,161,208,280], especially when conditioning is paired with a verbal suggestion [20,161,181]. Mental imagery of a future event or desired outcome entails actively generating a multisensory cognitive representation of an event and often involves relatively implicit suggestions [116,133]. For example, imagining an optimal future self or health can increase general positive expectations (i.e., optimism) [202,220,224] and correspondingly reduce pain and medical care utilization [119,157]. Thus, inducing

expectations of pain relief, through verbal suggestion, conditioning, and imagery, can reduce pain. However, the comparative effectiveness of these expectation inductions, particularly in clinical populations, is mostly unclear.

The primary aim of the current meta-analysis was to investigate the effects of brief and easy-to-implement expectation interventions for relieving patients' pain. Specifically, the effects of verbal suggestion, conditioning, and imagery on pain relief in clinical populations are investigated. Furthermore, we compared the effects on experimental versus clinical pain, and acute procedural (pain during or directly following a medical procedure, e.g., postoperative pain) versus chronic (long-lasting pain associated with a medical condition, e.g., chronic back pain or recurrent migraine) clinical pain. Additional outcome analyses explored the effects on expected pain, affective pain, and anxiety.

Methods

Protocol and registration

The systematic review and meta-analysis were performed in accordance with the PRISMA Statement [204] and the recommendations of the Cochrane Collaboration [127]. The study protocol was registered in the international prospective register of systematic reviews Prospero (CRD42013006575).

Information sources and search strategy

The electronic bibliographic databases PubMed, PsycINFO, EMBASE, Cochrane CENTRAL, and the Cochrane Methodology Register were searched from inception until June 19, 2015, using search terms describing the three expectation inductions and pain (see Supplementary section 3.1 for the full search strategy). The search was restricted to humans when possible in the databases. In addition, the reference lists of eligible studies and studies that cited the eligible studies were searched for relevant articles.

Eligibility criteria

Studies were included if they assessed the effect of one of the three expectation inductions (verbal suggestion, conditioning, or imagery) on pain relief in a clinical sample (i.e., adult patients with a somatic condition and/or undergoing medical treatment). The review was restricted to studies that compared a brief intervention (verbal suggestion, conditioning, or imagery; max. 1 day) that was believed to induce expectations of pain relief to a control condition consisting of no treatment/treatment as usual, or a control

treatment that was believed to not induce expectations of pain relief. If the studied intervention consisted of multiple components (e.g., both imagery and relaxation), the expectation induction had to be the main component of the intervention (i.e., duration > 50% of intervention time). Studies in which uncertain expectations of pain relief (e.g., 50/50 chance of receiving active or inactive treatment like during blinded treatment administration) were induced in either condition were excluded. Experimental (i.e., experimentally evoked pain), acute procedural (i.e., pain during or directly following a medical procedure), or chronic (i.e., long-lasting pain associated with a medical condition) pain had to be assessed with a self-report rating scale that provided numerical values of experienced pain intensity (e.g., visual analogue scale). Only original research results that were presented in full-length English language empirical articles were included (i.e., not abstracts, case studies, reviews, and reanalyses).

Study selection

Titles and abstracts of articles retrieved using the search strategy were screened by one of two review authors (K.J.P. or S.M.K.) to identify studies that potentially met the eligibility criteria outlined above. The full texts of these articles were retrieved (online, through Dutch academic libraries, or through study authors) and assessed for eligibility (K.J.P. or S.M.K.). Full texts that were considered to be eligible for inclusion or about which doubts existed were also assessed for eligibility by a second review author (K.J.P. or S.M.K.). Any remaining doubts were resolved through discussion with other review authors (A.W.M.E., A.I.M.v.L., and L.V.).

Data extraction

A standardized form was independently used by two review authors (K.J.P. and S.M.K.) to extract data regarding the following from the included studies: expectation induction, control condition, study design, study population, type of pain, and pain outcome measure. Statistical data for meta-analysis (i.e., sample size, mean, and standard deviation (SD) of all post-intervention pain measurements and secondary outcomes, or alternative values) were extracted by one review author (K.J.P.) and accuracy was checked by a second review author (S.M.K). If it was not possible to extract sufficient data for the calculation of post-intervention effect sizes for the primary and secondary outcomes, the study authors were contacted. When sufficient data could not be acquired, alternative statistics (e.g., standard error [SE], confidence interval [CI], *t* or *F* value, *p* value, or mean change scores) were inspected. When appropriate alternative statistics were available, effect sizes were calculated using these, otherwise the study was excluded from quantitative analysis (Table 3.1).

Risk of bias assessment

Risk of bias within each of the included studies was assessed independently by two review authors (K.J.P. and S.M.K.) with the Cochrane risk of bias tool, version 5.1.0 [127]. The following items were evaluated at study level: 'Random sequence generation' (selection bias), 'Allocation concealment' (selection bias), 'Incomplete outcome data' (attrition bias), 'Selective outcome reporting' (reporting bias), and 'Other bias' (focused on differences in sample characteristics - sex, age, and baseline pain). A priori, it was decided not to judge the items 'Blinding of participants and personnel' (performance bias) and 'Blinding of outcome assessors' (detection bias), because it is not possible to blind participants to the expectation inductions or to blind outcome assessors for self-reported outcomes. Disagreements between the authors regarding judgment of the risk of bias were resolved by discussion, with involvement of a third review author (A.I.M.v.L.) where necessary.

Considerations regarding data selection

The following choices were made regarding the selection of intervention and control conditions. When a study contained multiple relevant intervention or control conditions, data were selected from the intervention most directly aimed at pain reduction [313], the comparison of the most active expectation induction (e.g., the strongest verbal suggestion) versus the most passive control condition (e.g., no treatment) [112,122,129,148,166,180,227,313], or the control condition conducted before rather than after the intervention [235]. In two studies the control condition involving hidden administration of active medication was chosen rather than a no-treatment control condition, to avoid confusion with the effect of the active medication [226,227]. With regard to the study design, between-subjects comparisons were included in the quantitative analyses if possible [52,166], because the majority of studies used a between-subjects design. With regard to the outcome measures, in the four studies that included several pain measures [52,226,227,300], the data of the most clinically relevant type of pain were included (e.g., evoked visceral pain rather than evoked heat pain in patients with irritable bowel syndrome). See Supplementary Table 3.1 for an overview of the additional conditions and pain measures used in each study.

Data-analysis

All analyses were conducted by the first reviewer (K.J.P.) and checked by a second reviewer (S.M.K.), using Comprehensive Meta-Analysis software, version 3.3.070 (Biostat, Englewood, CO, USA). The effect size (Hedges' *g*) was calculated as the mean post-intervention pain intensity score for the control condition minus the mean post-

intervention pain intensity score for the intervention condition, divided by the pooled SD, and weighted according to the number of subjects in each study [127]. When pain was assessed at multiple post-intervention time points, the average effect across these time points was calculated. Positive values for *g* indicate lower post-intervention pain ratings (or secondary outcome values, e.g., expected pain) in the intervention condition than in the control condition. A value around 0.2 to 0.3 was considered a small effect, a value around 0.5 a medium effect, and a value of 0.8 or larger a large effect [55]. The pooled effects were analyzed using a random-effects model, given the variability in research characteristics (e.g., different expectation inductions and types of pain). The presence and magnitude of heterogeneity were assessed with the I^2 statistic, as well as by visual inspection of the forest plot. I^2 values of 25%, 50%, and 75% can be considered to indicate low, moderate, and high degrees of heterogeneity, respectively [128]. For within-subjects comparisons, the intervention-control condition correlation coefficient could not be derived from the included studies, therefore an *r* of 0.5 was imputed. For subset analyses, τ^2 was not pooled because we did not expect the between-study variance to be the same for all subsets. The effect sizes in the subsets were compared descriptively rather than with statistical tests, given the small number of studies in most subsets (i.e., insufficient statistical power). Meta-analysis was only conducted when the data of at least three studies were available.

The pooled effects of all three expectation inductions (verbal suggestion, conditioning, and imagery) were analyzed together and separately. Planned subset analyses compared the effects on different types of pain (experimental vs. clinical pain, and acute procedural vs. chronic clinical pain), which also served as a proxy for differential effects depending on the patient type (patients with somatic condition vs. those undergoing medical treatment). Post hoc subset analyses assessed the influence of the route of treatment administration (oral, injection, cutaneous, and other) and compared studies using active (e.g., analgesic medication) versus placebo (e.g., saline injection) treatments. Additional outcome analyses explored the effects of the expectation inductions on expected pain, affective pain, and anxiety. Sensitivity analyses assessed the stability of the overall effect size in relation to: 1) the risk of bias within studies (by removing studies for which at least one item was judged to involve a high risk of bias); 2) publication bias (inspection of funnel plot and trim and fill method); 3) the comparison with a control condition with or without a control treatment, as well as the inclusion of control treatments that might have induced some expectations; 4) the inclusion of both between-subjects and within-subjects comparisons; 5) the imputed intervention-control condition correlation coefficient (imputed r = 0.5, vs. $r = 0.1$ or $r = 0.9$); 6) the inclusion of post-intervention rather than change scores.

Results

Study selection

See Figure 3.1 for the flow chart of the selection process. Through the initial search in the databases 15,952 records were retrieved, three additional relevant studies were identified through other sources. Of these, 3,678 records were duplicates, 11,835 records were excluded on the basis of screening of the titles/abstracts, and the full text of 15 studies that were considered possibly relevant was not available. The full texts of 427 records were retrieved. Of the 62 full texts that were initially selected, 32 studies were excluded for various reasons (e.g., induction of negative expectations or no control condition). In total, 30 studies were included in the qualitative synthesis. For three studies a measure of variance (e.g., SD) was missing for the primary outcome (pain intensity) [129,178,181]. Sufficient data of 27 studies were available for meta-analysis.

Study characteristics

The characteristics of all included studies are reported in Table 3.1. The majority of the studies that could be included in the quantitative meta-analysis assessed the analgesic effects of verbal suggestions (67%, k = 18) such as "The agent you have just been given is known to powerfully reduce pain in some patients" [226,227,235,301] and *"This drug is a local anesthetic and we use it to reduce the pain of the next stimulus. It takes a couple of minutes to work. Rest assured, the next stimulus will be less painful"* [230]. Three studies assessed the effects of a conditioning procedure on pain, which was always combined with verbal suggestion of analgesic effects. Six studies assessed the effects of imagery, with images of pain reduction in four studies (e.g., by imagining numbness). The images used in the other two studies were not specified. Regarding the presence of multiple intervention components, we note that the intervention in four of the imagery studies incorporated relaxation instructions, to maximally engage participants in imagery. In no other studies there were indications of components of the interventions that could not be qualified as an expectation induction in themselves. Because verbal suggestions are inherently incorporated in almost all types of psychological interventions, suggestions were probably included in the studied imagery interventions. In total, 1,256 patients participated in the selected groups of the studies. The samples consisted of patients with various pathologies, e.g., patients with irritable bowel syndrome (k = 5) and patients experiencing long-lasting pain such as chronic back pain or recurrent migraine (k = 8). For most studies, measurements of clinical pain could be included: acute procedural pain (e.g., postoperative pain) was assessed in 12 studies, and chronic pain (e.g., chronic back pain, including cancer pain) in six studies. Measurements of experimentally evoked pain (e.g., electrical pain stimuli) were

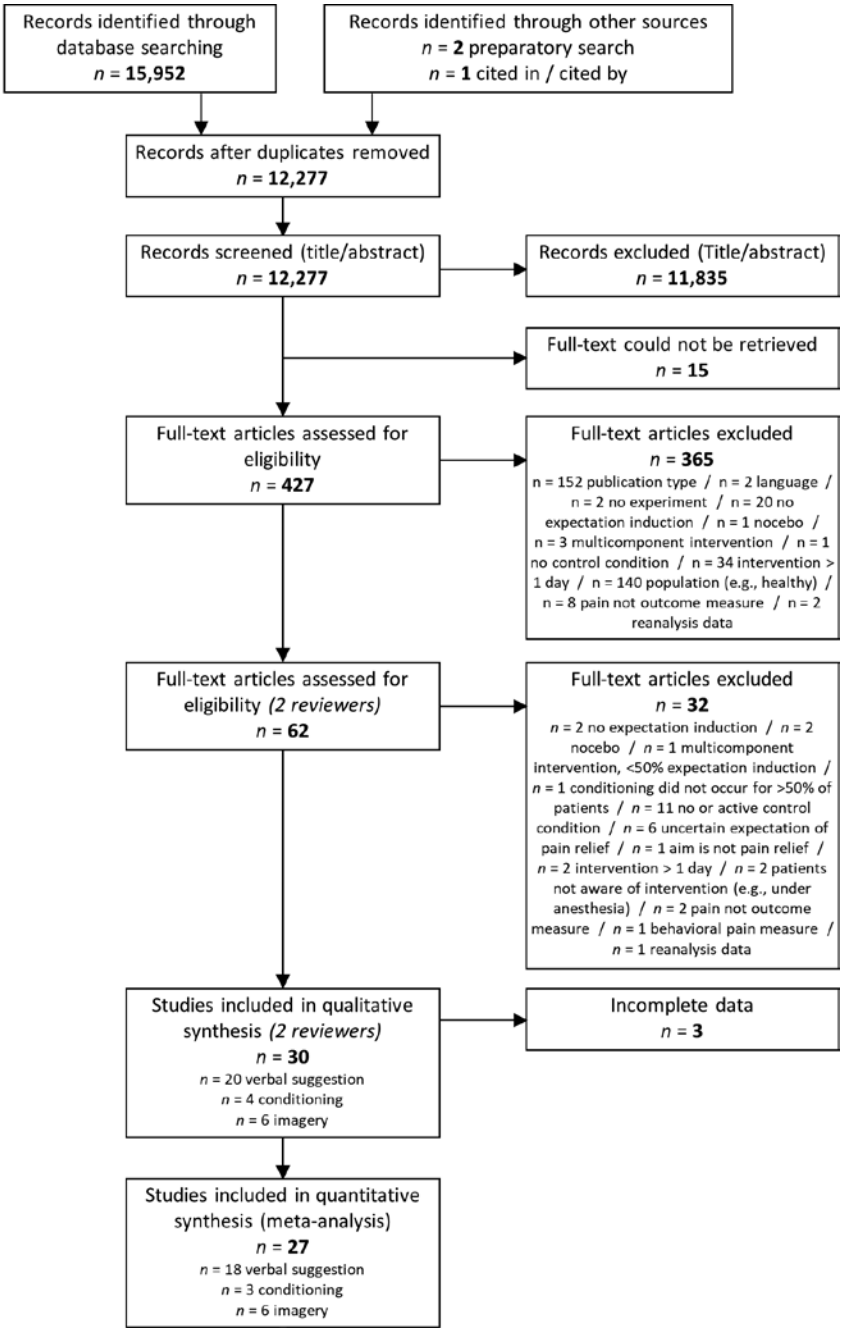

Figure 3.1. PRISMA flow diagram showing study selection process, including reasons for exclusion

Note. Selection was conducted by one reviewer unless otherwise stated.

Table 3.1. Study characteristics of all studies included in the quantitative and qualitative meta-analysis

Study	Intervention			Sample		Outcome	
Author	**Intervention (route of administration**	**Control condition**	**Compa-rison**	***N***	**Patient population**	**Pain type**	**Timing of pain measurement**
Verbal suggestion							
Amanzio et al. (2001) [5]	Verbal suggestion referring to active treatment [a] (injection)	Control treatment	Between subjects	73 / 69	Patients undergoing thoracic surgery	Acute procedural pain (postoperative pain)	15, 30, 45, and 60 min after intervention [d]
Benedetti et al. (1995) [25]	Verbal suggestion referring to placebo treatment [a] (injection)	Control treatment	Between subjects	13 / 11	Patients undergoing thoracic surgery	Acute procedural pain (postoperative pain)	15 and 60 min after intervention [f]
Benedetti et al. (2003) [30]	Verbal suggestion referring to active treatment [a] (injection)	Control treatment	Between subjects	21 / 21	Patients undergoing thoracic surgery	Acute procedural pain (postoperative pain)	30 and 60 min after intervention [d]
Benedetti et al. (2006) [28]	Verbal suggestion referring to active treatment [a] (cutaneous)	Control treatment	Within subjects	28	Patients with Alzheimer's disease	Acute procedural pain (pain after venipuncture)	15 min after intervention [g]
Bialosky et al. (2014) [35]	Verbal suggestion referring to placebo treatment (other)	No treatment	Between subjects	27 / 28	Patients with low back pain	Experimental pain (mechanical pain)	1 x post-intervention
Charron et al. (2006) [52]	Verbal suggestion referring to placebo treatment (injection)	Control treatment	Between subjects [c]	8 / 8	Patients with chronic low back pain	Chronic pain (low back pain)	every 2 min for 20 min after intervention [e,f]
De Craen et al. (2001) [70]	Verbal suggestion referring to placebo or active treatment (oral)	Control treatment	Between subjects	55 / 56	Patients with chronic pain	Chronic pain (chronic pain)	0.5, 1, 2, 4, 6, 8, and 24 h after intervention [d]
Gryll & Katahn (1978) [112]	Verbal suggestion referring to placebo treatment (oral)	No treatment	Between subjects	40 / 40	Patients undergoing dental surgery	Acute procedural pain (injection pain)	1 x post-intervention
Hashish et al. (1988) [122]	Verbal suggestion referring to placebo treatment (other)	No treatment	Between subjects	25 / 25	Patients undergoing dental surgery	Acute procedural pain (postoperative pain)	24 h post-intervention
Ho et al. (1988) [129]	*Verbal suggestion referring to placebo treatment (other)*	*No treatment*	*Between subjects*	*16 / 16*	*Patients undergoing dental surgery*	*Acute procedural pain (postoperative pain)*	*1 x post-intervention **

Table 3.1. *continued*

Study	Intervention			Sample		Outcome	
Author	**Intervention (route of administration**	**Control condition**	**Compa-rison**	***N***	**Patient population**	**Pain type**	**Timing of pain measurement**
Kam-Hansen et al. (2014) [148]	Verbal suggestion referring to placebo or active treatment (oral)	Control treatment	Within subjects	120	Patients with migraine (episodic)	Chronic pain (migraine pain)	2 h after intervention
Levine and Gordon (1984) [180]	Verbal suggestion referring to placebo treatment [a] (injection)	Control treatment	Between subjects	12 / 12	Patients undergoing dental surgery	Acute procedural pain (postoperative pain)	50 min after intervention [f]
Liberman (1964) [181]	*Verbal suggestion referring to placebo treatment (injection)*	*No treatment*	*Between subjects*	*51 / 30*	*Patients undergoing labor*	*Acute procedural pain (labor pain)*	*15 and 30 min during labor ***
Petersen et al. (2012) [227]	Verbal suggestion referring to active treatment [a] (cutaneous)	Control treatment	Within subjects	19	Patients with neuropathic pain	Chronic pain (spontaneous neuropathic pain)	1 x post-intervention
Petersen et al. (2014) [226]	Verbal suggestion referring to active treatment [a] (cutaneous)	Control treatment	Within subjects	18	Patients with neuropathic pain	Chronic pain (ongoing neuropathic pain)	1 x post-intervention
Pollo et al. (2003) [230]	Verbal suggestion referring to placebo treatment (injection)	No treatment	Between subjects	20 / 17	Patients undergoing assessment of autonomic functions	Experimental pain (electrical pain stimulus)	1 x post-intervention
Price et al. (2007) [235]	Verbal suggestion referring to placebo treatment (other)	No treatment	Within subjects	9	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	Last 5 of 7 consecutive stimuli [e]
Schmid et al. (2015) [261]	Verbal suggestion referring to placebo treatment (injection)	Control treatment	Within subjects	17	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	8 distensions post-intervention [d]
Vase et al. (2003) [300]	Verbal suggestion referring to placebo treatment (other)	No treatment	Within subjects	13	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	5, 15, 20, 40, and 50 min after intervention [h]

Table 3.1. *continued*

Study	Intervention			Sample		Outcome	
Author	**Intervention (route of administration**	**Control condition**	**Compa-rison**	***N***	**Patient population**	**Pain type**	**Timing of pain measurement**
Vase et al. (2005) [301]	Verbal suggestion referring to placebo treatment (other)	No treatment	Within subjects	16	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	5, 10, 15, 20, 25, 30, 35, and 40 min after intervention [d] (each time mean pain of 2 distensions)
Conditioning							
Hashmi et al. (2014) [123]	Conditioning with verbal suggestion referring to placebo or active treatment (other)	Control treatment	Within subjects	42	Patients with knee osteoarthritis	Experimental pain (heat pain)	2 x 6 stimuli post-intervention [e]
Klinger et al. (2007) [166]	Conditioning with verbal suggestion referring to treatment (cutaneous)	Control treatment	Between subjects [c]	12 / 12	Patients with atopic dermatitis	Experimental pain (electrical pain stimuli)	5 consecutive stimuli post-intervention [d]
Laska and Sunshine (1973) [178]	Conditioning referring to placebo treatment (after active treatment) (oral)	Control treatment	Between subjects	95 / 16	Patients with postoperative, fracture, or somatic pain	Acute procedural pain or chronic pain (postoperative, fracture, or somatic pain)	30, 60, 120, 180, 240, 300, and 360 min after intervention **
Lee et al. (2012) [179]	Conditioning with verbal suggestion referring to placebo treatment (injection)	Control treatment	Within subjects	17	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	1 x post-intervention
Imagery							
Danhauer et al. (2007) [66]	Imagery of sending warm energy to painful areas and of a pleasant place, and relaxation instructions (audio recording)	No treatment [b]	Between subjects	56 / 58	Patients undergoing colposcopy	Acute procedural pain (pain during colposcopy)	1 x post-intervention (retrospect, i.e., pain during procedure)

Table 3.1. *continued*

Study	Intervention			Sample		Outcome	
Author	Intervention (route of administration	Control condition	Compa-rison	*N*	Patient population	Pain type	Timing of pain measurement
Foji et al. (2015) [92]	Imagery contents not reported (audio recording)	No treatment	Between subjects	31 / 31	Patients undergoing coronary angiography	Acute procedural pain (post-angiography pain)	1 x post-intervention
Gonzales et al. (2010) [105]	Imagery and progressive relaxation, biorhythmic music with positive statements (audio recording)	No treatment	Between subjects	22 / 22	Patients undergoing head and neck surgery	Acute procedural pain (postoperative pain)	1 and 2 h after intervention [d]
Jacobson (2006) [142]	Imagery of a pleasant place and cooling gloves (audio recording)	No treatment [b]	Between subjects	41 / 40	Patients undergoing peripheral i.v. therapy	Acute procedural pain (i.v. insertion pain)	1 x post-intervention
Kwekkeboom et al. (2008) [174]	Imagery using glove anesthesia technique, transferring feeling of numbness to painful areas (audio recording)	Control treatment	Within subjects	31	Patients with cancer pain	Chronic pain (cancer pain)	1 x post-intervention
Wells et al. (1989) [313]	Imagery of transferring feeling of numbness to painful area (audio recording)	Control treatment	Between subjects	10 / 10	Patients undergoing abortion	Acute procedural pain (abortion pain)	1 x worst pain during abortion, and 1 x pain in recovery room [d]

Note: [a] used open/hidden design; [b] described by study authors as treatment as usual; [c] within-subjects comparison also possible; [d] average of effect sizes across time points is calculated; [e] only average across time points available; [f] only change from baseline available; [g] post-intervention score(s) calculated; [h] only effect size (Cohen's d) available. ** Insufficient data for meta-analysis. *N* = either total sample size or sample size per condition (intervention/control condition); i.v. = intravenous

included in nine studies. In all studies, patients reported their pain on a single-item pain scale (see Supplementary Table 3.1).

Description risk of bias within studies

Figures 3.2 and 3.3 show the results of the risk of bias (RoB) assessment in all included studies. Regarding selection bias, 63% of the studies reported that treatment allocation was random, but only 27% described adequate random sequence generation (low RoB). Randomization was not mentioned in 17% of the studies (unclear RoB), and incomplete or not performed at all in 20% of the studies (high RoB). Allocation concealment was reported adequately in only 13% of the studies (low RoB), in one study allocation concealment was described, but insufficiently (unclear RoB). None of the other studies mentioned allocation concealment, but a high RoB was inferred if randomization was incomplete or not performed at all (20%). In 40% of the studies there were no signs for attrition bias due to incomplete outcome reporting (low RoB). For 10% of the studies, drop out was unbalanced and/or related to the outcome measure (high RoB). The judgment of reporting bias was challenged for the majority of studies (93%) because no preregistered study protocol could be retrieved. When disregarding the presence of a protocol in the assessment (Figures 3.2 and 3.3), 63% of the studies could be judged as having a low RoB. For 1 study, there was discordance between some measures mentioned in the methods and results section, whereas in another study, analyses did not include all available measurements of the primary outcome (high RoB). In 30% of the studies, no imbalances in sample characteristics of sex, age, and baseline

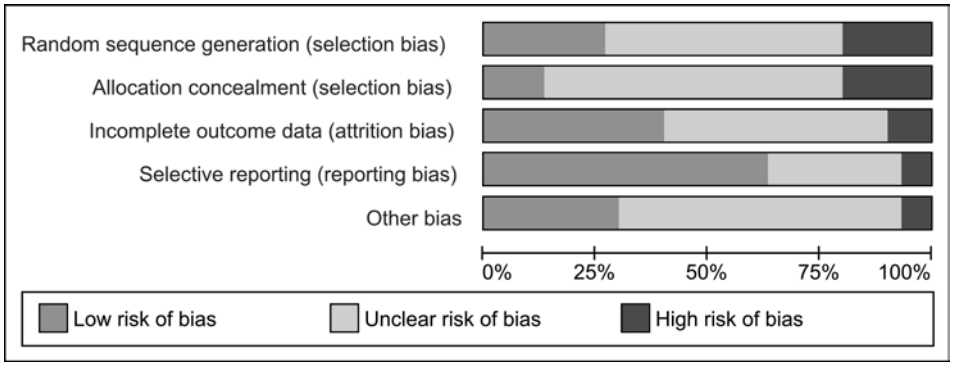

Figure 3.2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

Note. For the item 'Selective outcome reporting' (reporting bias) the absence of a preregistered study protocol did not affect the judgment, because a protocol was absent for 93% of the studies.

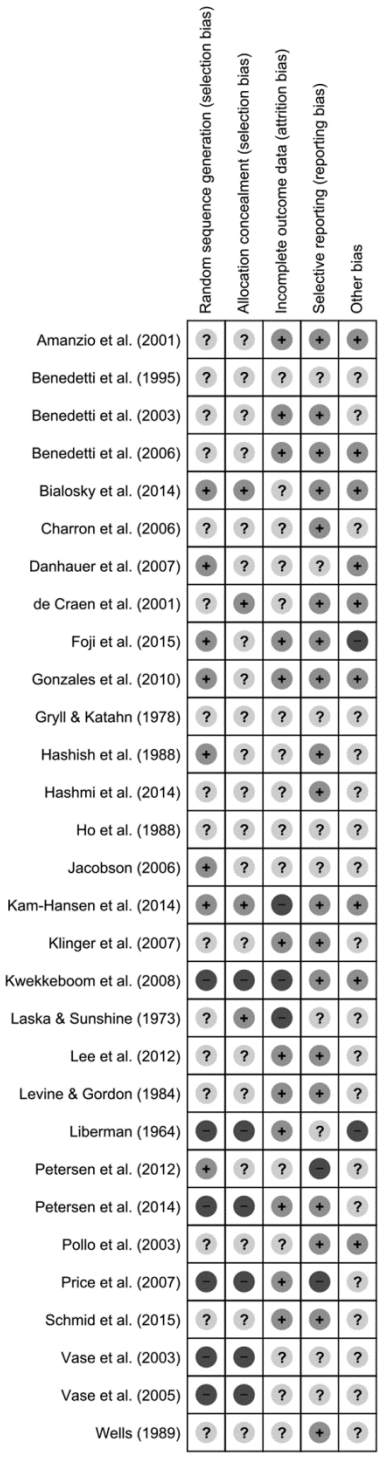

Figure 3.3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Note. For the item 'Selective outcome reporting' (reporting bias) the absence of a preregistered study protocol did not affect the judgment, because a protocol was absent for 93% of the studies.

pain were observed (low risk of 'other bias'). All other studies (70%) reported insufficient data regarding equality of one or more of these sample characteristics (unclear RoB). Last, the risk of 'other bias' was judged to be high in one study because of different study procedures in the intervention and control condition and in another study because of the insufficient reporting of study details such as the characteristics of the pain-reporting scale.

Primary meta-analysis: Effect of expectation inductions on pain

See Figure 3.4 for the effect sizes per study and the pooled effects. Meta-analysis indicated a medium overall effect of the expectation inductions on pain in clinical samples (k = 27, g = 0.61, 95% CI 0.42-0.79). A high degree of heterogeneity was observed (I^2 = 73%), with the study effect sizes ranging between g = -0.58 and g = 1.85. The effect sizes for the different expectation inductions varied from a medium to large pooled effect of verbal suggestion (k = 18, g = 0.75, 95% CI 0.50-1.00, I^2 = 78%), to a medium pooled effect of conditioning (always paired with verbal suggestion; k = 3, g = 0.65, 95% CI 0.18-1.11, I^2 = 56%), and to a small pooled effect of imagery (k = 6, g = 0.27, 95% CI 0.02-0.53, I^2 = 42%).

The overall effect of the expectation inductions corresponded with an average pain reduction of 1.16 points on a scale of 0-10 (95% CI 0.77-1.54). Verbal suggestion reduced pain with 1.39 points (95% CI 0.85-1.93), conditioning with 1.03 points (95% CI 0.30-1.76), and imagery with 0.62 points (95% CI 0.10-1.15).

The results of the studies for which sufficient data for meta-analyses were not available, were in line with the observed pooled effects. Ho et al. [129] found a mean difference of 18.3 on a scale of 0-100 between a verbal suggestion condition and a no-treatment condition. Liberman [181] observed that patients reported significantly less labor, postpartum, and experimental pain in a verbal suggestion condition compared with a control condition (p < .001). Laska and Sunshine [178] found that participants reported less pain when a placebo followed an active analgesic (i.e., conditioning) rather than when it followed a placebo (i.e., no conditioning; difference between 0.5 and 3.6 on a sum of pain intensity differences scale).

Subset analyses

Effects on different types of pain. A comparison of the effects of the expectation inductions on different types of pain (see Table 3.1 for specifications) indicated a medium to large pooled effect on experimental pain (k = 9, g = 0.72, 95% CI 0.43-1.01, I^2 = 52%) and a medium pooled effect on clinical pain (k = 18, g = 0.55, 95% CI 0.33-0.78, I^2 = 77%). A further comparison of acute procedural versus chronic clinical pain indicated

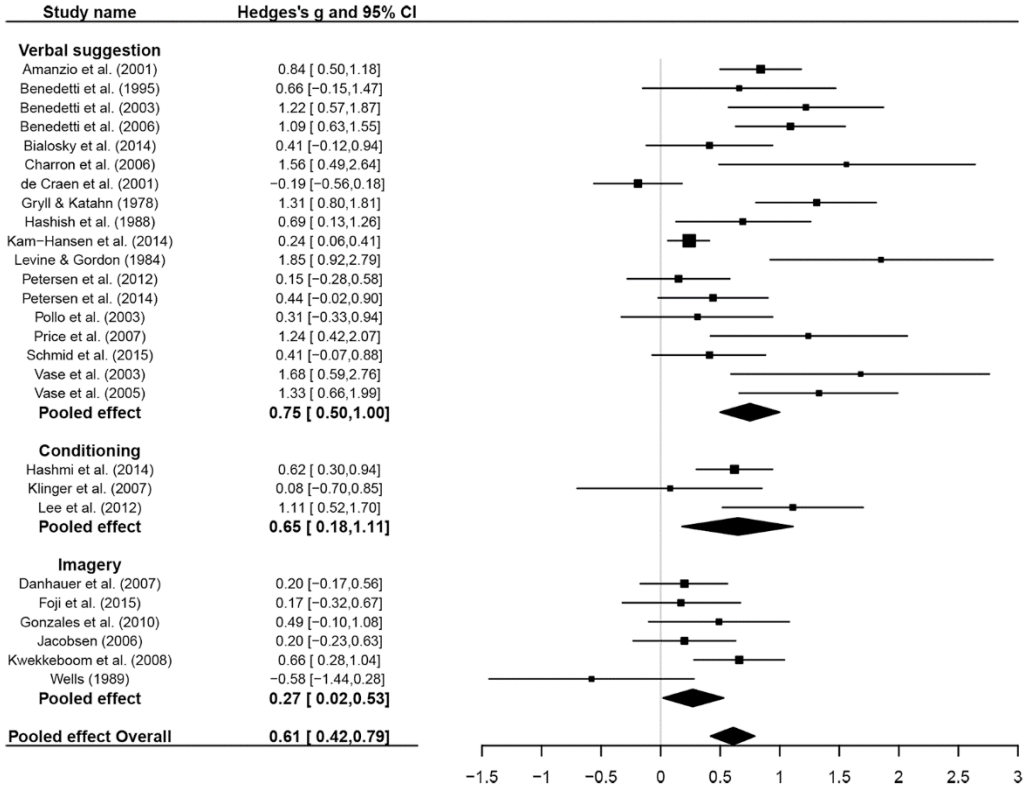

Figure 3.4. Forest plot of the random-effects meta-analysis indicating the effects of the expectation inductions (verbal suggestion, conditioning, and imagery) on pain relief in clinical samples

Note. Positive values for *g* indicate lower post-intervention pain ratings in the intervention condition than in the control condition.

a medium pooled effect on acute procedural pain (k = 12, g = 0.67, 95% CI 0.36-0.97, I^2 = 74%) compared with a small pooled effect on chronic pain (k = 6, g = 0.33, 95% CI 0.04-0.62, I^2 = 70%). Comparing the effects on the different types of pain for the separate expectation inductions was only possible for verbal suggestion. The effects of verbal suggestion on experimental pain were comparable to the overall effect (k = 6, g = 0.79, 95% CI 0.37-1.21, I^2 = 59%), but the difference between the effects on acute procedural and chronic pain was considerably larger (k = 7, g = 1.03, 95% CI 0.79-1.27, I^2 = 24% vs. k = 5, g = 0.25, 95% CI -0.06-0.56, I^2 = 66%, respectively).

Post hoc: Route of treatment administration. Verbal suggestions or conditioning referring to treatments that were administered via injection (see Table 3.1 for relevant studies) were associated with large pooled effects (k = 8, g = 0.90, 95% CI 0.58-1.21, I^2 = 52%), whereas oral and cutaneous treatments were associated with a small to medium pooled effect (k = 3, g = 0.42, 95% CI -0.23-1.07, I^2 = 91% and k = 4, g = 0.47, 95% CI 0.00-0.94, I^2 = 70%,respectively). When analyzing only the effects of verbal suggestion, comparable results were found (k = 7, g = 0.87, 95% CI 0.51-1.23, I^2 = 56% vs. k = 3, g = 0.42, 95% CI -0.23-1.07, I^2 = 91% vs. k = 3, g = 0.56, 95% CI 0.01-1.11, I^2 = 77%, respectively).

Post hoc: Active or placebo treatment. Studies that assessed the effects of verbal suggestion or conditioning that referred to an active treatment (see Table 3.1 for relevant studies) found a medium to large pooled effect (k = 5, g = 0.73, 95% CI 0.35-1.10, I^2 = 70%), compared with a large pooled effect in studies that used a placebo treatment (k = 13, g = 0.90, 95% CI 0.61-1.19, I^2 = 58%). When analyzing only the effects of verbal suggestion, comparable results were found (k = 5, g = 0.73, 95% CI 0.35-1.10, I^2 = 70% vs. k = 11, g = 0.95, 95% CI 0.63-1.26, I^2 = 58%, respectively). No differential effects were indicated in three studies in which both active and placebo treatments were used (g = 0.25, 95% CI -0.13-0.64, I^2 = 64% and g = 0.22, 95% CI -0.15-0.59, I^2 = 62%, respectively) [70,123,148].

Effect of expectation inductions on additional outcomes

See Figure 3.5 for the effect sizes per study and the pooled effects for each of the additional outcomes.

Expected pain. From five (of seven) studies, sufficient data were available to analyze the effects of expectation inductions (k = 5 verbal suggestion) on self-reported expectations of pain. A medium pooled effect was observed (g = 0.66, 95% CI 0.43-0.90, I^2 = 0%).

Affective pain. From seven (of ten) studies, sufficient data were available to analyze the effects of expectation inductions (k = 4 verbal suggestion, k = 3 imagery) on affective

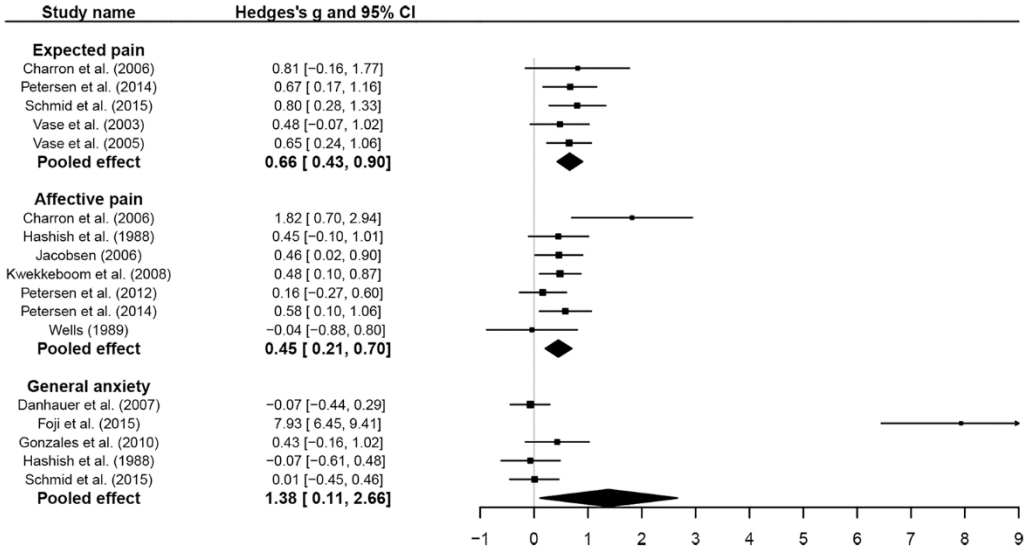

Figure 3.5. Forest plot of the random-effects meta-analysis indicating the effects of the expectation inductions (verbal suggestion, conditioning, and imagery) on expected pain, affective pain, and anxiety in clinical samples

Note. Positive values for *g* indicate lower post-intervention pain ratings in the intervention condition than in the control condition.

pain (i.e., pain unpleasantness or pain distress). A medium pooled effect was observed (g = 0.45, 95% CI 0.21-0.70, I^2 = 34%).

Anxiety. From five (of six) studies, sufficient data were available to analyze the effects of expectation inductions (k = 2 verbal suggestion, k = 3 imagery) on anxiety (measured with the state version of the State-Trait Anxiety Inventory or an anxiety visual analogue scale). A large pooled effect was observed (g = 1.38, 95% CI 0.11-2.66, I^2 = 96%); however, when excluding an extreme outlier (g = 7.93 [92]), no effect was observed (g = 0.03, 95% CI -0.21-0.26, I^2 = 0%).

Sensitivity analyses for overall effect of expectation inductions on pain

Risk of bias within studies. Excluding studies that were judged to have a high risk of bias on one or more items (k = 9, ~~see~~ Figure 3.3) did not substantially affect the overall effect size (g = 0.63, 95% CI 0.38-0.87).

Publication bias. The funnel plot (Figure 3.6) suggests publication bias. The trim and fill method indicated that six studies demonstrating below-average effects of an expectation induction on pain relief (the black dots in the figure) were estimated to be missing. Including these studies would lower the overall effect size to g = 0.43 (95% CI 0.24-0.62).

Type of control condition. When expectation inductions were compared to a control condition with a control treatment a pooled effect of g = 0.58 (k = 16, 95% CI 0.34-0.82) was observed, whereas for studies in which a no-treatment control condition was used, a pooled effect of g = 0.65 (k = 11, 95% CI 0.35-0.94) was found. Excluding three studies that involved a control condition in which some expectations of pain relief might have been induced [70,174,313], resulted in an overall effect of g = 0.67 (95% CI 0.49-0.86).

Between- versus within-subjects comparisons. The pooled effect for studies for which between-subjects comparisons were reported was g = 0.53 (k = 16, 95% CI 0.26-0.80), compared to g = 0.70 for studies in which within-subjects comparison were used (k = 11, 95% CI 0.45-0.96). Including within- rather than between-subjects comparisons of two studies for which both comparisons could be made did not affect the overall effect size (g = 0.60, 95% CI 0.43-0.78).

Imputed correlation coefficients. Sensitivity analyses testing whether the imputed intervention – control correlation of r = 0.5 for within-subjects comparisons affected the observed effects indicated a stable overall effect size (when r = 0.1, g = 0.60, 95% CI 0.41-0.79; when r = 0.9, g = 0.61, 95% CI 0.44-0.77).

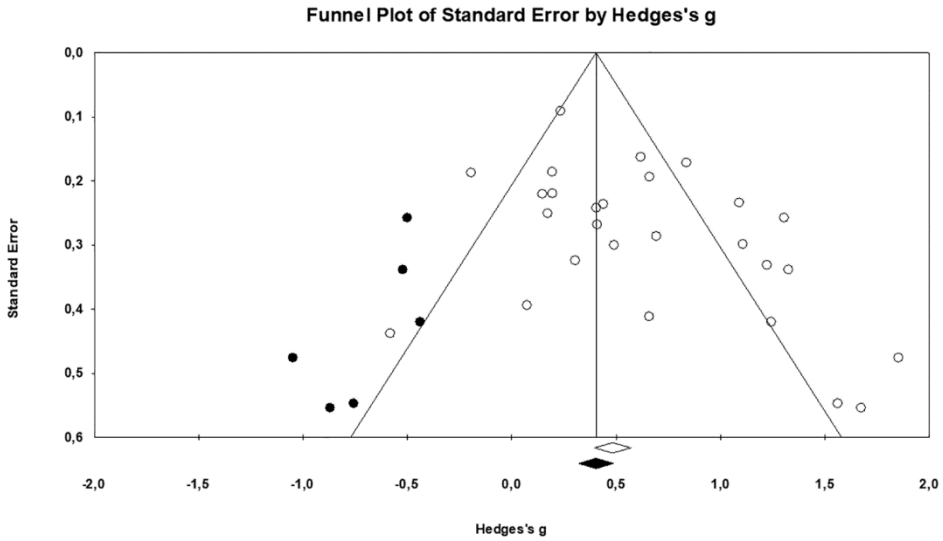

Figure 3.6. Funnel plot of SE by Hedges' g

Post-intervention versus change scores. When excluding three studies for which only change scores were available [25,52,180], rather than the preferred post-intervention scores, the overall effect size was *g* = 0.55 (95% CI 0.37-0.73). When selecting change scores rather than post-intervention scores (available for 12 studies) the overall effect size was *g* = 0.70 (95% CI 0.49-0.90).

In summary, these sensitivity analyses indicate a relatively stable overall effect size, ranging from *g* = 0.43 to *g* = 0.70.

Discussion

The current meta-analysis assessed the pain-reducing effects of three expectation interventions, i.e., verbal suggestion, conditioning, and imagery, in clinical samples. Meta-analysis of 27 studies showed an overall medium-sized (heterogeneous) effect of the interventions on patients' pain relief. The effects of verbal suggestion were most frequently studied and could be qualified as medium to large. Conditioning (always paired with verbal suggestion) and imagery were studied much less frequently, and were associated with medium and small effects, respectively. The effect sizes varied depending on the type of pain that patients experienced, with medium to large effects in the case of experimental and acute procedural pain, but small effects on chronic pain.

Thus, interventions that can induce analgesic expectations, particularly verbal suggestions for acute procedural pain, were found to relief patients' pain and can thus possibly be used to optimize the effectiveness of standard analgesic treatments in clinical practice.

The findings of this meta-analysis extend previous meta-analyses in which the pain-reducing effects of verbal suggestion and conditioning were studied in the context of placebo effects [298,299] and a meta-analysis and systematic reviews in which the pain-reducing effects of imagery were studied [231,232,291], by directly comparing the effects of these expectation inductions, while focusing on brief interventions in clinical samples. The observed medium to large effects of verbal suggestion on experimentally evoked and acute procedural pain were generally in line with the findings of a previous meta-analysis [299] and more recent studies in healthy participants [16,189,266], which supports the transferability of findings from healthy to clinical samples. In contrast, the effects of verbal suggestion on chronic pain were found to be small, possibly because of repeated negative treatment experiences in the past and consequently more negative expectations regarding pain treatment in general that cannot be easily molded by a brief verbal suggestion [95]. However, because within-study comparisons of experimental and chronic pain provided somewhat equivocal results [52,226,227], and given the heterogeneity of the studies, further research is required. Surprisingly, although conditioning procedures were always paired with corresponding verbal suggestions, their effects on pain in clinical samples were not larger than the effects of verbal suggestion alone. This finding is in contrast with previous research in healthy samples, where such procedures are generally observed to have more robust effects on pain than verbal suggestions alone [20,166,197]. However, because the effects of conditioning in clinical samples could be analyzed only in three studies and were studied only on experimental pain, and because conditioning procedures were always paired with verbal suggestion, no firm conclusions can be drawn yet about the size of conditioning effects in clinical samples. Imagery was found to have a small effect on clinical pain in our meta-analysis. This is partially in contrast with previous reviews that indicated small to large effects of imagery on pain [231,232,291]. Also, a priori, we considered that imagery might be more effective than verbal suggestion because visual thinking has been found to have a larger impact on emotions, and hence possibly also the subjective pain experience, than verbal thinking [116,133] and because imagery entails more active involvement [89]. Several factors might explain these findings. First, the selected imagery interventions were brief, maximally one day (to increase comparability between the expectation inductions). Possibly more practice time is required to obtain substantial effects (Van Kuiken, 2004a). Second, imagery instructions were always delivered through audio

recordings, whereas verbal suggestions were given by the experimenter. Personal communication might enhance the effects of expectation inductions.

Subsequent post hoc analyses demonstrated that the observed effects of verbal suggestion and conditioning varied depending on the route of administration of the medical treatment to which they referred, with larger effects for more invasive treatments (injections) than less invasive treatments (oral and cutaneous). This is in line with previous experimental placebo research and a meta-analysis of placebo arm data of clinical trials [71,152]. In addition, the effects of verbal suggestion and conditioning were slightly larger when they referred to a placebo rather than an active treatment. However, direct comparisons within three studies indicated no differential effects [70,123,148]. Also, research in healthy samples provides equivocal results regarding the relative effect sizes [15,259]. Nonetheless, these findings underscore that expectation interventions are not only relevant in the context of placebo effects, but also that they can enhance the analgesic effects of active treatments in clinical samples.

The core working mechanism of verbal suggestion, conditioning, and imagery is thought to be expectancy, as already implied by the term 'expectation inductions'. Our meta-analysis of the subset of studies in which expectations were measured demonstrated that verbal suggestion indeed induced expectations of pain relief, and the study authors showed that these expectations predicted effects on actually experienced pain [52,226,261,300,301]. Previous research in healthy samples confirmed that also conditioning and imagery induce expectations [40,119,160,161,202,224], but, because of a lack of research, this cannot yet be confirmed in clinical samples. Also, anxiety reduction has been considered as a possible psychological working mechanism [91,189,231,291]. However, our meta-analysis could not demonstrate an effect of the expectation inductions on anxiety in clinical samples, with the exception of one study in which large effects of imagery on anxiety were observed. Preliminary evidence from another study [301] suggests possible effects on pain specific anxiety. Several other psychological processes (e.g., general affect, attention, or sense of control) might be affected by the interventions, but this could not be assessed in the meta-analysis because necessary data were not available. We could not meta-analyze physiological and neuroimaging data, because of the paucity and complexity of the data. Although several previous reviews illustrate the neurobiological mechanisms of placebo effects and imagery, it was predominantly in healthy samples [14,201,256]. An inspection of the included studies in patient samples provides preliminary evidence that verbal suggestion might be able to reduce heart rate [28,230] and c-reactive protein [122], but not cortisol (possibly because of methodological issues) [122,134,261]. A study on imagery found no evidence for effects on physiological responses [92]. At a neurobiological level, the effects of verbal

suggestion and conditioning on pain have been found to be associated with pain-related brain activity and connectivity among different brain regions [28,123,179,235,261]. Further research is required to allow more conclusive inferences of the effects of expectation interventions on physiological and neurological processes in clinical populations.

When evaluating the current results, certain methodological factors that could have affected the observed effect sizes should be considered. Despite considerable heterogeneity, sensitivity analyses indicated a relatively stable overall effect size in relation to the research design (type of control condition, within- vs. between-subjects comparisons) and selected values for analyses (imputed correlation coefficients, post-intervention rather than change scores). However, there were indications for publication bias, which might have inflated the overall effect size (although the adjusted effect size could still be qualified as medium). Bias in the individual studies could frequently not be judged decisively due to insufficiently detailed reporting and the absence of preregistered study protocols. Also, response bias due to the (partial) infeasibility of blinding cannot be excluded. Nevertheless, because excluding studies with a known high risk of bias barely influenced the observed overall effect size, the influence of study bias seems minor. Last, the observed pairing of conditioning with verbal suggestion and the frequent inherent inclusion of relaxation, and possibly also verbal suggestion, in imagery interventions, could have affected the observed effects and hampers judgments of the effectiveness of the separate intervention components.

Based on this meta-analysis, several directions for future research can be considered. Most importantly, given the current positive but heterogeneous and still limited findings, future research might focus particularly on further examining the elements that determine the effectiveness of the different expectations inductions and on maximizing therapeutic effects. Research on active intervention elements (e.g., specifics of verbal suggestion and pure imagery), mediating factors (expectations, physiological and neurobiological responses, and e.g., anxiety and attention), moderating factors (e.g., previous pain experiences, pain treatment history, desire for pain relief, and personality characteristics), and outcome characteristics (e.g., type of pain) could provide insight into what determines the effects of the expectation interventions, and for whom and when they are effective. Also, combining different expectation inductions might enhance the effects, and for patients with chronic pain, more extensive interventions (e.g., also addressing general expectations regarding medical treatment and health) might be considered. Importantly, research should not only aim at inducing and/or enhancing positive expectations, but should also address negative expectations regarding adverse effects [225]. Furthermore, the current findings allow for conclusions regarding only the short-term effects of the expectation

interventions; further research is warranted to determine whether the interventions have a long-lasting clinical impact. Last, more detailed methodological reporting of the research, including preregistration, would further advance the field and facilitate future meta-analyses [127,264].

In conclusion, the current meta-analysis indicated that brief expectation interventions, especially verbal suggestion, can relief patients' acute procedural and, to a lesser extent, chronic pain. Most notably, the observed analgesic effects of verbal suggestions regarding placebo or active treatments underline the importance of the information a clinician provides when administering an analgesic treatment. Informing patients about, and emphasizing, the positive intended and expected outcomes of an analgesic intervention, without neglecting possible negative side effects, can optimize treatment effectiveness.

Acknowledgements

The authors thank Alice Tillema of the Library of Medical Sciences at Radboud University for her help in developing the search strategy.

Supplementary materials Chapter 3

Supplementary Section 3.1. Search strategy

PubMed
("Placebo Effect"[Mesh] OR "Conditioning (Psychology)"[Mesh:noexp] OR "Conditioning, Classical"[Mesh] OR "Imagery (Psychotherapy)"[Mesh] OR placebo effect[tiab] OR placebo effects[tiab] OR placebo analgesia[tiab] OR verbal suggestion[tiab] OR verbal suggestions[tiab] OR open-hidden [tiab] OR open-label placebo[tiab] OR (conditioning[tiab] NOT medline[sb]) OR imagery[tiab]) AND ("Pain"[Mesh] OR "Analgesia"[Mesh] OR pain[tiab] OR analgesia[tiab] OR analgesic[tiab]) NOT ("animals"[Mesh] NOT "humans"[Mesh])

PsycINFO (via OvidSP)
(exp placebo/ OR conditioning/ OR classical conditioning/ OR imagery/ OR conceptual imagery/ OR guided imagery/ OR (placebo effect OR placebo effects OR placebo analgesia OR verbal suggestion OR verbal suggestions OR open-hidden OR open-label placebo OR conditioning OR imagery).ti,ab,id.) AND (exp pain/ OR exp analgesia/ OR (pain OR analgesia OR analgesic).ti,ab,id.)

EMBASE (via OvidSP)
(placebo effect/ OR conditioning/ OR imagery/ OR guided imagery/ OR (placebo effect OR placebo effects OR placebo analgesia OR verbal suggestion OR verbal suggestions OR open-hidden OR open-label placebo OR conditioning OR imagery).ti,ab.) AND (exp pain/ OR exp analgesia/ OR (pain OR analgesia OR analgesic).ti,ab.) NOT ((nonhuman/ OR animal/) NOT human/)

Cochrane CENTRAL & Cochrane Methodology Register (via Cochrane library)
([mh "Placebo Effect"] OR [mh ^"Conditioning (Psychology)"] OR [mh "Conditioning, Classical"] OR [mh "Imagery (Psychotherapy)"] OR (“placebo effect” OR “placebo effects” OR “placebo analgesia” OR “verbal suggestion” OR “verbal suggestions” OR “open-hidden” OR “open-label placebo” OR conditioning OR imagery:ti,ab,kw)) AND ([mh Pain] OR [mh Analgesia] OR (pain OR analgesia OR analgesic:ti,ab,kw)) NOT ([mh animals] NOT [mh humans]

Supplementary Table 3.1. Additional study characteristics of all studies included in the quantitative and qualitative meta-analysis

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Verbal suggestion							
Amanzio et al. (2001) [5]	Active: buprenorphine, tramadol, ketorolac, or metamizol	I: 53.8 (8.1) C: 54.3 (7.9)	I: 53% M C: 57% M	NRS (0-10)	·	· first group of patients, data analyzed in terms of analgesic dose needed to obtain pain reduction of 50% · healthy sample (ischemic arm pain)	·
Benedetti et al. (1995) [25]	Placebo: analgesic	55 [b]	56% M [b]	NRS (0-10)	· open proglumide (0.05, 0.5, or 5 mg) · hidden proglumide (0.05, 0.5, or 5 mg)	·	·
Benedetti et al. (2003) [30]	Active: morphine	I: 56.5 (9.5) C: 53.9 (11.8)	I: 52% M C: 62% M	NRS (0-10)	· open interruption morphine · hidden interruption morphine	· thoractomized patients (state anxiety) · Parkinsonian patients (movement velocity) · healthy volunteers (beta-blockade) · healthy volunteers (muscarinic antagonism)	·
Benedetti et al. (2006) [28]	Active: lidocaine	73.5 (6.8)	39% M	NRS (0-10)	·	· healthy controls · retested after 1 year (incl. 10 additional Alzheimer disease patients without reduced connectivity)	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Bialosky et al. (2014) [35]	Placebo: spinal manipulative therapy	I: 31.6 (11.9) C: 29.9 (12.1) *[18-60]*	I: 26% M C: 32% M	M-VAS (100mm)	· placebo without verbal suggestion	·	· experimental pain: thermal pain sensitivity · clinical pain: low back pain intensity after 2 additional intervention weeks
Charron et al. (2006) [52]	Placebo: analgesic	39.8 (13.2) *[18-60]*	63% M	Numeric scale (0-100)	·	·	· experimental pain: cold pain
De Craen et al. (2001) [70]	Placebo: analgesic or Active: tramadol	I: 50.9 (14.5) C: 53.2 (15.3) *[incl ≥ 18]*	I: 42% M C: 39% M	VAS (10cm)	·	·	·
Gryll & Katahn (1978) [112]	Placebo: reduction of tension, anxiety, sensitivity to pain	33 *[incl ≥ 18]* [b]	53% M [b]	Semantic differen-tial (1-5)	· undersell, saliva suggestion · Note, a factorial design assessing multiple additional factors was used: 4 (suggestion: oversell, undersell, saliva, no pill) x 2 (status: dentist or dental technician) x 2 (warm vs neutral dentist) x 2 (warm vs neutral dental technician)	·	·
Hashish et al. (1988) [122]	Placebo: ultrasound	*[16-70]* [b]	F & M [b]	VAS (100mm)	· ultrasound · stationary ultrasound · self-massage	·	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Ho et al. (1988) [129]	Placebo: ultrasound	24 [b] *[15-44]*	30% M [b]	Scale	· ultrasound · stationary ultrasound · self-massage	·	·
Kam-Hansen et al. (2014) [148]	Placebo: maxalt or Active: maxalt	40.6 (12.7) *[incl ≥ 18]* [b,c]	15% M [b,c]	NRS (0-10)	· given placebo told "maxalt or placebo" · given maxalt told "maxalt or placebo"	·	·
Levine and Gordon (1984) [180]	Placebo: analgesic?	?	?	VAS (100mm)	· hidden placebo · open naloxone · hidden naloxone · machine naloxone · machine morphine 8 mg · machine morphine 12 mg	·	·
Liberman (1964) [181]	Placebo: analgesic	?	0% M	Verbal indications (4 points)	· verbal suggestion/control during postpartum · verbal suggestion/control 3 days after (ischemic muscle pain)	·	·
Petersen et al. (2012) [227]	Active: lidocaine	61.9 *[51-75]*	63% M	M-VAS (10cm)	· control condition (no lidocaine)	·	· experimental pain: brush-evoked, cold-evoked, pinprick, wind-up like pain
Petersen et al. (2014) [226]	Active: lidocaine	56.8 *[32-65]*	56% M	M-VAS (10cm)	· 2x control condition (no lidocaine) · open capsaicin · hidden capsaicin	·	· experimental pain: brush-evoked, pinprick, wind-up like pain

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Pollo et al. (2003) [230]	Placebo: local anesthetic	I: 38.0 (15.5) C: 34.8 (13.0)	I: 18% M C: 20% M	NRS (0-10)	·	· healthy controls (ischemic arm pain)	·
Price et al. (2007) [235]	Placebo: analgesic	27.7 (9.6)	0% M	Rating scale (100 units)	· placebo match · baseline 2	·	·
Schmid et al. (2015) [261]	Placebo: analgesic	39.0 (3.4) *[incl 18-65]*	12% M	VAS (100mm)	·	· patients with ulcerative colitis in remission · healthy controls	·
Vase et al. (2003) [300]	Placebo: analgesic	30 (13) *[incl pre-menopausal]*	0% M	M-VAS (10cm)	· rectal lidocaine · oral lidocaine · rectal nocebo	·	· experimental pain: heat pain
Vase et al. (2005) [301]	Placebo: analgesic	29 (9) *[incl pre-menopausal]*	0% M	M-VAS (10cm)	· rectal lidocaine after hidden saline · rectal placebo after hidden naloxone · natural history after hidden naloxone · rectal lidocaine after hidden naloxone	·	·
Conditioning							
Hashmi et al. (2014) [123]	Placebo: acupuncture or Active: acupuncture	57.9 (7.2)	48% M	Gracely Sensory Scale (0-20)	·	·	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Klinger et al. (2007) [166]	Placebo: analgesic	27.4 (8.2) *[17-38]* [b]	50% M [b]	NRS (0-8)	· conditioning with neutral suggestion · no conditioning with analgesic suggestion	· healthy controls	·
Laska and Sunshine (1973) [178]	Active -> placebo: propoxyphene HCL or propoxyphene napsylate, each in 3 different dosages	adult	F & M	NRS (0-3)	·	·	·
Lee et al. (2012) [179]	Placebo: analgesic	35.9 (10.8) *[incl 18-55]*	35% M	VAS (100mm)	·	· healthy controls	·
Imagery							
Danhauer et al. (2007) [66]	n.a.	I: 29.1 (10.2) C: 28.9 (9.5) *[incl ≥ 18]*	0% M	VAS (100mm)	· music	·	·
Foji et al. (2015) [92]	n.a.	I: 56.8 (1.46) C: 57.3 (1.8) *[incl 35-69]*	I: 58% M C: 61% M	NRS (0-10) ?	·	·	·
Gonzales et al. (2010) [105]	n.a.	I: 35.9 (15.1) C: 33.3 (10.8) *[18 -71]*	I: 59% M C: 59% M	VAS (100mm)	·	·	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Jacobson (2006) [142]	n.a.	55 (16) [b] *[18-93]*	I: 22% M C: 33% M	NRS (0-10)	· music · kaleidoscope · choice between the 3 interventions	·	·
Kwekkeboom et al. (2008) [174]	n.a.	48.9 (16.3) *[18-75]*	45% M	NRS (0-10)	· progressive muscle relaxation	·	·
Wells et al. (1989) [313]	n.a.	25 *[16-35]* [b]	0% M	graphic rating scale (10cm)	· relaxation, pleasant imagery	·	·

Note. [a] Sample characteristics are reported for the experimental and control conditions together, unless otherwise indicated, I = intervention condition, C = control condition, Incl = inclusion criteria age; [b] Sample characteristics of the full sample, which also included other conditions/groups that were not included in the meta-analysis; [c] Characteristics of the sample excluding drop outs, data also available for drop outs (very similar); [d] NRS = numerical rating scale, VAS = visual analogue scale, M-VAS = mechanical visual analogue scale; [e] The data from additional groups and measures were not analyzed in the meta-analysis since they did not fit within the scope of the review.

CHAPTER 4

INDUCING EXPECTATIONS FOR HEALTH: EFFECTS OF VERBAL SUGGESTION AND IMAGERY ON PAIN, ITCH, AND FATIGUE AS INDICATORS OF PHYSICAL SENSITIVITY

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Abstract

Research into placebo effects has convincingly shown that inducing positive outcome expectations can reduce pain and other physical sensations. However, the comparative effects of different expectation inductions, such as verbal suggestion or mental imagery, and their generic effects on physical sensitivity, to different sensations such as pain, itch, and fatigue, are still largely unknown. In the current study, we assessed the individual and combined effects of verbal suggestion and imagery on pain, itch, and fatigue as indicators of physical sensitivity in a randomized study design. Healthy participants (n = 116) were given an inert (placebo) capsule that was said to be effective for reducing physical sensitivity in either the majority (positive verbal suggestion) or the minority (control verbal suggestion) of users. Subsequently, they imagined either their best possible health (positive imagery) or a typical day (control imagery). Sensitivity to pain, itch, and fatigue was tested using a cold pressor test, histamine iontophoresis, and a bicycle test, respectively. Heart rate and skin conductance were recorded continuously. Results showed that positive verbal suggestion and imagery successfully induced positive expectations, but they did not affect physical sensitivity, as indicated by sensitivity to pain, itch, or fatigue, or concurrent physiological responses. These results could indicate that the specificity and concreteness of expectation inductions might be important for their applicability in the treatment of physical symptoms.

Introduction

Patients' expectations are important predictors of the outcome of treatment for medical conditions such as chronic pain [206,240]. Particularly research into the mechanisms of placebo effects has convincingly shown the influence of expectations on physical sensations [159,236,298]. Inducing positive expectations, for example via verbal suggestion or mental imagery, could thus possibly enhance the effectiveness of treatments, such as analgesic interventions.

Verbal suggestion, i.e., instructional learning, is often used in placebo research, and there is a substantial body of research showing that inducing positive expectations via verbal suggestion (e.g., saying that an inert substance is a strong painkiller) can elicit pain relief, although the effects vary across studies [27,52,166,168,190,248,262,299,300]. Alternatively, imagery, i.e., the formation of mental images, has been investigated as a technique to induce positive expectations. In comparison to verbal suggestion, imagery of a future event or desired outcome involves a relatively implicit suggestion, at a visual rather than verbal cognitive level. Additionally, imagery involves a more active experience and is often associated with a larger impact on emotions [116,133]. An example is best possible self (BPS) imagery, during which one imagines one's best possible future self (e.g., when one has an optimal private and work life) [157]. BPS imagery has been found to increase general positive expectations (i.e., optimism) [202,224] and to reduce pain and medical care utilization [119,157], although the results are not always consistent [40]. Thus, there is some evidence that positive expectations induced via verbal suggestion or imagery can reduce pain. However, the comparative effects of verbal suggestion and imagery, each addressing expectations at different cognitive levels (i.e., verbal and visual), are still largely unknown. Furthermore, there is a lack of information about the generic effects of these expectation inductions on physical sensitivity. For example, it is largely unknown whether the expectation inductions can affect other sensations, such as itch and fatigue, which are similarly prevalent and debilitating sensations that frequently co-occur with pain and that are associated with partially overlapping mechanisms [23,41,54,173,185,199,279,305]. There are only some preliminary indications that verbal suggestion can reduce itch [20,295], and the few studies that assessed the effects of verbal suggestion on fatigue, all in the context of sports performance, yielded equivocal results [47,79,229]. The effects of future-oriented imagery on itch and fatigue have, to our knowledge, not yet been studied systematically.

The primary aim of the current study was to investigate the individual and combined effects of positive expectation inductions, specifically verbal suggestion and imagery, on physical sensitivity, as indicated by sensitivity to pain, itch, and fatigue, in a

healthy sample. It was hypothesized that both positive verbal suggestion (that a placebo capsule would reduce physical sensitivity) and imagery (of ones best possible health) would reduce physical sensitivity compared with control verbal suggestion and imagery. In addition, we explored whether the combination of both verbal suggestion and the imagery exercise would result in lower physical sensitivity than each manipulation individually. A secondary aim was to explore the effects of the expectation inductions on corresponding physiological responses (i.e., heart rate and skin conductance), as indicators of activity of the autonomic nervous system, since previous research has found pain to be associated with corresponding heart rate and skin conductance responses [186,230,285]. A further secondary aim was to explore the effects on and the possible moderating roles of psychological characteristics, based on previous research indicating that expectation inductions might influence not only expectations, but also, for example, affect and that e.g., optimism can moderate the effects of the expectation inductions [100,135,159,226].

Method

Ethics statement

The protocol was approved by the local Medical Ethics Committee (CMO Regio Arnhem-Nijmegen) and the study followed the rules stated in the Declaration of Helsinki. The study was registered at the Nederlands Trial Register (registration code: NTR3641). All participants gave written informed consent.

Participants

The sample consisted of 116 healthy participants. Exclusion criteria were severe physical or psychological morbidity (e.g., heart disease or DSM-IV psychiatric disorders), chronic (≥ 6 months) pain, itch, or fatigue currently or in the past, Raynaud's disease, instable asthma or allergic rhinitis, inadequate health for physical exercise, use of pacemaker or medications that influence heart rate, and pregnancy. Participants were aged 18-27 years (M = 21.8, SD = 2.1). Eighty-five percent of the participants were students, 71% were women (of whom 70% used hormonal contraceptives), and 39% had a partner (of whom 29% lived with their partner). All participants could speak and write Dutch fluently. At the beginning of the test session, participants reported low baseline pain, itch, and fatigue levels (M = 0.1, SD = 0.4; M = 0.3, SD = 0.6; M = 0.6, SD = 0.9 on scales from 0 to 10, respectively). These participant characteristics did not differ between the conditions (see section *Expectation inductions* for the conditions), except

that participants in the positive imagery conditions were significantly older than participants in the control imagery conditions (Δ = 0.9 years).

General procedure

Potential participants were informed that the study assessed the effects of a new substance and an imagery exercise on the sensitivity to physical sensations. After registration, potential participants filled out several online screening and psychological characteristics questionnaires. If they were eligible for inclusion, they were invited to the laboratory. Participants were asked to refrain from using painkillers, sleep-inducing medication, alcohol or other drugs, and heavy physical exercise in the 24 hours prior to the test session as not to bias the primary outcome measures, and not to consume caffeine-containing drinks or a heavy meal, or to smoke in the hour prior to the test session, in view of the physiological measures [125,162]. Recruitment and testing took place between December 2012 and October 2013 at the Department of Medical Psychology of the Radboud university medical center, Nijmegen, the Netherlands. The full procedure per participant was done by one of three female experimenters at a standard time (start at 9 am, duration 3 hours). On the test day, all participants gave their written informed consent. Subsequently, baseline pain, itch, and fatigue were assessed, and psychological questionnaires and physiological measures were administered. Then expectations were induced according to a 2 (positive vs. control verbal suggestion) x 2 (positive vs. control imagery) factorial design. Participants were randomly allocated to one of the four conditions (which differed only in the way expectations were induced) according to a randomization sequence that was generated by an independent researcher with an online random number generator (www.randomization.com; stratified by sex with a 1:1:1:1 allocation using block sizes of 4 and 8). Allocation was concealed from the experimenter in sequentially numbered, opaque, sealed envelopes until after the baseline assessments. Participants were unaware of randomization or differences between conditions during the experiment. Participants received either positive or control verbal suggestion along with a placebo capsule, after which the positive or control imagery exercise was carried out. Afterwards, psychological questionnaires were re-administered. Subsequently, physical sensitivity, specifically sensitivity to induced pain, itch, and fatigue was assessed, with a cold pressor test, histamine iontophoresis, and a bicycle test, respectively, in randomized order. Before each test, resting measurements were recorded (1 min) and participants were briefly reminded about the induced expectations. Between tests, there was a 10-minute break. The session was concluded with several questions regarding imagery quality and an oral debriefing by the experimenter. All participants

completed the study. Participants were compensated with gift vouchers or participant credits (students of Psychology and of Education and Child Studies are required to earn credits through participation in research).

Expectation inductions

The expectation inductions were tested in four conditions: 1) *Verbal suggestion condition* (*n* = 30, positive verbal suggestion and control imagery); 2) *Imagery condition* (*n* = 29, control verbal suggestion and positive imagery); 3) *Combination condition* (*n* = 28, positive verbal suggestion and positive imagery); and 4) *Control condition* (*n* = 29, control verbal suggestion and control imagery).

Verbal suggestion. All participants were told that they would receive a new substance (labeled as 'AKF nr 1898') that had been developed to reduce sensitivity to physical sensations (such as pain, itch, and fatigue) through its effect on processes in the central nervous system. It was explained that we were studying the working mechanisms to gain a better understanding of the effects of the drug on pain, itch, and fatigue. Participants were told that the drug would take effect after 20 minutes and that the effect would last for at least 2 hours. Additionally, to improve credibility, they were told that there was a small chance that they would experience side effects (e.g., headache). The condition-specific verbal suggestion, based on our previous research on verbal suggestion effects on pain and itch [295], then followed. The positive verbal suggestion stated: "Recent research has shown that this substance is effective in 95% of users. Most people become less sensitive to physical sensations after taking this substance". The control verbal suggestion stated: "Recent studies have shown that this substance is effective in only 5% of users. Only some people become less sensitive to physical sensations after taking this substance". Along with the verbal suggestion, all participants ingested an inert red gelatin capsule (6 x 17 mm) containing microcrystalline cellulose (manufactured by the Department of Clinical Pharmacy, Radboud university medical center). Before each of the physical sensitivity tests, the verbal suggestion ("effective in 95% / 5% of users") was briefly repeated.

Imagery. For positive imagery, participants were asked to imagine their best possible health, i.e., they imagined themselves in a future when they would be optimally fit and healthy, full of energy, and not limited by physical problems. They imagined what this would feel like during, for example, physical exercise or work. This exercise is an adjusted version of the best possible self-imagery exercise [157,224]. For control imagery, participants were asked to imagine the details of a typical day, for example how they start the day and common work or school activities [224,269]. All participants were asked to imagine their best possible health or typical day as detailed and as vividly as possible.

To make sure that participants understood the exercise, they were asked to briefly describe the images that first came to mind and feedback was provided when required. Participants then wrote about their best possible health or typical day (15 min), after which they mentally imagined it (5 minutes). During both writing and imagery, the experimenter was in an adjacent room, where she could observe participants unobtrusively. Before each of the physical sensitivity tests, participants briefly (1 min) imagined their best possible health or typical day again.

Manipulation checks. To check whether positive verbal suggestion indeed induced positive expectations, the participants indicated, before taking the capsule, how effective they thought the capsule would be on a numerical rating scale (NRS) ranging from 0.0 (*not effective at all*) to 10.0 (*very effective*). To check whether positive imagery indeed induced positive expectations, positive and negative general expectations were assessed with the questionnaire for Future Expectations (FEX [119]; an adaptation of the Subjective Probability Task [193]). The FEX consists of 10 positive and 10 negative statements referring to future outcomes, e.g., 'you will be very fit and healthy'. Participants judged the likelihood of each statement on a scale from 1 (*not likely at all*) to 7 (*extremely likely*). Cronbach's alpha ranged from 0.82 to 0.86 for the positive scale and from 0.85 to 0.86 for the negative scale in this study. To check imagery quality, participants rated the valence of their image on a visual analogue scale (VAS) ranging from 0 (*very negative*) to 10 (*very positive*), and they rated how well they could concentrate on and visualize these images during writing and imagery, on VASs ranging from 0 (*not at all*) to 10 (*very well*).

Primary outcome: Physical sensitivity

To assess physical sensitivity, moderate pain, itch, and fatigue were induced using a cold pressor test, histamine iontophoresis, and a bicycle test, respectively, in random order. Participants reported the experienced intensity of the sensations on a NRS ranging from 0.0 (*no pain/itch/fatigue at all*) to 10.0 (*worst pain/itch/fatigue ever experienced*). If participants rated the intensity above 0, they also rated the unpleasantness of the sensation on a NRS ranging from 0 (*not unpleasant at all*) to 10 (*very unpleasant*). The same NRSs were used to assess pain, itch, and fatigue at baseline and prior to each test, and to assess average induced pain, itch, and fatigue at the end of each test, and every 30 seconds for 4 minutes after each test.

Cold pressor test. Pain was induced with a cold pressor test [119,292]. Participants were instructed to place their dominant hand up to the wrist in a Styrofoam tank (2.7 liter) with cold water at 4°C (M = 4.0, SD = 0.1) for 1 minute. Participants were not aware of the duration of the test, but were instructed to keep their hand in the water until the

experimenter gave a signal. Participants rated pain intensity and unpleasantness on the NRSs every 15 seconds during immersion.

Histamine iontophoresis. Itch was induced with a histamine iontophoresis procedure [292]. Histamine dihydrochloride (0.5%) was dissolved in a gel of methylcellulose and propylene glycol in distilled water (manufactured by the department of Clinical Pharmacy, Radboud university medical center) and 2.5 ml was placed in a disposable iontophoresis electrode (IOGEL medium, Chattanooga, Hixson, TN, USA), which was placed on the non-dominant forearm, 2 cm distal to the lateral epicondyle of the humerus. The reference electrode was applied to the skin on the lateral side of the triceps brachial muscle. The histamine solution was delivered with a dose controller (Chattanooga ionto, Chattanooga Group, Hixson, TN, USA) for 2.5 minutes at a current level of 0.4 mA. Participants rated itch intensity and unpleasantness on the NRSs every 30 seconds during histamine application.

Bicycle test. Fatigue was induced with a submaximal bicycle test, which was based on the Åstrand bicycle test [12,124,214,272] and validated in a pilot study (n = 10; 50% female; age M = 27.2, SD = 4.4; NRS fatigue intensity during test phase M = 6.6, SD = 1.1, min = 5.0, max = 8.5; heart rate M = 153.5, SD = 6.3). Participants cycled on an exercise ergometer (Optibike Med, Ergoline, Bitz, Germany) for 10 minutes at 60-80 revolutions per minute at an individualized target heart rate. The individualized target heart rate was calculated by using the Karvonen formula: intensity x heart rate reserve + resting heart rate [153,316]. More specifically, the intensity was set within a range of 60% to 70% of the heart rate reserve, which equals the estimated maximal heart rate (220 – age) minus the resting heart rate (determined during the last minute of a 5-min resting measurement at the beginning of the testing session). The first 6 minutes of the test were used to determine the workload (watts) required to reach the target heart rate (the preparation phase). Participants continued cycling at their target heart rate (M = 152.4, SD = 6.1) for 4 minutes (the test phase). They rated fatigue intensity and unpleasantness on the NRSs every 60 seconds during the preparation phase and every 30 seconds during the test phase.

Secondary outcome: Physiological responses

Heart rate and skin conductance were measured continuously using a MP150 system and AcqKnowledge software, version 4.2.0 (BIOPAC Systems Inc., Goleta, CA, USA). For heart rate (HR) measurements, after abrading the skin (Nuprep, Weaver and Company, Aurora, CO, USA), a disposable electrode (Ø 38 mm; Kendall 200 Foam Electrode, Covidien, Mansfield, MA, USA) was placed on the sternum and another a few centimeters below the lower rib on the left side. The electrocardiography (ECG) signals

were recorded with an ECG100C amplifier at 1000 Hz with a gain of 1000, a 0.5-Hz high pass filter, a 35-Hz low pass filter, and a 50-Hz notch filter. For skin conductance (SC) measurements, after cleaning the skin with water, two disposable Ag/AgCl electrodes (Ø 32 mm; DBF3D77, Multi Bio Sensors Inc., El Paso, TX, USA) were placed on the medial phalanges of the index and middle finger of the non-dominant hand. Skin conductance was recorded with a GSR100C amplifier at 1000 Hz with a gain of 10 µmho/V and a 1.0-Hz low pass filter. Visual inspection of the ECG and SC data, HR calculation, and calculation of the mean HR and SC levels during baseline and the pain, itch, and fatigue tests was conducted in MATLAB (version R2012b, the MathWorks, Inc., Natick, Ma, USA).

Additional salivary data to assess the effects of the expectation inductions on cortisol and alpha-amylase were collected (prior to and after the expectation inductions and after the physical sensitivity tests), as well as salivary data to assess the possible influence of genotypes, such as the 5-HTTLPR genotype, but these data were not analyzed in view of the non-significant results of the primary and other secondary analyses.

Secondary outcome: Psychological characteristics

Prior to and after the expectation inductions, the following questionnaires were administered to assess the effects of the expectation inductions on psychological characteristics and their possible moderating role in the effects of the expectation inductions on physical sensitivity. A short version of the Positive and Negative Affect Schedule (PANAS) [155,223] was used to measure positive and negative affect. Cronbach's alpha ranged from 0.73 to 0.75 for positive affect and from 0.67 to 0.72 for negative affect in this study. A short version of the State-Trait Anxiety Inventory, State version (STAI-S) [196,290] was used to measure state anxiety. Cronbach's alpha ranged from 0.67 to 0.68 in this study. The revised Life Orientation Test (LOT-R) [224,258] was used to measure dispositional optimism. Cronbach's alpha ranged from 0.72 to 0.74 in this study.

Additional questionnaires were administered, along with the online screening questionnaires, to assess the possible moderating role of psychological characteristics in the effects of the expectation inductions on physical sensitivity: Eysenck Personality Questionnaire, Revised Neuroticism and Extraversion subscales [253]; Hospital Anxiety and Depression Scale [324]; Beliefs about Medication Questionnaire [137]; Sheehan–Betts Quality of Mental Imagery Scale [268]; Pain Catastrophizing Scale, adjusted for physical sensations [282]; Body Vigilance Scale [263]; Pain Vigilance and Awareness Questionnaire, adjusted for physical sensations [200]; International Physical Activity Questionnaire [64].

Statistical analyses

The required sample size for the primary analyses was calculated in G*power 3.1 [88], for a 2 x 2 factorial ANOVA testing main and interaction effects, with desired power = .80 and α = .05. The expected effect sizes were based on the average effect size found in a meta-analysis on the effects of verbal suggestion on placebo analgesia (*d* = 0.85, for main effect of verbal suggestion) [299] and the available research on the effects of best possible health imagery on pain during cold pressor immersion (*d* = 0.56, for main effect of imagery) [119]. The largest required sample size (*n* = 104) was used and increased with 10% in case of missing data due to, e.g., technical problems (total *n* = 116).

Prior to analyses, missing NRS intensity and unpleasantness scores, due to participants prematurely ending the pain test (*n* = 3, of whom 1 in the *Combination condition,* and 2 in the *Control condition*) or fatigue test (*n* = 3, of whom 2 in the *Imagery condition* and 1 in the *Control condition*), were replaced using the last observation carried forward method. Of one participant in the *Verbal suggestion condition* all pain scores were missing due to prematurely ending the test. Missing data was equally distributed across conditions and no participant dropped out of more than one test. Full HR and SC data were missing for one participant and SC data was missing for one additional participant during the bicycle test, due to technical problems. Using IBM SPSS Statistics version 21 for Windows (IBM Corporation, Armonk, NY, USA), data were analyzed with analyses of (co)variance (AN(C)OVAs), with baseline variables as covariate when available, and a two-tailed significance level of α = .05. In case the assumptions of the statistical tests (e.g., of normality) were violated, the data were transformed or otherwise non-parametric tests were used if feasible (indicated in description of specific analyses if applicable). The effects on PANAS negative affect scores were not analyzed due to strong floor effects (post-intervention, 81% of participants reported the minimum negative affect score). If significant between-group differences in sex (chi-square test), age (2 x 2 ANOVA), NRS baseline pain, itch, or fatigue levels (Kruskal-Wallis tests), or baseline FEX, PANAS, STAI-S, or LOT-R scores (2 x 2 ANOVAs) were found, and if the respective variable significantly correlated with the primary outcome measure, sensitivity analyses were conducted for the primary analyses with the variable(s) as covariate(s).

The manipulation check for verbal suggestion was conducted with univariate ANOVAs with verbal suggestion (VS) as independent variable and the NRS score for expected effectiveness of the capsule as dependent variable. The manipulation check for imagery was conducted with univariate AN(C)OVAs with imagery (Imag) as independent variable, FEX positive and negative scores, and the imagery quality questions (writing and imagery scores taken together) as dependent variables, and the

available baseline scores of the respective measures as covariates (only available for the FEX positive and negative scores).

To test the primary hypotheses, a composite intensity score, as a measure of physical sensitivity, was calculated (thereby also controlling for multiplicity [140,286]) by summing the standardized mean NRS intensity scores for all pain ratings during the cold pressor test (assessed at 0:15, 0:30, 0:45, and 1:00 min during immersion in the cold water), all itch ratings during histamine iontophoresis (assessed at 0:30, 1:00, 1:30, 2:00, and 2:30 min during histamine application), and all fatigue ratings during the bicycle test (assessed at 0:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30 and 4:00 min during the test phase). A 2 (VS) x 2 (Imag) ANOVA with the composite intensity score as dependent variable was used. The main effects were examined to assess the individual effects of verbal suggestion and imagery on physical sensitivity. The interaction effect was examined to explore whether the combination of both expectation inductions was more effective than either expectation induction alone. The same analyses were performed for a composite unpleasantness score. Additionally, in order to enhance the comprehension of the results for the composite scores, ANOVAs were performed to investigate the effects of the expectation inductions on the NRS scores for pain, itch, and fatigue separately. Post hoc sensitivity analyses were performed to assess the possible influence of the method of missing data handling, order effects, and including baseline pain, itch, and fatigue levels on the primary analyses.

Secondary, the effects of the expectation inductions on heart rate and skin conductance were explored with 2 (VS) x 2 (Imag) ANCOVAs, with as dependent variables mean heart rate and mean log transformed skin conductance during the pain, itch, and fatigue tests, and with as covariates the baseline scores for the respective physiological measure. Since heart rate was tailored during the fatigue test, heart rate during this test was not included as dependent variable. Exploratively, Pearson correlations between the NRS intensity scores for pain, itch, and fatigue and mean HR and SC during the corresponding tests were calculated. The effects of the expectation inductions on the psychological variables were explored with 2 (VS) x 2 (Imag) ANCOVAs, with PANAS-PA, STAI-S, and LOT-R as dependent variables and the baseline scores of the respective measures as covariates. The possible moderating influence of psychological characteristics (e.g., neuroticism, imagery ability) on the effects of the expectation inductions on physical sensitivity was explored via separate regression analyses for each psychological characteristic. Predictors in each analysis were the interactions of the psychological characteristic with the expectation inductions, after having controlled for the separate contribution of the psychological characteristic and expectation inductions.

Results

Manipulation checks

Participants expected the capsule to be more effective after the positive verbal suggestion than after the control verbal suggestion, as indicated by a univariate ANOVA (M = 6.4, SD = 1.9 and M = 2.8, SD = 1.7, respectively, $F(1, 114) = 119.66$, $p < 0.001$, $\eta_p^2 = 0.51$). Participants reported more positive and less negative general expectations on the FEX after positive imagery than after control imagery, as indicated by univariate ANCOVAs (positive expectations: M = 56.3, SD = 5.7 and M = 54.8, SD = 6.2, respectively, $F(1, 113) = 5.88$, $p = .02$, $\eta_p^2 = 0.05$; negative expectations: M = 26.7, SD = 7.8 and M = 30.1, SD = 9.0, respectively, $F(1, 113) = 5.91$, $p = .02$, $\eta_p^2 = 0.05$). The positive image of a best possible health was rated as more positive than the control image of a typical day, as indicated by a Mann-Whitney test (M = 8.8, SD = 1.2 and M = 7.6, SD = 1.7, respectively, U = 978.00, z = -3.89, $p < .001$, r = -.37). Participants could concentrate equally well on the different images (M = 6.8, SD = 1.5 and M = 7.2, SD = 1.6, respectively, $F(1, 114) = 2.28$, $p = .13$, $\eta_p^2 = 0.02$), but they could visualize the positive image less well than the control image (M = 6.8, SD = 1.7 and M = 7.9, SD = 1.5, respectively, $F(1, 114) = 12.60$, $p = .001$, $\eta_p^2 = 0.10$).

Primary outcome: Physical sensitivity

Intensity scores. Figure 4.1 and Table 4.1 display the NRS intensity scores for pain, itch, and fatigue during the respective tests. The composite intensity score (i.e., the standardized sum score of mean pain, itch, and fatigue intensity during the respective tests indicating physical sensitivity) was not affected by verbal suggestion, imagery, or the combination of both, as indicated by a 2 x 2 ANOVA ($F(1, 112) = 0.03$, $p = .87$, $\eta_p^2 < 0.01$; $F(1, 112) = 0.49$, $p = .49$, $\eta_p^2 < 0.01$; $F(1, 112) = 1.94$, $p = .17$, $\eta_p^2 = 0.02$, respectively). Age was the only variable that differed significantly between the conditions and that was associated with the composite intensity score, but including age as a covariate did not affect the results.

Exploratory ANOVAs for the separate physical sensitivity tests, conducted to enhance the comprehension of the results for the composite intensity score, indicated that verbal suggestion and imagery did not affect pain, itch, or fatigue (all $p > .05$). There was an interaction effect on itch ($F(1, 112) = 4.57$, $p = .04$, $\eta_p^2 = 0.04$), participants in the *Combination condition* reported less itch than participants in the *Verbal suggestion condition* ($F(1, 56) = 5.71$, $p = .02$, $\eta_p^2 = 0.09$), but there were no interaction effects on pain and fatigue (all $p > .05$).

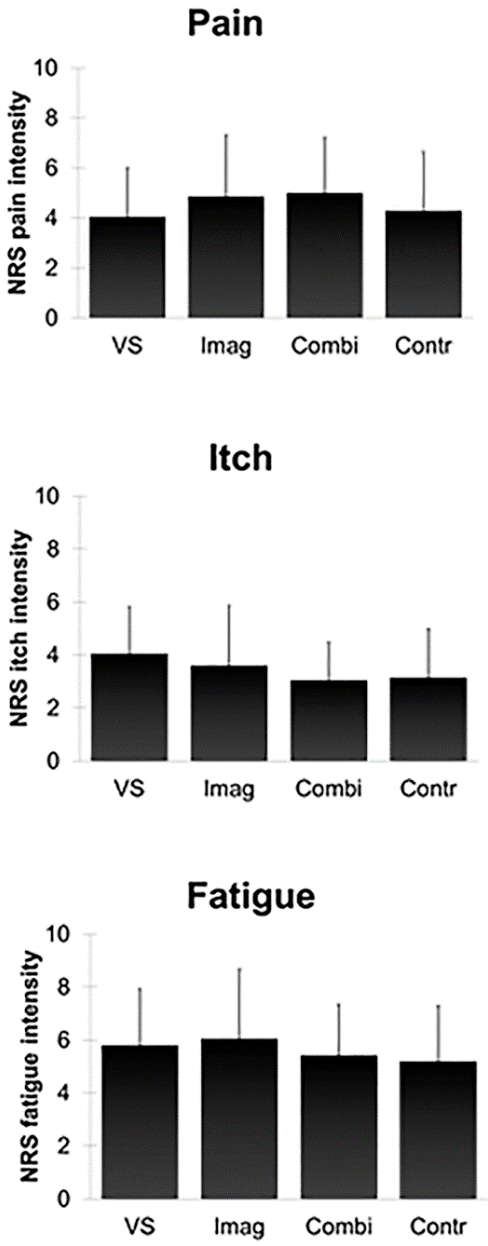

Figure 4.1. Means and standard deviations of NRS intensity scores for pain, itch, and fatigue during the respective tests

Note. VS = Verbal suggestion condition; Imag = Imagery condition; Combi = Combination condition; Contr = Control condition. Error bars represent standard deviations.

Table 4.1. Means and standard deviations of NRS intensity and unpleasantness scores of pain, itch, and fatigue during the respective tests

Condition / Sensation	Verbal suggestion (*n* = 30)	Imagery (*n* = 29)	Combination (*n* = 28)	Control (*n* = 29)
Pain intensity	4.1 ± 1.9	4.9 ± 2.4	5.0 ± 2.2	4.3 ± 2.4
Itch intensity	4.1 ± 1.8	3.6 ± 2.3	3.0 ± 1.4	3.1 ± 1.8
Fatigue intensity	5.8 ± 2.1	6.1 ± 2.6	5.4 ± 1.9	5.2 ± 2.1
Pain unpleasantness	4.6 ± 2.3	5.3 ± 2.8	5.7 ± 2.4	4.8 ± 2.7
Itch unpleasantness	3.3 ± 2.0	3.2 ± 2.5	2.8 ± 1.7	2.6 ± 1.7
Fatigue unpleasantness	4.1 ± 2.5	3.9 ± 3.1	3.6 ± 2.3	3.8 ± 2.5

Post hoc sensitivity analyses indicated that other methods of handling missing data (i.e., not replacing the values, excluding all data from participants with missing values, or replacing missing values with the last observation heightened with the group difference between the missing and preceding value) yielded comparable results. Further post hoc sensitivity analyses provided no evidence of order or time effects: 1) frequency analyses showed that the majority of participants reported no or hardly any remaining or spontaneous pain, itch, or fatigue prior to a subsequent test (≥ 95% NRS scores ≤ 2); 2) univariate repeated measures ANOVAs indicated that pain, itch, and fatigue intensities prior to each test did not significantly differ from or where lower than baseline levels; 3) separate 2 x 2 ANOVAs regarding pain, itch, or fatigue during only the first, second, or third test yielded the same conclusions as the primary analyses; and 4) including the order of the physical sensitivity tests as a covariate did not affect the results. Furthermore, post hoc sensitivity analyses showed that including baseline pain, itch, and fatigue levels as covariates did also not affect the results.

To determine whether the null results should be interpreted as evidence for the absence of an effect of the expectation inductions, we reanalyzed our data within a Bayesian framework [68, 69]. We calculated the Bayes factor (BF_{A0}) using the JASP software package, in which default priors are used (the null hypothesis is compared to the alternative hypothesis that the effects may occur in either direction) [70-72]. A BF_{A0} smaller than 0.33 is commonly considered to indicate substantial evidence for the null hypothesis, a BF_{A0} larger than 3 is considered to indicate evidence for the alternative hypothesis, whereas a Bayes factor between 0.33 and 3 indicates merely anecdotal or inconclusive evidence for either hypothesis [68,69]. The Bayes factors for the effects of verbal suggestion and imagery on physical sensitivity (BF_{A0} = 0.20 and BF_{A0} = 0.24,

respectively) indicated that there was substantial evidence for the absence of an effect of the expectation inductions on physical sensitivity.

Unpleasantness scores. Table 4.1 displays the NRS unpleasantness scores for pain, itch, and fatigue during the respective tests. The composite unpleasantness score (i.e., the standardized sum score of mean pain, itch, and fatigue unpleasantness during the respective tests) was also not affected by verbal suggestion, imagery, or the combination of both, as indicated by a 2 x 2 ANOVA ($F(1, 112) = 0.10$, $p = .75$, $\eta_p^2 < 0.01$; $F(1, 112) = 0.47$, $p = .50$, $\eta_p^2 < 0.01$; $F(1, 112) = 0.49$, $p = .49$, $\eta_p^2 < 0.01$, respectively). Exploratory ANOVAs for the separate physical sensitivity tests indicated that verbal suggestion, imagery, or the combination of both did not affect pain, itch, or fatigue unpleasantness (all $p > .05$).

Secondary outcome: Physiological responses

Table 4.2 displays heart rate and skin conductance at baseline and during the pain, itch, and fatigue tests. Heart rate during the pain and itch tests was not affected by verbal suggestion, imagery, or the combination of both, as indicated by 2 x 2 ANCOVAs (all $p > .05$). The results were similar after exclusion of the data of three participants with irregular heartbeats (detected during visual inspection of the ECG signals). Skin conductance during the pain, itch, and fatigue tests was also not affected by verbal suggestion, imagery, or the combination, as indicated by 2 x 2 ANCOVAs (all $p > .05$). The

Table 4.2. Means and standard deviations of heart rate and skin conductance at baseline and during the pain, itch, and fatigue tests

Condition / Sensation	Verbal suggestion (n = 30)	Imagery (n = 29)	Combination (n = 28)	Control (n = 29)
Heart rate [a,b]				
Baseline	70.5 ± 10.6	67.5 ± 9.6	67.2 ± 9.2	67.8 ± 9.1
Pain test	72.5 ± 10.8	71.9 ± 11.5	69.6 ± 11.2	72.6 ± 11.7
Itch test	68.6 ± 10.1	67.1 ± 11.3	65.6 ± 9.8	68.6 ± 11.5
Skin conductance				
Baseline	1.9 ± 1.8	2.0 ± 2.1	2.0 ± 1.3	2.9 ± 3.2
Pain test	5.6 ± 3.6	5.7 ± 3.2	6.0 ± 2.9	7.3 ± 6.0
Itch test	5.4 ± 3.3	5.1 ± 2.9	5.6 ± 2.7	7.2 ± 5.4
Fatigue test	6.2 ± 3.3	5.6 ± 2.6 [c]	6.2 ± 2.0	7.8 ± 5.6

Note. [a] Heart rate during the fatigue test is not reported here because it was tailored during this test; [b] Full heart rate data missing for 1 participant due to technical problems (*Imagery condition*); [c] Skin conductance data fatigue test missing for 1 participant due to technical problems (*Imagery condition*).

results were similar after the exclusion of the data of one participant who had a very high skin conductance (z > 3.29). Non-significant Pearson correlation coefficients were found between the NRS intensity scores for pain, itch, and fatigue during the respective tests and concurrent heart rate and skin conductance (all p > .05).

Secondary outcome: Psychological characteristics

Positive affect (PANAS PA) and optimism (LOT-R) were not influenced by verbal suggestion, imagery, or their combination, as indicated by 2 x 2 ANCOVAs (all p > .05). Participants only reported less anxiety (STAI-S) after control imagery than after positive imagery (M = 25.7, SD = 5.5 and M = 27.0, SD = 6.7, respectively, F(1, 111) = 4.38, p = .04, η_p^2 = 0.04), but anxiety was not influenced by verbal suggestion or the combination (all p > .05).

None of the psychological characteristics (e.g., neuroticism, imagery ability) moderated the effects of the expectation inductions on physical sensitivity, as indicated by non-significant beta-coefficients for all interactions of the psychological characteristics with verbal suggestion, imagery, or verbal suggestion x imagery (all p > .05).

Discussion

The current study investigated, for the first time, the individual and combined effects of positive verbal suggestion and imagery on physical sensitivity, as indicated by sensitivity to pain, itch, and fatigue. Although both positive verbal suggestion and imagery induced positive expectations, these expectation inductions did not affect physical sensitivity (neither pain, nor itch, nor fatigue), or concurrently measured heart rate and skin conductance.

The finding that the verbal suggestion of reduced physical sensitivity due to a (placebo) capsule did not affect physical sensitivity is in contrast with a substantial body of research that showed that verbal suggestion of the effects of a placebo treatment can effectively reduce pain [27,52,166,262,299]. Other research has also provided preliminary indications that verbal suggestion can reduce itch and fatigue [20,47,79,295]. However, there are several other studies that could also not confirm the effects of verbal suggestion on pain [248] and fatigue [229]. An important distinction between the current study and previous research is that in our study the verbal suggestion addressed physical sensitivity, encompassing multiple sensations simultaneously, whereas in the majority of other studies verbal suggestion addressed just one sensation. The current findings

might thus indicate that generic suggestions are less effective than specific suggestions, although this needs further research. Another important difference concerns the distinction between the experimental and control conditions. Generally, the suggestion that a drug is potent is contrasted with the suggestion that a drug is ineffective [52,79,166,229,248,262] or with no treatment [190], whereas we used a more subtle comparison, between effectiveness in the majority or minority of users. Even though participants expected the capsule to be more effective after positive verbal suggestion than after control verbal suggestion, with a large effect size, indicating that the verbal suggestions were distinguishable, these instructions did not affect sensitivity to physical sensations. However, a similar verbal suggestion regarding the relief of pain or itch for the majority of participants was effective in an earlier study by our group [295]. Thus, especially the specificity of suggestions might be an important predictor of their effectiveness. In future research, this can be further assessed by comparing, for example, instructions addressing physical sensitivity with instructions addressing a single sensation, either alone or in combination with another procedure.

Positive imagery generated more positive and less negative general expectations than control imagery of a typical day, with a small to moderate effect size, but it did not affect physical sensitivity. The original, more general, best possible self (BPS) imagery, however, has previously been found to reduce pain sensitivity and medical care utilization [119,157], although a more recent study using BPS imagery could not replicate the effects on pain [40]. Our adjustment of BPS imagery to enhance specificity and applicability to physical health might have resulted in imagery that was too abstract for participants, possibly because health is often conceptualized in negative terms (e.g., absence of symptoms). Indeed, the participants indicated that they could visualize their best possible health less well than a typical day. Additionally, we found that imagery of health did not increase positive affect, in contrast to BPS imagery [40,157,202,224], possibly because health is generally only considered when one does not feel healthy and health consequently has a somewhat negative, rather than just a positive, connotation. More specific and concrete images of a desired and positively valued outcome, e.g., imagining diminished pain when a painful hand is bathed in analgesic fluid, might be more effective [53,174]. In addition, it is important to note that participants were not told of the intended effects of the imagery exercise and thus might not have recognized the imagery exercise as an intervention. Although this design allowed us to assess the effects of imagery per se, combining imagery with information about the purpose of imagery (i.e., verbal suggestions) might be essential to its effectiveness. Indeed, neither psychological nor medical treatments are commonly provided without a treatment rationale.

The effectiveness of the combination of positive verbal suggestion and imagery was also explored in the present study. Such a combination is also found in hypnosis [108], which has been found to be able to reduce pain [76,207]. In addition, the combination of verbal suggestion with a more implicit learning procedure, conditioning, has often been found to have larger effects on physical sensitivity than either expectation induction alone [20,166,197]. Our negative finding might partially be explained by the degree of integration of the two expectation inductions; since we were also interested in their separate effects, the capsule and imagery exercise were presented as two different interventions in the current study. This procedure might have been insufficient to generate an additive effect and might even have reduced or counteracted the effects of each individual method. A more effective integration might be achieved by imagery of a suggested treatment outcome or by providing suggestions about the effectiveness of imagery itself.

Lastly, it is important to note a few limitations of this study. First, the assessment of the sensitivity to induced pain, itch, and fatigue in one study allowed us to assess the generic effects of expectation inductions on physical sensitivity, but it might have caused order or time effects. For example, it is known that pain can inhibit itch, that analgesia can induce itch [211,279,319], and that physical exercise can reduce pain [78,130]. However, such interactions are not likely to have affected the results because the physical sensitivity tests were presented in random order with standardized 14-minute intervals between tests [292,293,296]. Additionally, to prevent time effects, participants were reminded about the expectation inductions before each test. Sensitivity analyses provided no evidence of order or time effects: 1) participants' pain, itch, and fatigue were adequately diminished after the between tests intervals, 2) participants reported equally low or lower pain, itch, and fatigue prior to each of the tests as compared to baseline pain, itch, and fatigue levels, 3) analyses of pain, itch, or fatigue during only the first, second, or third test, yielded the same conclusions as the primary analyses, and 4) statistically controlling for order did not yield differential results for the primary analyses. Second, since we used a sample consisting of healthy participants who were relative young and mostly female, the generalizability of our findings to patients is limited. Third, due to the use of different measures to assess expectations, specifically a numerical rating scale for verbal suggestion and the questionnaire for Future Expectations for imagery, the effects of verbal suggestion and imagery on expectations cannot be directly compared. In future research comparable measures of expectations that are closely related to the contents of the intervention are recommended. Fourth, the possible moderating role of the psychological characteristics (e.g., neuroticism, imagery ability) could only be explored [85]. Future research with larger sample sizes is

required to further investigate which psychological characteristics predict the effectiveness of expectation inductions.

In conclusion, the results provide more insight into the essential characteristics of different expectation inductions for reducing physical sensitivity, such as sensitivity to pain, itch, and fatigue, although the limitations should be kept in mind. Our finding that relatively general verbal suggestions and imagery did not affect physical sensitivity, to neither pain, nor itch, nor fatigue, in contrast to previous research, suggests that the level of specificity and concreteness of expectation inductions might be crucial for the applicability of expectation inductions to the treatment of physical symptoms.

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Chapter 5

Placebo-like analgesia via response imagery

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Abstract

Background: Placebo effects on pain are reliably observed in the literature. A core mechanism of these effects is response expectancies. Response expectancies can be formed by instructions, prior experiences, and observation of others. Whether mental imagery of a response can also induce placebo-like expectancy effects on pain has not yet been studied systematically.

Methods: In Study 1, 80 healthy participants were randomly allocated to 1) response imagery or 2) control imagery. In Study 2, 135 healthy participants were randomly allocated to 1) response imagery with a verbal suggestion regarding its effectiveness, 2) response imagery only, or 3) no intervention. In both studies, expected and experienced pain during cold pressor tests were measured pre- and post-intervention, along with psychological and physiological measures.

Results: Participants rated pain as less intense after response imagery than after control imagery in Study 1 (p = .044, η_p^2 = .054) and as less intense after response imagery (with or without verbal suggestion) than after no imagery in Study 2 (p < .001, η_p^2 = .154). Adding a verbal suggestion did not affect pain (p = .068, η_p^2 = .038). The effects of response imagery on experienced pain were mediated by expected pain.

Conclusions: Thus, in line with research on placebo effects, the current findings indicate that response imagery can induce analgesia, via its effects on response expectancies.

Introduction

Placebo effects demonstrate the importance of expectancies in pain treatment. A rapidly accumulating body of research on the mechanisms of placebo effects indicates that merely expecting that a treatment will provide relief (i.e., response expectancies) can cause pain relief, regardless of the presence of active treatment ingredients [24,159,221]. The formation of response expectancies is generally understood to occur by instructions (including verbal suggestion), personal experiences (including conditioning processes), and observation of others (i.e., observational learning) [59,159]. Placebo-like expectancy effects (i.e., expectancy effects without administration of a placebo [24]) on pain can possibly also be induced via mental imagery, or simulation, of reduced pain. Mental imagery plays a crucial role in thinking about the past, present, and future, and patients with chronic pain commonly experience spontaneous pain-related mental images [34,201]. Importantly, imagery of sensations largely draws on the same physiological processes as the actual experience of these sensations [86,171,201], suggesting that imagery might have effects comparable to actual experiences. Evidence for the effects of imagery on expectations comes from research in which participants who were instructed to imagine an event gave a higher estimate of the likelihood of that event happening [48,109]. Furthermore, instructed imagery of a best possible future self or health can affect general expectations of future events [119,220,224]. Imagery exercises that include images of pain relief have frequently been studied and applied in both experimental and clinical settings and have been found to provide pain relief [22,74,86,174,221]. However, effects on pain are not unfailingly observed [66,115,142,313]. Moreover, inferences about the working mechanisms are limited due to the designs employed, e.g., imagery during pain, diverse and multifaceted imagery content, combination with verbal suggestion regarding intended effect, and lack of expectancy measures. Thus, although the literature suggests that response imagery of reduced pain may induce placebo-like expectancy effects on pain, systematic research is lacking.

We aimed to assess whether imagery of reduced pain (i.e., response imagery) could induce analgesia. In Study 1, response imagery was compared to control imagery. In Study 2, response imagery was compared to no intervention, and the effects of adding a verbal suggestion regarding the effectiveness of imagery were assessed. Cold pressor tests were used to assess pain pre- and post-intervention. Our primary hypothesis was that participants would experience less pain after response imagery than after control imagery or no intervention. Secondary, we hypothesized that a verbal suggestion would enhance these effects. Furthermore, we explored whether the effects would be mediated by expected pain. We also explored the possible moderating role of psychological characteristics, evaluations of the imagery intervention, and effects on

psychological and physiological responses, based on previous literature suggesting that these factors may also be involved [e.g., 91,100,256].

Study 1 - Methods

The primary aim of Study 1 was to assess the effects of response imagery on pain, as compared to control imagery.

Participants

In Study 1, 80 healthy adults participated (power analysis based on previous research [22,74,174]). Inclusion criteria were age between 18 and 30 years, and fluency in the Dutch language. See Supplementary Section 5.1 for specific health-related exclusion criteria.

Procedure

The study protocol was approved by the institute's ethics committee (Commissie Ethiek Psychologie). Testing took place from March to May 2014 at Leiden University, Leiden, the Netherlands. Participants were recruited via advertisements at and around the university. Potential participants were informed about the evocation of pain with a cold pressor test (CPT) and the use of cognitive tasks. Potential participants filled out screening, demographic, and psychological characteristics (optimism, neuroticism) questionnaires (online via Qualtrics, Provo, UT, US; approx. 10 min). Eligible participants were invited to the laboratory and asked to refrain from using medication, alcohol, or other drugs in the 24 hours prior to the test session, to awaken at least one hour before the test session, and not to smoke or consume caffeine-containing drinks or a meal in the hour preceding the session. Testing was done by two experimenters to enable blinding of the outcome assessor. At the beginning of the test session, experimenter A obtained written informed consent from all participants. Subsequently, experimenter A obtained the following pre-intervention measures consecutively: baseline and expected pain, psychological questionnaires (affect, state anxiety, general expectations), physiological measures (5-min resting for heart rate and skin conductance; saliva sample for cortisol and alpha-amylase), and experienced pain, heart rate, and skin conductance during the first CPT. Experimenter B then supervised the performance of undemanding filler tasks (e.g., Sudoku puzzles) and obtained two saliva samples (10 and 20 min after CPT). Next, experimenter B introduced the imagery exercise matching the condition to which participants had been randomly allocated (*Response imagery condition* or *Control*

imagery condition). For details about the randomization and blinding procedure, see Supplementary Section 5.2. Post-intervention, experimenter A obtained the following measures consecutively: expected pain, experienced pain, heart rate, and skin conductance during the second CPT, psychological questionnaires (affect, state-anxiety, general expectations), questions regarding imagery evaluation, and saliva samples (10 and 20 min after CPT). The test session was concluded with an oral debriefing. See Supplementary Figure 5.1 for a flow diagram. The total duration of the test session was 1.5 hours. All participants completed the study.

Intervention

Participants in the *Response imagery (Imag) condition* were guided in imagining reduced pain during the imagery exercise that took place prior to the second CPT. They were instructed to vividly imagine that they would experience no or hardly any pain when they would hold their dominant hand in the cold water during the second CPT. They were instructed to do so by imagining that they were wearing a glove, which was described as warm and impermeable to water, and as protecting against the pain one could experience from the cold water. To control for the effects of the content of imagery, participants in the *Control imagery (Contr) condition* merely imagined their hand, without any reference to pain or the cold water. They were instructed to vividly imagine their dominant hand by, for example, closely observing the fingers and palm of the hand and attending to the feeling of moving the hand. In both conditions, the imagery exercise was briefly introduced by the experimenter. Subsequently, audio-recordings of the detailed instructions were presented via a headphone, using E-prime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Participants in both conditions first wrote about their image (3 min), after which they mentally imagined it as vividly as possible (3 min), as in previous studies [119,224]. The total duration of the imagery exercise was approximately 12 minutes in both conditions. Participants did not receive instructions regarding imagery during the CPT.

Imagery evaluation

Participants rated how well they could visualize and concentrate on the image on a visual analogue scale (VAS) ranging from 0 (*not at all*) to 100 (*very well*). Participants rated the valence of their image on a VAS ranging from 0 (*very negative*) to 100 (*very positive*), and how much they thought about the image during the post-intervention CPT on a VAS ranging from 0 (*not at all*) to 100 (*very much*).

Cold pressor test

Pain was evoked with a cold pressor test (CPT) [220]. A Styrofoam tank was filled with noncirculating cold water of which the temperature was regulated and assessed directly prior to commencing the test (3.9 ± 0.1 °C). Participants immersed their dominant hand up to the wrist in the water and were instructed to hold their hand still and refrain from making a fist or touching the walls of the tank. Participants were unaware of the test duration and were instructed to keep their hand in the water until the experimenter gave a signal (after 1 minute). During immersion, participants rated pain intensity every 15 seconds. The mean pain rating was used for analyses.

Expected and experienced pain

Participants verbally rated expected and experienced pain intensity on a numerical rating scale ranging from 0.0 (*no pain at all*) to 10.0 (*worst pain ever experienced*).

Psychological characteristics

The revised Life Orientation Test (LOT-R) and the neuroticism scale of the revised short version of the Eysenck Personality Questionnaire (EPQ-RSS) were used to measure optimism and neuroticism, respectively. For details of the questionnaires see Appendix S5.3.

Psychological responses

A short version of the Positive and Negative Affect Schedule (PANAS-PA and PANAS-NA), a short version of the State-Trait Anxiety Inventory (STAI-S), and the questionnaire for Future Expectations (FEX) were used to measure positive and negative affect, state anxiety, and positive and negative general expectations for future events, respectively. The negative affect data (PANAS-NA) were not analyzed due to floor effects and low internal consistency. For details of the questionnaires see Appendix S5.3.

Physiological responses

Heart rate (HR) and skin conductance (SC) were measured continuously using a MP150 system and AcqKnowledge software, version 4.3.1 (BIOPAC Systems Inc., Goleta, CA, USA) according to standard procedures. Saliva samples were collected with cotton swabs (Salivette, Sarstedt, Nümbrecht, Germany) for assessments of cortisol and alpha-amylase. The samples were processed according to standard procedures. For more details see Appendix S5.4.

Statistical analyses

All data were analyzed using IBM SPSS Statistics version 21 (IBM Corporation, Armonk, NY, USA), with a two-tailed significance level of $\alpha = .05$. Descriptives are reported as means and standard deviations (*M* ± *SD*). The effects of response imagery on post-intervention experienced pain (primary outcome), expected pain, positive affect, state anxiety, general expectations, heart rate, skin conductance, cortisol, and alpha-amylase were analyzed with separate univariate analyses of covariance (ANCOVAs; determined *a priori*) [289]. Imagery was the independent variable (*Imag* vs. *Contr condition),* the post-intervention measures were dependent variables, and the corresponding pre-intervention measures and stratification variables (sex and time of day) were covariates. The possible mediating role of expected pain in the effect of response imagery on experienced pain was explored using an ordinary least squares regression approach. To determine mediation, bias-corrected 95% confidence intervals were calculated for the indirect effect using 1000 bootstrapping samples via the Process SPSS macro [126]. Mediation was confirmed if the confidence interval did not include zero [126]. The pre-intervention measures, and stratification variables were included as covariates in the mediation model. The possible moderating influence of trait optimism and neuroticism on the effects of imagery on experienced pain was explored via separate multiple regression analyses. Moderation was confirmed if the interaction of the psychological characteristic in question with the imagery conditions was significant in the regression model in which the psychological characteristic, imagery conditions, pre-intervention experienced pain, stratification variables, and the interaction were simultaneously entered as predictors of post-intervention experienced pain. Imagery evaluations were compared between conditions with separate univariate ANCOVAs, with the stratification variables as covariates. Means and standard deviations for all measures are reported in Supplementary Table 5.1.

Additional post hoc correlation analyses (associations of post-intervention experienced pain with post-intervention imagery evaluation, psychological responses, and physiological responses) and sensitivity analyses (in case of violation of the assumptions of statistical tests and doubts about inclusion) are described in Supplementary Section 5.5 and reported in Supplementary Section 5.6. In Supplementary Section 5.5 also detailed information on missing data is reported.

Study 1 - Results

Participants

Thirty-nine participants were allocated to the *Imag condition* (age 20.8 ± 2.4, 67% women) and 41 to the *Contr condition* (age 21.1 ± 2.0, 66% women). Participants in both conditions reported low baseline pain (0.1 ± 0.2 and 0.1 ± 0.4, respectively). There were no significant differences between the conditions in age, sex, and baseline pain.

Effects on experienced pain

In line with the primary hypothesis, mean ratings of experienced pain during the post-intervention CPT (see Figure 5.1) were significantly lower after response imagery than after control imagery ($F(1, 74) = 4.192$, $p = .044$, $\eta_p^2 = .054$).

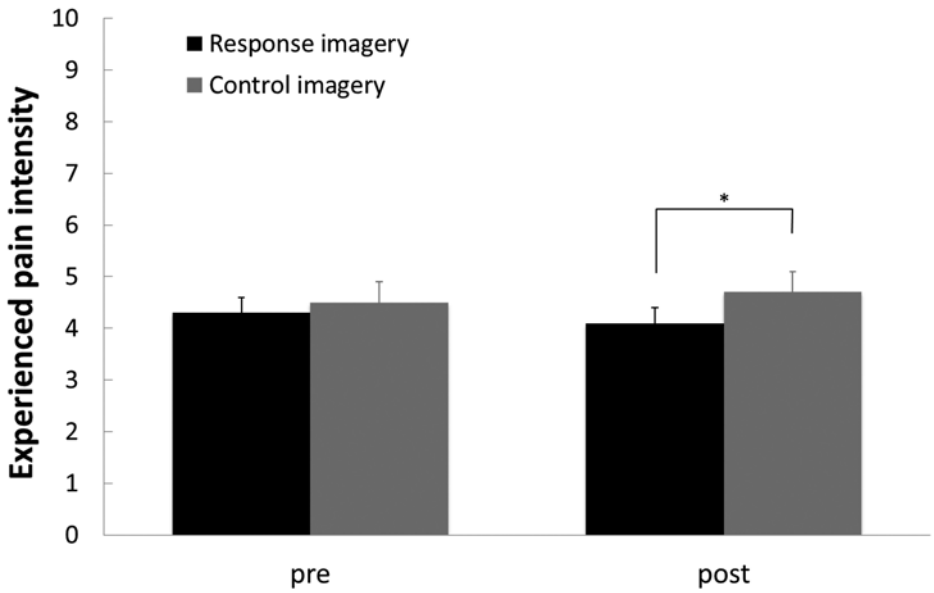

Figure 5.1. Means and standard errors of experienced pain intensity ratings for the pre- and post-intervention cold pressor tests per condition in Study 1

Note. * p < .05; ** p < .01; *** p < .001.

Mediation by expectancy

Expected pain ratings were significantly lower after response imagery than after control imagery ($F(1, 75) = 4.030$, $p = .048$, $\eta_p^2 = .051$). Moreover, the effect of response imagery on experienced pain was mediated by expected pain ($b = -0.417$, 95% CI [-0.685; -0.203]). See Figure 5.2 for the coefficients of all paths in the mediation model.

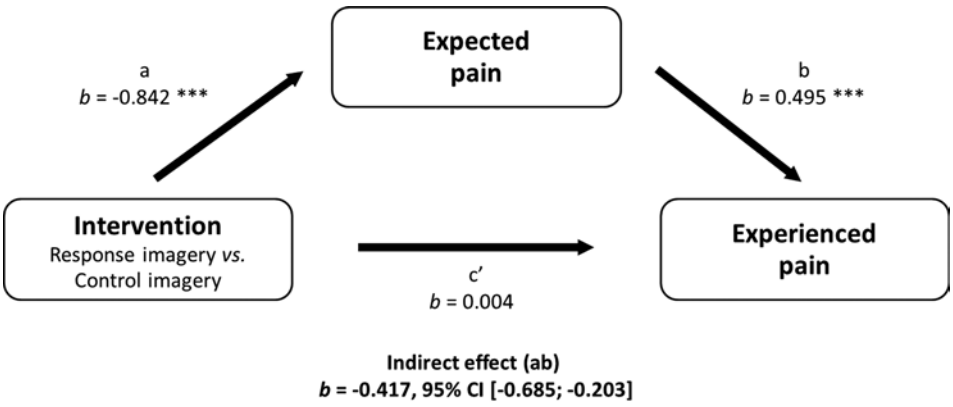

Figure 5.2. Mediation of effect of response imagery on experienced pain by expected pain, Study 1

Note. * p < .05; ** p < .01; *** p < .001.

Moderation by psychological characteristics

The effect of imagery on experienced pain was not significantly moderated by optimism or neuroticism, as indicated by non-significant interactions of the imagery conditions with the LOT-R ($\beta = 0.131$, $t = 0.815$, $p = .418$) and EPQ-RSS scores ($\beta = 0.046$, $t = 0.280$, $p = .780$).

Imagery evaluation

There were no significant differences between the response imagery and control condition in how participants rated the quality of the visualization ($F(1, 75) = 0.369$, $p = .546$, $\eta_p^2 = .005$) or their concentration on the image ($F(1, 75) = 0.655$, $p = .421$, $\eta_p^2 = .009$). Participants in the *Imag condition* rated the image as significantly more positive ($F(1, 75) = 5.542$, $p = .021$, $\eta_p^2 = .069$) and thought more about the image during the post-intervention CPT ($F(1, 75) = 42.157$, $p < .001$, $\eta_p^2 = .360$) than participants in the *Contr condition*.

Effects on psychological responses

There were no significant effects of response imagery on positive affect (PANAS-PA; $F(1, 75) = 0.637$, $p = .427$, $\eta_p^2 = .008$), state anxiety (STAI-S; $F(1, 75) = 0.009$, $p = .924$, $\eta_p^2 < .001$), general positive expectations (FEXpos; $F(1, 75) = 3.718$, $p = .058$, $\eta_p^2 = .047$), or general negative expectations (FEXneg; $F(1, 75) = 3.297$, $p = .073$, $\eta_p^2 = .042$).

Effects on physiological responses

There was no significant effect of response imagery on heart rate during the post-intervention CPT ($F(1, 73) = 1.461$, $p = .231$, $\eta_p^2 = .020$). Excluding the data of one participant who had a very irregular heart rate did not significantly affect the results ($F(1, 72) = 1.368$, $p = .246$, $\eta_p^2 = .019$). There were also no significant effects of response imagery on skin conductance during the post-intervention CPT ($F(1, 74) = 0.005$, $p = .943$, $\eta_p^2 < .001$), cortisol and alpha-amylase 10 minutes after the post-intervention CPT ($F(1, 74) = 0.131$, $p = .718$, $\eta_p^2 = .002$ and $F(1, 73) = 0.069$, $p = .794$, $\eta_p^2 = .001$, respectively), or cortisol and alpha-amylase 20 minutes after the post-intervention CPT ($F(1, 75) = 1.936$, $p = .168$, $\eta_p^2 = .025$ and $F(1, 74) = 2.026$, $p = .159$, $\eta_p^2 = .027$, respectively).

Study 2 - Methods

The aim of Study 2 was to replicate and extend the findings of Study 1. We again assessed the effect of response imagery on pain, but in this study we used a different control condition. While participants in the control condition of Study 1 imagined their hand, to assess the influence of the specific contents of imagery rather than the process of imagery, participants in the control condition of Study 2 did nothing, to assess the effects of the mere passage of time (natural history), and to thereby allow for a comparison that is more representative of clinical practice. An additional reason for using a different control condition in Study 2, was that we were concerned that the image used in the control condition of Study 1 might also affect pain; merely imagining one's hand, which was previously immersed in the cold water, might reduce pain via mindfulness-like processes [243], or might alternatively increase pain by enhancing awareness of the pain [19]. Secondary, we aimed to assess whether the effects of response imagery on pain could be enhanced by adding a verbal suggestion. We therefore added a third condition, in which the response imagery exercise was preceded by a verbal suggestion of its effectiveness. We did not assess salivary cortisol and alpha-amylase in Study 2, since these measures were not sensitive to the intervention in Study 1.

Participants

In Study 2, 135 healthy adults participated (power analysis based on Study 1 and previous research [22,74,174]). Inclusion and exclusion criteria were the same as in Study 1, except that current use of all types of medication was now an exclusion criterion. In addition, people could not participate in Study 2 if they had participated in Study 1.

Procedure

Following approval by the institute's ethics committee, testing took place from October 2014 to February 2015 at Leiden University, Leiden, the Netherlands. The general procedure was the same as in Study 1, with the exception of the specific intervention given, the omission of salivary cortisol and alpha-amylase assessments (and consequently omission of instructions regarding waking time and eating prior to participation), and the addition of the following measures: a pain catastrophizing questionnaire was administered with the pre test-session questionnaires; an extra assessment of expected pain was done after the pre-intervention CPT to obtain a pre-intervention expectancy score that was informed by the actual pain induced by a CPT; and pain anxiety was assessed directly following each expected pain assessment. See Supplementary Figure 5.2 for a flow diagram.

Intervention

As in Study 1, participants in the *Response imagery (Imag) condition* imagined reduced pain by using the image of a glove during the imagery exercise that took place prior to the second CPT. The imagery instructions were largely the same, but the phrasing of the instructions was slightly improved (e.g., 'Imagine that you can fully relax your hand and that you feel hardly or no pain…' in Study 1 vs. 'Imagine that you feel hardly or no pain [...]. You will be able to fully relax your hand' in Study 2). Participants first wrote about their image (3 min), after which they imagined it as vividly as possible (2 min). Participants in the *Response imagery with verbal suggestion (Imag+VS) condition* did the same response imagery exercise, but this was preceded by a verbal suggestion that described the effectiveness of the exercise, by stating, among other things, 'we know from previous scientific research that this imagery exercise is effective' and 'almost everyone experiences much less pain due to this exercise'. Participants in the *No treatment control (NT Contr) condition* waited, while reading a magazine, for the same duration as the imagery exercise (~12 min).

Measures

In addition to the measures used in Study 1, two additional measures were used. The pain catastrophizing scale (PCS) was used to measure pain catastrophizing. A numerical rating scale (0.0–10.0) was used to assess pain anxiety, but the data were not analyzed due to floor effects. For details of the questionnaires, see Supplementary Section 5.3.

Statistical analyses

The same procedures and analyses were used as in Study 1 to assess the effects of response imagery and of adding a verbal suggestion on pain (primary and secondary analyses, respectively), and to explore the possible mediation by expected pain, the possible moderating role of psychological characteristics, differences in imagery evaluation, and the effects on the other self-reported and physiological measures. To assess the effects of response imagery, the *Imag condition* and the *Imag+VS condition* were taken together and compared to the *NT Contr condition* in all analyses. We determined to pool the imagery conditions *a priori*, to maximize power and readability. However, for the primary outcome, we also reported post hoc comparisons of the individual imagery conditions with the control condition for completeness. To assess the effects of adding a verbal suggestion to the response imagery exercise, the *Imag condition* and the *Imag+VS condition* were compared with each other in all analyses. Means and standard deviations for all measures are reported in Supplementary Table 5.2.

As in Study 1, additional post hoc correlation analyses and sensitivity analyses are described in Supplementary Section 5.5 and reported in Supplementary Section 5.6. In Supplementary Section 5.6 also detailed information on missing data is reported.

Study 2 - Results

Participants

Forty-seven participants were allocated to the *Imag+VS condition* (age 21.8 ± 2.7, 85% women), 45 to the *Imag condition* (age 20.6 ± 1.8, 82% women), and 43 to the *NT Contr condition* (age 21.1 ± 2.9, 81% women). Participants in all conditions reported low baseline pain (0.0 ± 0.2; 0.1 ± 0.3; 0.1 ± 0.3, respectively). There were no significant differences between the conditions in age, sex, and baseline pain, except for significantly older age in the *Imag+VS condition* than in the *Imag condition* ($F(1, 89) = 7.254$, $p = .008$, $\eta_p^2 = .075$).

Effects on experienced pain

In line with the primary hypothesis, mean ratings of experienced pain during the post-intervention CPT (see Figure 5.3) were significantly lower after response imagery (regardless of verbal suggestion) than after no intervention ($F(1, 130) = 23.613$, $p < .001$, $\eta_p^2 = .154$). Further post hoc comparisons of the individual imagery conditions with the control condition, showed this difference both when a verbal suggestion was added to response imagery ($F(1, 86) = 24.896$, $p < .001$, $\eta_p^2 = .225$) and when response imagery was given alone ($F(1, 83) = 12.420$, $p = .001$, $\eta_p^2 = .130$). In contrast to the secondary hypothesis, adding a verbal suggestion did not affect experienced pain ratings, although a trend was observed ($F(1, 87) = 3.423$, $p = .068$, $\eta_p^2 = .038$).

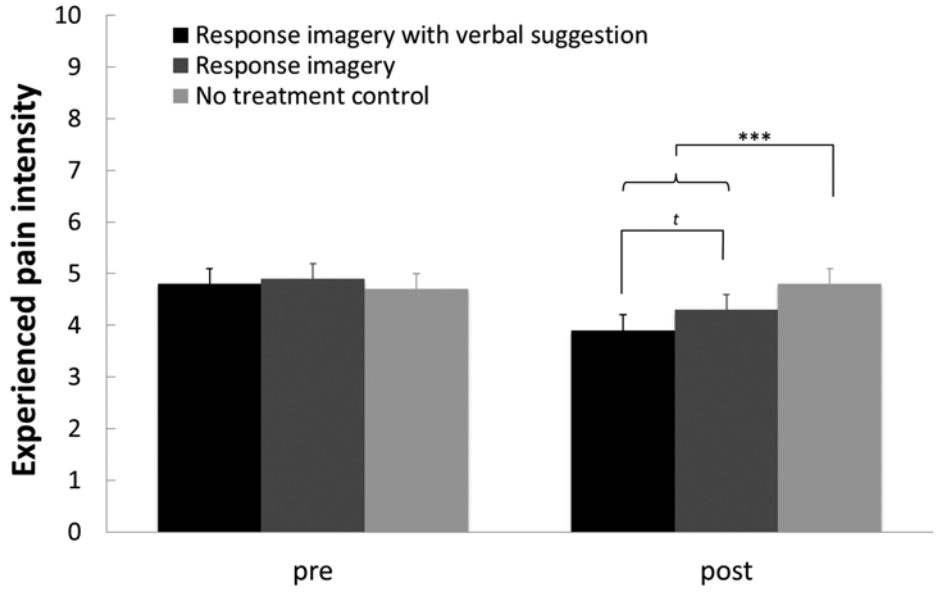

Figure 5.3. Means and standard errors of experienced pain intensity ratings for the pre- and post-intervention cold pressor tests per condition in Study 2

Note. ^{t} p < .10; * p < .05; ** p < .01; *** p < .001.

Mediation by expectancy

Expected pain ratings were significantly lower after response imagery than after no intervention ($F(1, 129) = 30.908$, $p < .001$, $\eta_p^2 = .193$). Similarly, adding a verbal suggestion to the imagery exercise led to significantly lower expected pain intensity

ratings in the *Imag+VS condition* than in the *Imag condition* ($F(1, 86) = 4.981$, $p = .028$, $\eta_p^2 = .055$). The effect of response imagery on experienced pain was mediated by expected pain ($b = -0.271$, 95% CI [-.493;-0.077]), while the effect of adding a verbal suggestion on experienced pain was not mediated by expected pain ($b = -0.134$, 95% CI [-0.334;0.003]). See Figures 5.4 and 5.5 for the coefficients of all paths in the mediation models.

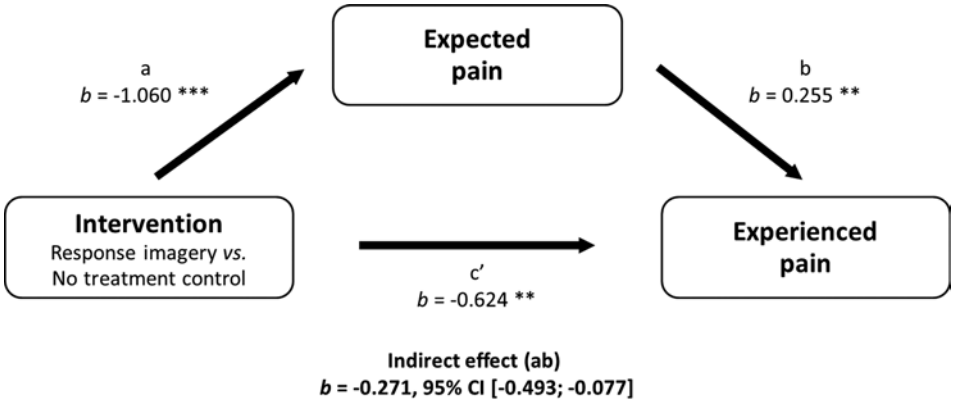

Figure 5.4. Mediation of effect of response imagery on experienced pain by expected pain, Study 2

Note. * p < .05; ** p < .01; *** p < .001.

Moderation by psychological characteristics

The effect of response imagery on experienced pain was not moderated by optimism, neuroticism, or pain catastrophizing, as indicated by non-significant interactions of the LOT-R ($\beta = -0.004$, $t = -0.056$, $p = .955$), EPQ-RSS ($\beta = -0.032$, $t = -0.404$, $p = .687$), and PCS scores ($\beta = 0.087$, $t = 1.125$, $p = .263$) with the imagery conditions. Similarly, the effect of adding a verbal suggestion on experienced pain was not significantly moderated by optimism or pain catastrophizing ($\beta = -0.064$, $t = -0.407$, $p = .685$; and $\beta = 0.126$, $t = 0.786$, $p = .434$, respectively). The effect of adding a verbal suggestion on experienced pain did appear to be moderated by neuroticism ($\beta = 0.326$, $t = 2.024$, $p = .046$). Follow-up analyses indicated that an effect of verbal suggestion was only present for participants who scored high on neuroticism (1 SD above the mean; $b = 0.740$, $t = 2.554$, $p = .012$).

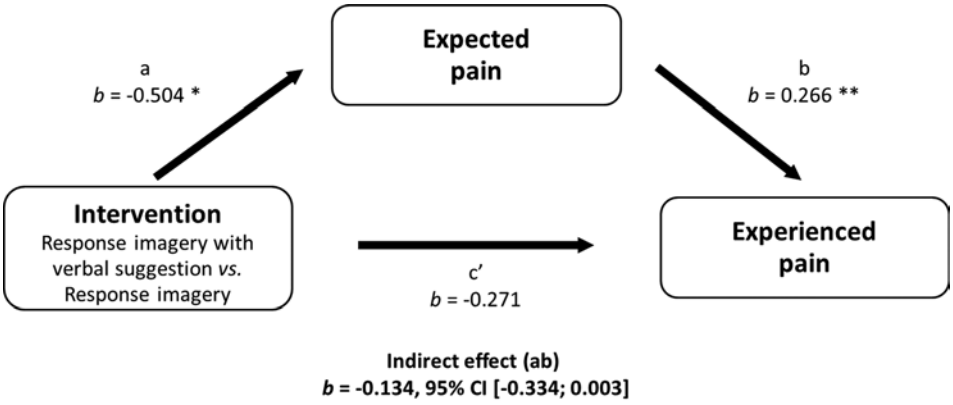

Figure 5.5. Mediation of effect of verbal suggestion about response imagery on experienced pain by expected pain, Study 2

Note. * p < .05; ** p < .01; *** p < .001.

Imagery evaluation

There were no significant differences between the imagery conditions in vividness of the image ($F(1, 87) = 0.426$, $p = .515$, $\eta_p^2 = .005$), concentration on the image ($F(1, 87) = 0.068$, $p = .796$, $\eta_p^2 = .001$), valence of the image ($F(1, 87) = 0.811$, $p = .370$, $\eta_p^2 = .009$), and thinking about the image during the post-intervention CPT ($F(1, 87) = 2.580$, $p = .112$, $\eta_p^2 = .029$).

Effects on psychological responses

Participants in the response imagery conditions reported significantly higher general positive expectations (FEXpos; $F(1, 130) = 5.261$, $p = .023$, $\eta_p^2 = .039$) than participants in the *NT Contr condition*. There were no significant effects of response imagery on positive affect (PANAS-PA; $F(1, 130) = 3.896$, $p = .051$, $\eta_p^2 = .029$), state anxiety (STAI-S; $F(1, 130) = 0.152$, $p = .697$, $\eta_p^2 = .001$), or general negative expectations (FEXneg; $F(1, 130) = 0.130$, $p = .719$, $\eta_p^2 = .001$). Adding a verbal suggestion to the response imagery exercise did not significantly influence positive affect (PANAS-PA; $F(1, 87) = 0.003$, $p = .956$, $\eta_p^2 < .001$), state anxiety (STAI-S; $F(1, 87) = 2.439$, $p = .122$, $\eta_p^2 = .027$), general positive expectations (FEXpos; $F(1, 87) = 0.330$, $p = .567$, $\eta_p^2 = .004$), or general negative expectations (FEXneg; $F(1, 87) = 1.028$, $p = .313$, $\eta_p^2 = .012$).

Effects on physiological responses

There was no significant effect of response imagery on heart rate ($F(1, 128) = 3.885$, $p = .051$, $\eta_p^2 = .029$) or skin conductance ($F(1, 128) = 3.261$, $p = .073$, $\eta_p^2 = .025$) during

the post-intervention CPT. Adding a verbal suggestion did not significantly influence heart rate ($F(1, 87) = 0.367$, $p = .546$, $\eta_p^2 = .004$) or skin conductance ($F(1, 87) = 2.490$, $p = .118$, $\eta_p^2 = .028$).

Discussion

In two experimental studies, response imagery, i.e., imagery of reduced pain, was found to induce analgesia via its effects on response expectancies, with statistically small to medium effects in Study 1 and large effects in Study 2. An additional verbal suggestion regarding the effectiveness of imagery did not significantly affect pain. These findings suggest that response imagery can affect future pain responses and can be viewed as a possible technique for inducing placebo-like effects (i.e., expectancy effects without administration of a placebo [24]).

The current findings extend previous research on the mechanisms of placebo effects by showing that placebo-like expectancy effects on pain can be induced not only by instructions, direct experience, and observation of other people [59,159], but also by mental imagery of a response (i.e., simulated experience). This is consistent with response expectancy theory [159] and neurobiological findings indicating that brain activation is similar during actual and imagined sensations [86,201]. The observed effects of response imagery on pain support our primary hypothesis and are in line with previous studies that demonstrate that imagery exercises including images of pain reduction can reduce experimentally evoked pain as well as acute and chronic clinical pain (although effect sizes are heterogeneous) [22,74,86,174,221]. The effects in Study 2 are comparable in size with placebo effects in healthy controls and patients with pain [221,298,299]. By instructing participants to imagine reduced pain prior to the pain experience (rather than during as is common in clinical interventions) [291], and by including a measure of expected pain, we found, for the first time, evidence that the effects of response imagery on experienced pain can be mediated by expected pain. Hereby, we further increase the knowledge on the working mechanisms of imagery. These findings suggest that response imagery might provide an additional manner to harness placebo-like expectancy effects, without placebo administration or deception.

In addition to the effect of imagery, we studied the effects of providing a positive verbal suggestion regarding the effectiveness of the response imagery intervention. Such a verbal suggestion corresponds with procedures in previous research and in clinical practice, where imagery interventions are generally introduced with information regarding the intended and/or expected outcomes. Contrary to our secondary

hypothesis, participants who had received the verbal suggestion did not experience less pain than participants who only received the imagery instructions, although a statistical trend in this direction was observed and participants expected less pain. Possibly, a ceiling effect occurred where verbal suggestion could not elicit a significant effect on pain above that of response imagery alone. Our finding is partially consistent with a large body of research demonstrating the successful induction of placebo effects by verbal suggestion [221,299]. Future research might elucidate whether adding a verbal suggestion can indeed enhance the effects of response imagery, taking into account factors such as the specific phrasing of the suggestion, and perhaps providing a suggestion more frequently to enhance encoding and effects.

Expectancies are generally seen as the core mechanism of placebo effects, but other psychological working mechanisms could also be considered when trying to explain the effect of response imagery on pain. For example, negative emotions have been suggested to mediate the effects of placebos on pain [91] (although previous imagery and placebo studies had equivocal results [9,221,278]) and attention processes might also partially explain effects of response imagery on pain [19,80] [but see 45]. Exploratory analyses of the current data showed that general expectancies, positive affect, and state anxiety are unlikely to have played a substantial role in bringing about the effects of response expectancy. The involvement of attention processes during both the imagery exercise and the CPT cannot be fully excluded. For example, our findings indicate that participants in the response imagery conditions thought about the image during the post-intervention CPT, even though they had not received instructions to do so, which could have distracted them from the evoked pain. Future research might investigate the mechanisms further, e.g., by including other measures and/or directly comparing the mediation by response expectancies with mediation by emotions, attention, and general expectations.

In the current studies, our exploratory analyses did not indicate reliable effects of response imagery on autonomic and endocrine responses, even though response imagery was found to affect pain. This could give rise to concerns about the influence of demand characteristics. However, since previous studies did find the effects of pain-focused imagery on pain and placebo analgesia to be associated with corresponding effects on the autonomic nervous system and with the activation of brain responses that are known to be involved in pain experiences and expectancies [14,86,171,201,256], it is likely that the autonomic nervous system was also involved in the effects of response imagery on pain in the current studies. The existing evidence for the involvement of the endocrine system is less convincing [90,261]. Methodological factors are likely to have affected our results regarding physiological responses. It is possible that effects on

physiological responses were obscured by large inter-individual variability and lower sensitivity of the responses; we observed large variability of particularly the alpha-amylase responses, and heart rate was only slightly affected by the CPTs, even though the CPTs evoked moderate pain (comparable to previous studies [220,293]). Furthermore, the cortisol and alpha-amylase responses appeared to be affected by the circadian rhythm. Future studies using more sensitive physiological responses and/or measurement techniques, more rigorous controlling of circadian rhythm [163,249], larger sample sizes, and possibly also other types of experimental as well as clinical pain, might allow more definite conclusions regarding the physiological correlates of the effects of response imagery. Furthermore, additional self-report measures, such as social desirability questionnaires, may also provide more insight into the possible influence of demand characteristics, although previous research using such measures did not find this to be a significant factor [209,295].

Finally, individual differences in psychological characteristics might determine the effectiveness of response imagery. Although some previous studies have found optimism, neuroticism, and pain catastrophizing to be associated with the analgesic effects of imagery or placebo-related expectation inductions [67,100,119], several other studies did not find any such association [120,220,295]. In the current studies, we found no evidence for the moderation of the effects of imagery on pain by optimism or pain catastrophizing, but some indications that neuroticism might play a role in the effects of verbal suggestion. Future research might further investigate the determinants of response imagery and placebo effects, by studying not only individual differences in psychological characteristics, but also in pre-existing expectancies (e.g., due to previous experiences), and different types of pain (e.g., acute vs. chronic pain) [135,221]. Furthermore, participants received standardized and detailed instructions for the imagery exercise. An advantage was that all participants could imagine a concrete image of an otherwise abstract concept. This is especially helpful for people who otherwise have trouble constructing an image themselves [174]. Moreover, as postulated in the simulation heuristic [287] and observed in several studies [43,241], the ease with which a mental image can be constructed has been associated with its effects on individuals' expectations of events. Many chronic pain patients, however, experience spontaneous, highly individual, pain-related images [34], and it might be beneficial for them to form their own personal images of pain reduction instead of visualizing a standard image. Indeed, one study found the rescripting of pain patients' most distressing pain image to a preferred, self-generated, image to be very beneficial [228].

In conclusion, the current findings indicate that a brief response imagery intervention can induce placebo-like expectancy effects on pain. If these findings can be

replicated and extended, in both healthy and clinical samples, response imagery could ultimately be implemented in clinical practice to optimize expectations and thereby improve the effectiveness of standard pain treatments.

Acknowledgements

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Supplementary materials Chapter 5

Supplementary Section 5.1. Health-related exclusion criteria

In Study 1, health-related exclusion criteria were severe physical or psychological morbidity (e.g., heart disease or DSM-IV psychiatric disorders) that would adversely affect participation, current chronic (≥ 6 months) pain complaints, Raynaud's phenomenon, extensive injuries to the hand to be immersed, current medication use (specifically, analgesics, anti-inflammatory drugs, antihistamines, antibiotics, beta-blockers, or other medications that influence heart rate), use of pacemaker, and pregnancy.

In Study 2, exclusion criteria were the same as in Study 1, except that current use of all types of medication was now an exclusion criterion.

Supplementary Section 5.2. Randomization & blinding procedure

In Study 1, the randomization sequence was generated by an independent researcher with an online random number generator (www.randomization.com; stratified by sex and time of day [morning vs. afternoon], with a 1:1 allocation using blocks of 4 and 6). Allocation was concealed by using sequentially numbered, opaque, sealed envelopes. As indicated, testing was done by two experimenters to enable blinding of the outcome assessor. Experimenter A, who conducted the measurements, was unaware of allocation throughout the test session. Experimenter B, who led the intervention (including the preceding filler tasks), was unaware of allocation until intervention onset. The experimenters did not communicate about any aspects of the procedure that could lead to unblinding. To maximize blinding of the participants, they were not informed about the different experimental conditions until debriefing.

In Study 2, the randomization sequence was generated according to the same procedures as used for Study 2, except for stratification by sex only (i.e., omission of stratification on time of day), and 1:1:1 allocation using blocks of 3, 6, and 9. The blinding procedures were the same as in Study 1.

Supplementary Section 5.3. Psychological characteristics & responses

Dispositional optimism. In Study 1 and 2, the revised Life Orientation Test (LOT-R) [224,258] was used to measure dispositional optimism (3 positive, 3 negative, and 4 filler items, 5-point Likert scale). The total score ranges from 0 to 24.

Neuroticism. In Study 1 and 2, the neuroticism scale of the revised short version of the Eysenck Personality Questionnaire (EPQ-RSS) [253] was used to measure neuroticism (12 items, dichotomous (yes/no) scale). The total score ranges from 0 to 12.

Pain catastrophizing. In Study 2, the Pain Catastrophizing Scale (PCS) [282] was used to measure pain catastrophizing (13 statements, 5-point Likert scale). The total score ranges from 0 to 52.

Affect. In Study 1 and 2, a short version of the Positive and Negative Affect Schedule (PANAS) [155,223] was used to measure positive and negative affect (5 positive items, i.e., PANAS-PA, and 5 negative items, i.e., PANAS-NA, 5-point Likert scale). The PANAS-PA and PANAS-NA scores both range from 5 to 25.

State anxiety. In Study 1 and 2, a short version of the State-Trait Anxiety Inventory, State version (STAI-S) [196,290] was used to measure state anxiety (3 negative and 3 positive statements, 4-point Likert scale). The total score ranges from 20 to 80 (after multiplication by 3.33 for comparability with the full scale).

General expectations. In Study 1 and 2, the questionnaire for Future Expectations (FEX) [119] was used to measure positive and negative general expectations for future events (10 positive future events, i.e., FEXpos, and 10 negative future events, i.e., FEXneg, 7-point Likert scale). The FEXpos and FEXneg both range from 10-70.

Pain anxiety. In Study 2, a numerical rating scale ranging from 0.0 (*not anxious at all*) to 10.0 (*most anxious ever experienced)* was used to assess pain anxiety, i.e., anxiety regarding the coming CPT.

Psychometric properties questionnaires. Cronbach's alpha of the questionnaires was satisfactory for almost all questionnaires at pre- and post-intervention, except for the PANAS-NA (Study 1 and 2) and the FEXpos (Study 1) (see the table below). The PANAS-NA data were not analyzed due to the low internal consistency and floor effects (Study 1: post-intervention, 85% of participants reported minimum score; Study 2: post-intervention, 77% of participants reported the minimum score). For the FEXpos a satisfactory Cronbach's alpha for this scale was obtained after excluding item 4 in Study 1 (α = .68 to .71). Last, the pain anxiety data were not analyzed due to floor effects (post-intervention, 47% of participants reported no pain anxiety).

Cronbach's alpha

	Study 1	**Study 2**
LOT-R	.77	.69
EPQ-RSS	.80	.72
PCS	n.a.	.89
PANAS-PA		
pre-intervention	.70	.71
post-intervention	.76	.73
PANAS-NA		
pre-intervention	.67	.65
post-intervention	.45	.49

	Study 1	**Study 2**
STAI-S		
pre-intervention	.73	.82
post-intervention	.66	.74
FEXpos		
pre-intervention	.56	.84
post-intervention	.51	.87
FEXneg		
pre-intervention	.68	.81
post-intervention	.68	.84

Supplementary Section 5.4. Physiological responses

Heart rate and skin conductance. In Study 1 and 2 heart rate (HR) and skin conductance (SC) were measured continuously using a MP150 system and AcqKnowledge software, version 4.3.1 (BIOPAC Systems Inc., Goleta, CA, USA). For HR measurements, a disposable electrode (Kendall 200 Foam Electrode, Covidien, Mansfield, MA, USA) was placed on the sternum and another on the left lower rib, after abrading the skin. Electrocardiography (ECG) signals were recorded with an ECG100C amplifier (1000 Hz, gain 1000, 0.5 Hz high pass filter). For SC measurements, disposable Ag/AgCl electrodes (EL507-10, BIOPAC Systems Inc., Goleta, CA, USA) were placed on the medial phalanges of the index and middle finger of the non-dominant hand, after cleaning the skin with water. SC level (µS) was recorded with a GSR100C amplifier (1000 Hz, gain 5 µmho/V, 10.0 Hz low pass filter). Inspection of the ECG and SC data, HR calculation, and calculation of the mean HR and SC levels during baseline and the CPTs was conducted in MATLAB (version R2012b, the MathWorks, Inc., Natick, Ma, USA). Epochs were marked using triggers via E-prime 2.0 software.

Cortisol and alpha-amylase. In Study 1, saliva samples were collected with cotton swabs (Salivette, Sarstedt, Nümbrecht, Germany) for assessments of cortisol and alpha-amylase [162,163,249]. The samples were initially stored at -20°C. After the samples had been thawed and centrifuged, 0.5 ml aliquots were stored at -80°C until biochemical analyses at the Department of Clinical Chemistry and Laboratory Medicine of the Leiden University Medical Center, Leiden, the Netherlands. Cortisol (nmol/L) was measured with a Modular P800 (Roche, Mannheim, Germany). Alpha-amylase (U/L) was measured, in a 25µL sample diluted with 2475 µL saline, with an Integra 800 (Roche, Mannheim, Germany).

Supplementary Section 5.5. Additional analyses (methods)

Correlation of experienced pain with other outcomes Study 1 and 2. Post hoc partial correlation analyses were conducted in the imagery condition(s) to explore the association of post-intervention experienced pain with post-intervention imagery evaluation, psychological responses, and physiological responses; in these analyses we controlled for the matching pre-intervention measures (e.g., pre-intervention experienced pain and positive affect when assessing the association between post-intervention experienced pain and positive affect) and the stratification variable(s).

Sensitivity analyses Study 1 and 2. In case the assumptions of statistical tests (e.g., of normality) were violated, sensitivity analyses were conducted by 1) calculating bias-corrected 95% confidence intervals around the relevant parameter using 1000 bootstrapping samples, 2) transforming the data (e.g., log transformation), and/or 3) reanalyzing the data without outliers.

Sensitivity analyses were also conducted to assess the influence of excluding the data of participants who had inadvertently used medication that might have affected their responses (Study 1) or who had indicated complaints that could be characterized as Raynaud's phenomenon (Study 2).

Missing data Study 1. Some data were missing due to practical and/or technical issues: experienced pain ratings (pre-intervention, *n* = 1), heart rate (pre-intervention, *n* = 1; full data, *n* = 1), and skin conductance levels (pre-intervention, *n* = 1), cortisol and alpha-amylase (10 min after first CPT, *n* = 1), and imagery evaluation data (*n* = 1). For one participant alpha-amylase values were unreliably low and therefore not analyzed. All participants completed both cold pressor tests.

Missing data Study 2. One participant withdrew from participation during the pre-intervention CPT due to illness unrelated to the study. Experienced pain ratings were partially missing for four participants (1 in the *Imag+VS condition*, i.e., 2%, 3 in the *Imag condition*, i.e., 7%) who ended the pre-intervention CPT prematurely (< 1 min), and one participant (in the *Imag+VS condition*) who ended the post-intervention CPT prematurely due to pain intensity. These missing ratings were replaced using the last observation carried forward method. Some data were missing due to practical and/or technical issues: imagery evaluation data (*n* = 1), expected pain rating (pre-intervention*, n* = 1), or heart rate and skin conductance data (*n* = 2).

Supplementary Section 5.6. Additional analyses (results)

Correlation of experienced pain with other outcomes Study 1. Post hoc partial correlation analyses in the response imagery condition indicated a significant association of post-intervention experienced pain with concentration on the image ($r(32) = .549$, $p = .001$), indicating that participants who were more concentrated during the imagery exercise, experienced more pain during the post-intervention CPT. Post-intervention experienced pain was not significantly associated with the other imagery evaluation variables, psychological or physiological responses.

Correlation of experienced pain with other outcomes Study 2. Post hoc partial correlation analyses in the response imagery conditions indicated a significant association of post-intervention experienced pain with thinking about the image during the CPT ($r(86) = -.295$, $p = .005$) and post-intervention positive affect ($r(86) = -.223$, $p = .036$), indicating that participants who thought about the image more and/or had higher positive affect, experienced less pain during the post-intervention CPT. Post-intervention experienced pain was not significantly associated with the other imagery evaluation variables, the other psychological responses, or physiological responses.

Sensitivity analyses Study 1. When assumptions of statistical tests were violated, bootstrapped confidence intervals around the parameters, transformations of variables, and/or removing outliers did not significantly affect the results, with two exceptions. When one extreme outlier was excluded, heart rate during the post-intervention CPT was significantly lower after response imagery than after control imagery ($F(1,72) = 4.221$, $p = .044$, $\eta_p^2 = .055$). Bootstrapped 95% confidence intervals around Pearson's *r* indicated a significant association between experienced pain and thinking about the image during the post-intervention CPT ($r(32) = -.320$, 95% CI [-.629;-.058)].

When excluding three participants who had inadvertently used medication that might have affected their responses (1 participant used an analgesic, 1 ointment for eczema, and 1 antihistamine), experienced pain was not found to be significantly lower after response imagery than after control imagery, but a trend was still observed ($F(1,71) = 3.397$, $p = .050$, $\eta_p^2 = .053$). Excluding these participants did not significantly affect the results of other analyses.

Sensitivity analyses Study 2. When assumptions of statistical tests were violated, bootstrapped confidence intervals around the parameters, transformations of variables, and/or removing outliers did not significantly affect the results, with one exception. The moderation of the effect of adding a verbal suggestion on experienced pain by neuroticism was non-significant when the variables were square-root transformed ($b = 0.215$, $t = 1.323$, $p = .190$).

When one participant who indicated having complaints that can be characterized as Raynaud's phenomenon was excluded, heart rate during the post-intervention CPT was found to be significantly higher in the imagery conditions than in the *NT Contr condition* ($F(1,127) = 4.042$, $p = .046$, $\eta_p^2 = .031$), and the moderation of the effect of adding a verbal suggestion on experienced pain by neuroticism was found to be non-significant when untransformed ($b = 0.323$, $t = 1.984$, $p = .051$) or square root transformed ($b = 0.213$, $t = 1.301$, $p = .197$). Excluding this participant did not significantly affect the results of other analyses.

Supplementary Table 5.1. Means and standard deviations for all measures in Study 1

Measure \ Condition	Response imagery (*n* = 39)	Control imagery (*n* = 41)
Pre test-session		
LOT-R	16.6 ± 3.5	16.9 ± 3.8
EPQ-RSS neuroticism	3.1 ± 2.6	3.0 ± 2.9
Pre-intervention		
Resting heart rate	72.7 ± 11.4	74.0 ± 11.5
Resting skin conductance level	5.2 ± 3.5	5.1 ± 2.3
Resting cortisol	13.1 ± 6.1	15.0 ± 9.5
Resting alpha-amylase	822.9 ± 750.3	823.9 ± 962.5
Expected pain	4.3 ± 2.0	4.5 ± 1.7
Experienced pain during CPT	4.3 ± 2.1	4.5 ± 2.3
PANAS-PA	13.3 ± 3.3	12.4 ± 3.0
PANAS-NA	6.0 ± 1.0	6.0 ± 1.7
STAI-S	32.6 ± 8.0	31.9 ± 6.8
FEXpos*	45.9 ± 5.0	46.0 ± 5.0
FEXneg	31.9 ± 6.2	33.3 ± 6.9
Heart rate during CPT	76.5 ± 14.3	76.8 ± 12.1
Skin conductance during CPT	7.3 ± 3.2	7.5 ± 2.2
Cortisol 10 min after CPT	12.3 ± 4.7	14.2 ± 8.2
Cortisol 20 min after CPT	13.0 ± 5.7	13.7 ± 7.9
Alpha-amylase 10 min after CPT	742.5 ± 565.1	782.4 ± 734.1
Alpha-amylase 20 min after CPT	972.2 ± 1151.2	701.8 ± 652.9

Continues on next page

Supplementary Table 5.1. *continued*

Measure \ Condition	Response imagery (n = 39)	Control imagery (n = 41)
Post-intervention		
Concentration on image	63.9 ± 17.9	60.7 ± 15.7
Quality visualization	66.6 ± 14.1	64.3 ± 17.2
Valence of image	75.4 ± 16.1	66.4 ± 18.4
Thinking about image during CPT	56.3 ± 28.6	16.9 ± 24.9
Expected pain	4.8 ± 2.2	5.8 ± 2.2
Experienced pain during CPT	4.1 ± 2.1	4.7 ± 2.3
PANAS-PA	12.3 ± 3.6	11.2 ± 3.5
PANAS-NA	5.5 ± 1.2	5.2 ± 0.6
STAI-S	34.0 ± 8.3	33.8 ± 7.5
FEXpos [a]	46.2 ± 4.7	45.4 ± 4.7
FEXneg	32.5 ± 6.7	32.5 ± 6.3
Heart rate during CPT	71.4 ± 12.7	73.4 ± 10.7
Skin conductance during CPT	6.1 ± 3.2	6.4 ± 2.4
Cortisol 10 min after CPT	10.4 ± 4.0	11.4 ± 5.4
Cortisol 20 min after CPT	9.7 ± 3.4	10.8 ± 5.0
Alpha-amylase 10 min after CPT	913.9 ± 740.8	911.5 ± 860.6
Alpha-amylase 20 min after CPT	1049.4 ± 782.5	1161.4 ± 1377.4

Note. Means and standard deviations ($M \pm SD$) are presented for all available data. The data used for analyses sometimes differ due to list-wise deletions in the case of missing values (see statistical analyses section Study 1 of main text). See Methods section of main text for more information on the measures.

[a] excluding FEX item 4, to obtain a satisfactory Cronbach's alpha for this scale.

Supplementary Table 5.2. Means and standard deviations for all measures in Study 2

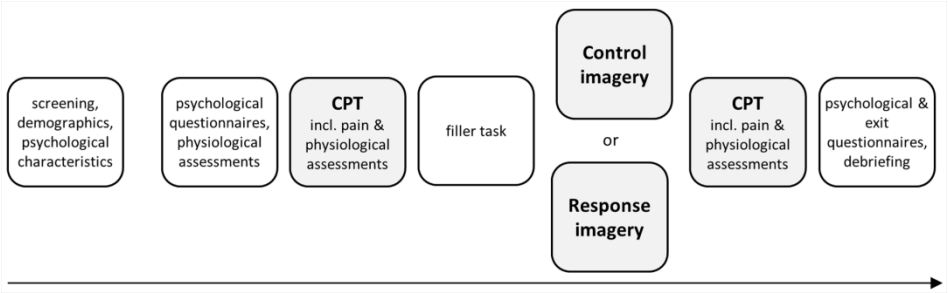
Measure \ Condition	Response imagery with verbal suggestion (n = 47)	Response imagery (n = 45)	No treatment control (n = 43)
Pre test-session			
LOT-R	16.6 ± 3.1	16.7 ± 3.4	16.3 ± 3.1
EPQ-RSS neuroticism	2.4 ± 2.0	3.4 ± 2.4	3.1 ± 2.7
PCS	9.3 ± 6.9	10.5 ± 7.8	11.3 ± 6.7
Pre-intervention			
Resting heart rate	77.9 ± 10.5	75.7 ± 8.0	76.6 ± 11.0
Resting skin conductance level	4.3 ± 2.4	4.3 ± 2.3	4.1 ± 2.5
Expected pain before CPT	4.5 ± 1.7	4.2 ± 1.6	4.3 ± 1.6
Pain anxiety before CPT	1.1 ± 1.3	1.1 ± 1.3	1.3 ± 1.4
Experienced pain during CPT	4.8 ± 2.2	4.9 ± 2.0	4.7 ± 2.3
Expected pain after CPT	5.4 ± 1.9	5.2 ± 1.8	5.0 ± 2.4
Pain anxiety after CPT	1.1 ± 1.3	1.5 ± 1.8	1.3 ± 1.7
PANAS-PA	13.4 ± 3.7	12.2 ± 2.9	12.3 ± 3.3
PANAS-NA	6.1 ± 1.7	6.2 ± 1.9	6.4 ± 1.4
STAI-S	32.8 ± 7.9	35.0 ± 9.0	35.1 ± 10.0
FEXpos	54.7 ± 5.3	53.9 ± 6.1	53.1 ± 7.4
FEXneg	27.8 ± 7.7	27.8 ± 7.9	28.9 ± 8.2
Heart rate during CPT	80.0 ± 10.6	77.7 ± 9.1	80.2 ± 10.2
Skin conductance during CPT	6.3 ± 2.5	7.1 ± 2.4	6.6 ± 2.7

Continues on next page

Supplementary Table 5.2. *continued*

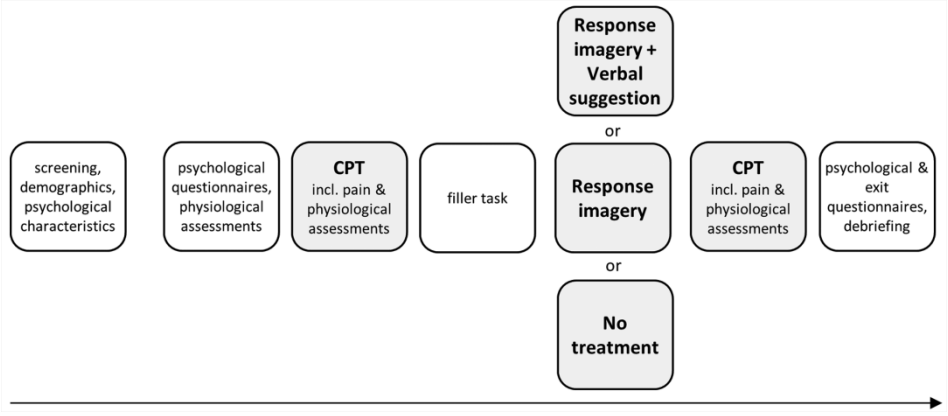
Measure \ Condition	Response imagery with verbal suggestion	Response imagery	No treatment control
	(*n* = 47)	(*n* = 45)	(*n* = 43)
Post-intervention			
Concentration on image	68.6 ± 14.3	69.3 ± 12.9	-
Quality visualization	68.5 ± 15.2	70.7 ± 14.7	-
Valence of image	78.0 ± 18.7	81.5 ± 18.0	-
Thinking about image during CPT	76.1 ± 18.7	69.3 ± 21.6	-
Expected pain	3.8 ± 1.9	4.3 ± 1.9	4.8 ± 2.3
Pain anxiety	0.9 ± 1.1	1.1 ± 1.5	1.5 ± 1.8
Experienced pain during CPT	3.9 ± 2.2	4.3 ± 1.9	4.8 ± 2.3
PANAS-PA	13.0 ± 3.6	12.2 ± 3.4	11.4 ± 3.2
PANAS-NA	5.3 ± 0.9	5.4 ± 0.7	5.5 ± 0.9
STAI-S	30.6 ± 6.8	33.7 ± 7.9	32.3 ± 9.0
FEXpos	55.8 ± 5.7	54.6 ± 5.8	53.2 ± 7.9
FEXneg	27.7 ± 8.1	26.9 ± 8.1	28.1 ± 8.4
Heart rate during CPT	79.4 ± 11.1	76.3 ± 8.5	76.9 ± 9.5
Skin conductance during CPT	5.6 ± 1.8	6.5 ± 2.3	6.5 ± 2.7

Note. Means and standard deviations (*M* ± *SD*) are presented for all available data. The data used for analyses sometimes differ due to list-wise deletions in the case of missing values (see statistical analyses section Study 2 of main text). See Methods section of main text for more information on the measures.



Supplementary Figure 5.1. Flow diagram showing the experimental procedures of Study 1 in chronological order

Note. CPT = cold pressor test.



Supplementary Figure 5.2. Flow diagram showing the experimental procedures of Study 2 in chronological order

Note. CPT = cold pressor test.

CHAPTER 6

EXPECTATIONS ABOUT THE EFFECTIVENESS OF PAIN- AND ITCH-RELIEVING MEDICATION ADMINISTERED VIA DIFFERENT ROUTES

To be published as
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Abstract

Background: Placebo effects on pain have been found to vary in size for different routes of medication administration (e.g., oral vs. injection). This has important implications for both clinical research and practice. To enhance our understanding of these differential placebo effects, research on the underlying expectations about multiple routes and symptoms other than pain is vital.

Methods: A cross-sectional, internet-based survey was conducted in a representative sample of the Dutch population (*n* = 508). Respondents rated the expected effectiveness of pain- and itch-relieving medication in six forms, representing oral, injection, and topical routes of administration.

Results: Injected medication was expected to be most effective for relieving pain, and topical medication for relieving itch. Furthermore, exploratory analyses showed that injections were expected to have the most rapid onset and long-lasting effects, and to be most frightening and expensive, while topical medication was expected to be safest and easiest to use, and oral medication to have the most side effects. Higher expected effectiveness was moderately associated with expectations of more rapid onset and long-lasting effects, and better safety and ease of use. Associations of expected effectiveness with respondent characteristics (e.g., medication use and personality characteristics) were statistically small or non-significant.

Conclusions: Expected effectiveness of medication differed depending on route of administration and targeted symptom. These findings have important implications for the design and interpretation of clinical trials, and suggest that medication effects might be enhanced by prescribing medicine via the route that patients expect to be most effective for their complaint.

Introduction

Placebos have repeatedly been found to relieve pain and other symptoms, presumably through expectancies [24,159,221]. Not all placebos affect pain equally. An important treatment characteristic that has been associated with differential placebo effects on pain is the route of medication administration. It is frequently suggested that more invasive routes of medication administration (such as injections) lead to enhanced placebo effects [150,177,265]. Indeed, placebo injections have been found to be more effective for relieving pain than oral placebos [18,71,221,323]. However, many research findings, looking also into other routes, are mixed regarding the possible enhanced effectiveness of more invasive routes for relieving pain [18,87,192,203], while one study did not show substantial differences between different routes at all [265]. Since differential placebo effects have important implications for clinical trials and clinical practice, further research into the underlying expectations about the effectiveness of medication administered via different routes is required.

For further research, several factors should be considered. First, most previous research compared the placebo control conditions of separate clinical trials, while direct comparisons between multiple routes of medication administration are relatively scarce. Second, research is generally limited to pain, while research into multiple symptoms is vital to examine whether differential placebo effects of different routes may depend on the targeted symptom. In this regard, itch is of particular interest. Like pain, itch imposes a heavy burden on many patients [199,312], and the underlying mechanisms of pain and itch overlap considerably [260,279]. Only one meta-analysis has assessed differential placebo effects on itch, suggesting that oral and injected placebos did not differ [294]. Comparisons with topical routes, which are most frequently used for itch, could however not be made in this analysis. In addition, our understanding of differential placebo effects can be improved by looking at expectations about other characteristics, such as side effects and cost [33,308], which have previously been found to affect placebo effects. Also, possible correlates of the expectations about the effectiveness of medication, including these other characteristics of the routes and respondent characteristics (e.g., frequency of medication use and personality characteristics [59,135]), are rarely explored.

In this cross-sectional study, we used a survey to directly compare expectations about medication administered via three common routes for relieving pain and itch in a large sample representative of the Dutch population. Our primary aim was to assess differences between the expected effectiveness of medication administered via oral (tablet, capsule), injection (syringe, infusion), and topical (cream, gel) routes for relieving pain and itch. In addition, we explored expectations about multiple other characteristics

of the routes (i.e., side effects, long-lasting effect, rapid onset, safety, being frightening, cost, and ease of use), as well as possible correlates of the expected effectiveness (i.e., expectations about the aforementioned characteristics of the routes, and the following respondent characteristics: demographics, health, frequency of medication use, medication attitude, and personality characteristics).

Methods

Respondents

The sample consisted of adults (≥18 years) who were fluent in the Dutch language. Respondents were recruited via online research panels; Qualtrics (Provo, UT, USA) panel members from the Dutch population were invited via e-mail to complete the online survey in return for incentives or cash honorarium, according to the standard procedures of Qualtrics. To obtain a sample that was representative of the adult Dutch population in terms of age, sex, and province of residence [51], the data of respondents who were over quota were not analyzed.

Procedure

The study protocol was approved by the institute's ethics committee (*Commissie Ethiek Psychologie*, PREC15-0828_33). The study was a cross-sectional, internet-based survey. After providing informed consent, upon receiving information about the study purpose and procedures, respondents filled out a series of questionnaires via the secured online system Qualtrics (Provo, UT, USA). Median completion time was 19 minutes. Data collection took place in autumn 2015.

Questionnaires

Expectations about medication. A questionnaire developed specifically for this study was used to measure respondents' expectations about six different forms of medication administration, representing three common routes of administration, specifically oral (i.e., tablet, capsule), injection (i.e., syringe, infusion), and topical (i.e., cream, gel) routes. See Supplementary Section 5.1 for an English version of the questionnaire. This questionnaire evolved from a pilot study conducted in a sample of 100 volunteers (mostly young female university students), which provided preliminary indications that expected effectiveness of medication depends on the route of administration and targeted symptom. Based on the pilot, the questionnaire was optimized for the current research questions (e.g., rephrasing questions, focus on

specific routes, symptoms, and characteristics). First, a brief description of each of the forms of administration was shown along with a photo on which the form was presented in a standardized manner (see Supplementary Section 5.1). Subsequently, respondents rated the expected effectiveness of pain- and itch-relieving medication administered in the different forms ("How effective do you think pain-relieving/itch-relieving medications are when they are used in the following forms?") on a horizontal visual analogue scale (VAS) ranging from *not effective at all* (0) to *very much effective* (100). Next, respondents rated to what extent they expected 7 other characteristics to be applicable to each of the forms of administration, irrespective of the targeted symptom, specifically: 1) side effects, 2) long-lasting effect, 3) rapid onset, 4) safe, 5) frightening, 6) expensive, 7) easy to use. These items were rated on a horizontal VAS ranging from *not at all applicable* (0) to *very much applicable* (100). While the aforementioned sub-parts of the questionnaire (i.e., expected effectiveness and expected other characteristics) were always presented in the same order, the presentation of the forms of medication administration, symptoms, and other characteristics within these sub-parts was automatically randomized.

Demographics. Respondents reported several demographic characteristics, including age, sex, province of residence, educational level, nationality, mother tongue, fluency in Dutch language, religious or ideological affiliation, and marital status.

Health. To assess health, respondents answered questions about being in treatment for long-lasting (≥ 1 month) medical or psychological complaints or diseases (e.g., diabetes, pain, high blood pressure, or depression; dichotomous scale), presence of chronic pain (≥ 3 months) or itch (≥ 6 weeks) at present or in the past (dichotomous scale), and intensity of current pain and itch (0-100 VAS). The Short Form-12 (SF-12) [205] was used to measure health status (12 items, various Likert scales). Scores on the physical component summary and the mental component summary of the SF-12 were calculated using item response theory [205], with higher scores indicating a better physical or mental health status, respectively.

Frequency of medication use. To assess medication use, respondents reported how often they used pain- and itch-relieving medication in each form of administration throughout their lives (7-point Likert scale, higher scores indicate more frequent use).

Medication attitude. To measure general beliefs about the harmfulness of medication and doctor's over-prescription of medication, the general harm and overuse scales of the Beliefs about Medication Questionnaire (BMQ) [137] were used (2 x 4 items, 5-point Likert scale). The total score of each scale ranges from 4 to 20, with higher scores indicating more negative beliefs. Cronbach's alpha was .73 for the harm scale and .78 for the overuse scale in this study. Respondents also reported whether they were

employed in health care at any time point and, if so, whether they prescribed medication to patients (dichotomous scales).

Personality characteristics. To measure dispositional optimism, the revised Life Orientation Test (LOT-R) [258] was used (3 positive, 3 negative, and 4 filler items, 5-point Likert scale). The total score ranges from 0 to 24, with higher scores indicating higher optimism. Cronbach's alpha was .76 in this study. To measure neuroticism, the neuroticism scale of the revised short version of the Eysenck Personality Questionnaire (EPQ-RSS) [253] was used (12 items, dichotomous scale). The total score ranges from 0 to 12, with higher scores indicating more neuroticism. Cronbach's alpha was .88 in this study.

Response quality

To assess whether respondents were paying attention to the questions, two control items were included (after around 1/3 and 2/3 of the survey) [73] that instructed respondents to answer on the lowest or highest end of a 0-100 VAS, respectively. Answers deviating more than 10 points from the required answer were considered incorrect. The survey ended with two questions to assess how well respondents understood and read the questions (4-point Likert scale) to filter out respondents who did not understand or read many or all questions well. Respondents were also given the opportunity to report questions and remarks, and survey completion time was recorded. By using *forced response* validation, participants were required to answer all questions to prevent missing data.

Statistical analyses

The 6 different forms of medication administration were grouped into 3 categories - indicating the oral (i.e., tablet and capsule), injection (i.e., syringe and infusion), and topical (i.e., cream and gel) routes of medication administration - by averaging the values of the two forms within each category. Confirmatory principal component analysis with oblimin rotation confirmed this three-factor structure of the expected effectiveness for both relieving pain and itch, separately (see Supplementary Tables 6.1 & 6.2).

For the primary research question, regarding the expected effectiveness of medication administered via the different routes for relieving pain and itch, a 3 x 2 repeated measures analysis of variance (RM–ANOVA) was used. Within-subjects independent variables were 1) route of medication administration (oral, injection, or topical) and 2) symptom (pain or itch), and the dependent variable was expected effectiveness. First, the interaction effect of route-by-symptom was inspected. If the

interaction was significant, the main effects of route on expected effectiveness were analyzed with separate RM-ANOVAs for pain and itch. In case no interaction of route-by-symptom was observed, the main effect of route was examined irrespective of symptom. If a significant main effect of route was observed, pairwise comparisons between the different routes of administration were examined.

Expectations about other characteristics of the routes of medication administration (e.g., side effects), which were assessed irrespective of symptom, were explored using a separate RM-ANOVA for each of the characteristics. For each analysis, the independent variable was the route (oral, injection, or topical), and the dependent variable was the expectation about the characteristic. If a significant main effect of route was observed, pairwise comparisons between the different routes were examined.

Furthermore, we explored possible correlates of expected effectiveness of medication. For continuous variables, correlation analyses were used to explore the association of expected effectiveness of medication overall (i.e., mean value across routes and symptoms) with expectations about the other characteristics of the routes and with respondent characteristics. For categorical variables, univariate ANOVAs were used with the characteristics as between-subjects independent variable and expected effectiveness of medication overall as dependent variable.

All data were analyzed using SPSS Statistics version 23 (IBM Corporation, Armonk, NY, USA), with a two-tailed significance level of $\alpha = .05$. For the primary analyses, the inheritance procedure was used to correct for multiple testing ($3/5\alpha$ for main effects, $\alpha/4$ for contrasts [104]). For the additional analyses the *p* values were not corrected given the exploratory nature of these analyses. Because of the large sample size and number of analyses, we focused on effect sizes rather than on *p* values. For (RM) ANOVAs, generalized eta squared (η_G^2) was calculated, with .01, .06, and .14 indicating small, medium, and large effects, respectively [176]. For correlation analyses, Pearson's *r* values of .10, .30, and .50 were interpreted as indicating small, medium, and large correlations, respectively [55]. In case the assumptions of the RM ANOVAs for the primary analyses were violated, sensitivity analyses were conducted using 1) transformed data and/or 2) winsorized data, i.e., where the effect of outliers (absolute *z* score > 3.29) is reduced by replacing the raw score with the most extreme raw score that was not an outlier, plus/minus 1 for each consecutive outlier. The results of these sensitivity analyses yielded the same conclusions as the uncorrected analyses. For all RM ANOVAs in which variables with more than 2 levels were compared, violations of the assumption of sphericity were corrected using the Greenhouse-Geisser (if $\varepsilon < .75$) or Huynh-Feldt (if $\varepsilon > .75$) procedures.

Results

Respondents

In total 904 respondents reacted to the invitation to participate in the study. Of these, 112 respondents did not actually begin participation, and 234 respondents did not complete the survey and/or answered one or both of the control questions incorrectly (i.e., deviation of more than 10 points from the required answer). Two respondents were not fluent in the Dutch language. Another 40 respondents were over quota (in terms of sex, age, or province of residence). Five respondents completed the survey very fast (in less than 1/3 of the median time, i.e., < 6.4 min), causing uncertainty about the reliability of the data, and 3 respondents indicated not having understood or read many or all questions well. After excluding the data of all these respondents, the complete data of 508 respondents were available for analyses. Demographics, health, frequency of medication use, medication attitude, and personality characteristics of the final sample are reported in Table 6.1.

Expected effectiveness

The expected effectiveness of pain- and itch-relieving medication administered via each of the 3 routes is depicted in Figure 6.1 (see Supplementary Table 6.3 for the exact values). The RM ANOVA showed a large interaction effect of route by symptom on expected effectiveness (F (1.41, 714.22) = 448.99, p < .001, η_G^2 = .24). Subsequent ANOVAs showed a large main effect of route for pain (F (1.66, 839.37) = 628.29, p < .001, η_G^2 = .47) and a medium main effect of route for itch (F (1.50, 761.86) = 50.12, p < .001, η_G^2 = .07). Pairwise comparisons indicated medium and large differences for pain; injected medication was expected to be more effective than oral medication (F (1, 507) = 148.61, p < .001, η_G^2 = .11) and topical medication (F (1, 507) = 875.34, p < .001, η_G^2 = .50), and oral medication was expected to be more effective than topical medication (F (1, 507) = 572.39, p < .001, η_G^2 = .37). For itch, effect sizes indicated small and medium differences between the routes; topical medication was expected to be more effective than injected medication (F (1, 507) = 38.58, p < .001, η_G^2 = .05) and oral medication (F (1, 507) = 80.28, p < .001, η_G^2 = .10), and injected medication was expected to be more effective than oral medication (F (1, 507) = 10.25, p = .006, η_G^2 = .01).

Table 6.1. Demographics, health, frequency of medication use, medication attitude, and personality characteristics of the final sample (*n* = 508)

	Mean / *n*	***± SD* / %**
Demographics		
Age *(range 18-75)*	47.0	(±16.1)
Sex *(% men)*	247	(48.6%)
Educational level		
Primary	6	(1.2%)
Secondary	304	(59.8%)
Tertiary	198	(39.0%)
Nationality		
Dutch	497	(97.8%)
Other	6	(1.2%)
Multiple	5	(1.0%)
Religious or ideological affiliation		
None	300	(59.1%)
Christian	178	(35.0%)
Other	30	(5.9%)
Marital status		
Single	175	(34.4%)
In relationship	333	(65.6%)
Health		
Currently in treatment for long-lasting medical or psychological complaints or diseases	218	(42.9%)
Chronic pain past	148	(29.1%)
Chronic itch past	66	(13.0%)
Chronic pain present	140	(27.6%)
Chronic itch present	51	(10.0%)
Current pain intensity *(0-100 VAS)*	25.9	(±30.4)
Current itch intensity *(0-100 VAS)*	12.0	(±21.7)
Physical health status (SF-12)	47.9	(±11.5)
Mental health status (SF-12)	46. 3	(±12.1)
Frequency of medication use		
Frequency of pain-relieving medication use *(1-7 Likert scale)*	2.1	(±0.9)
Frequency of itch-relieving medication use *(1-7 Likert scale)*	1.3	(±0.5)
Medication attitude		
Beliefs about medication – general harm (BMQ) *(theoretical range 4-20)*	10.6	(±2.7)
Beliefs about medication – general overuse (BMQ) *(theoretical range 4-20)*	12.5	(±3.0)
Health care employee in past or present	75	(14.8%)
If health care employee: prescribed medication in past or present	38	(7.5%)
Personality characteristics		
Optimism (LOT-R) *(theoretical range 0-24)*	13.9	(±3.8)
Neuroticism (EPQ-RSS) *(theoretical range 0-12)*	3.8	(±3.6)

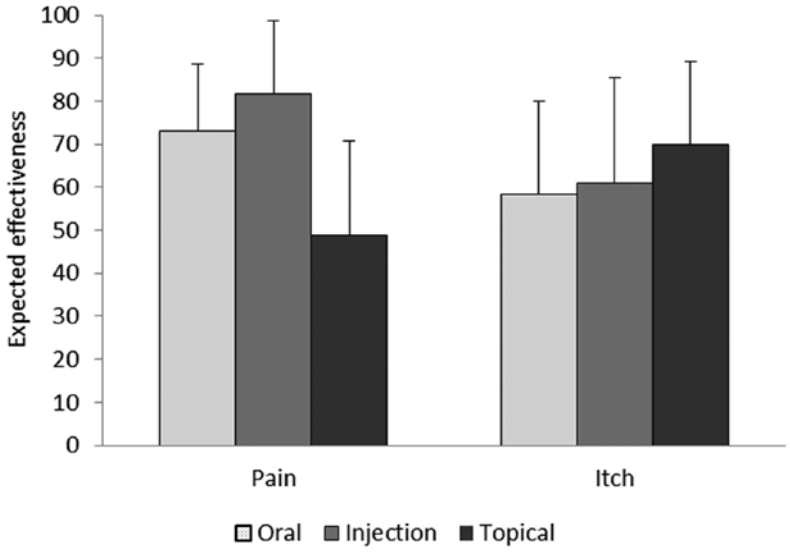


Figure 6.1. Expected effectiveness of pain- and itch-relieving medication administered via the 3 routes as rated on a visual analogue scale ranging from not effective at all (0) to very much effective (100) (mean, error bars indicate standard deviation)

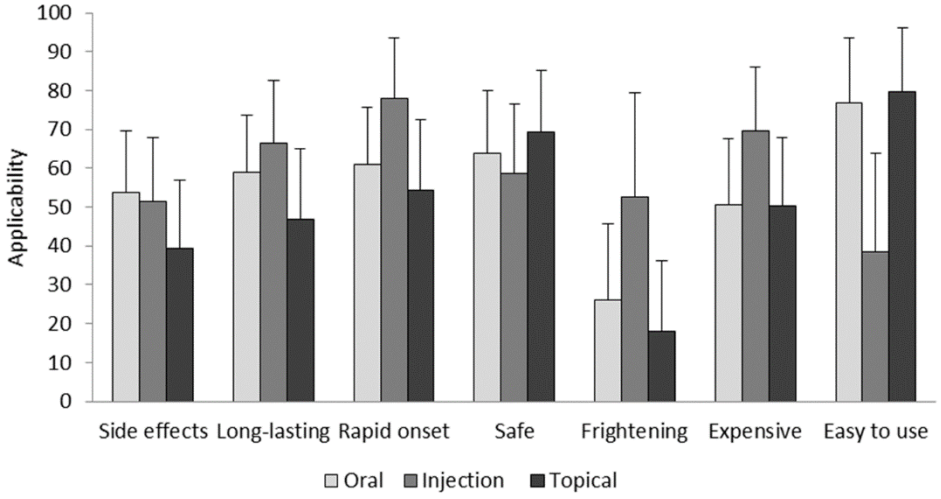


Figure 6.2. Expectations about other characteristics of the 3 routes of medication administration (irrespective of the targeted symptom) as rated on a visual analogue scale ranging from not at all applicable (0) to very much applicable (100) (mean, error bars indicate standard deviation)

Other expected characteristics of the routes of administration

Expectations about the other characteristics of the routes of administration (side effects, long-lasting, rapid onset, safe, frightening, expensive, easy to use) are depicted in Figure 6.2 (see Supplementary Table 6.3 for the exact values). A significant medium or large main effect of the 3 routes was observed for all 7 characteristics (all $p < .001$, $\eta_G^2 = .10 - .55$). Pairwise comparisons further showed significant differences between all routes for all characteristics (all $p \leq .003$), varying in size ($\eta_G^2 = .01 - .55$), with one exception; oral and topical medication did not significantly differ in expected cost ($p = .53$, $\eta_G^2 < .01$). Test-statistics for all pairwise comparisons are reported in Supplementary Table 6.4.

Correlates of expected effectiveness

The test-statistics of all analyses testing associations of the overall expected effectiveness (irrespective of route and symptom) with other route and respondent characteristics are reported in Table 6.2 (see Supplementary Table 6.5 for associations per route and symptom). A higher expected effectiveness was moderately ($r \geq .30$) associated with expectations of medication having more long-lasting effects, a more rapid onset, and being more safe and easy to use (all $p < .001$). Statistically significant but small associations ($r \geq .10$ or $\eta_G^2 \geq .01$) were observed between higher expected effectiveness and expectations of medication being less frightening, having experienced chronic pain in the past, more frequent use of itch-relieving medication, less negative general beliefs about harm and overuse of medication, and having been or being employed in health care (all $p < .05$). Associations with all other variables did not reach statistical significance (see Table 6.2).

Discussion

The current study set out to gain a better understanding of differential placebo effects by studying underlying expectations about the effectiveness of medication administered via different routes for relieving both pain and itch. The survey, in a large and representative sample of the Dutch population, showed for the first time that the expected effectiveness of medication depended not only on the route of medication administration (oral, injection, or topical), but also on the targeted symptom (pain or itch). Specifically, while pain-relieving medication was expected to be most effective when administered via injection (and least effective when administered topically), itch-

Table 6.2. Associations between overall expected effectiveness of medication with other route and respondent characteristics

	[a]	**Expected effectiveness** [b]
Other expected characteristics of the routes [c]		
Side effects	*r*	-.06
Long-lasting effect	*r*	**.44*** **
Rapid onset	*r*	**.49*** **
Safe	*r*	**.42*** **
Frightening	*r*	-.20***
Expensive	*r*	.05
Easy to use	*r*	**.31*** **
Demographics		
Age	*r*	.04
Sex	η_G^2	< .01
Educational level	η_G^2	< .01
Religious or ideological affiliation	η_G^2	< .01
Marital status	η_G^2	< .01
Health		
Currently in treatment for long-lasting medical or psychological complaints or diseases	η_G^2	< .01
Chronic pain past	η_G^2	.01*
Chronic itch past	η_G^2	< .01
Chronic pain present	η_G^2	.01
Chronic itch present	η_G^2	< .01
Current pain intensity	*r*	.05
Current itch intensity	*r*	-.01
Physical health status (SF-12)	*r*	-.07
Mental health status (SF-12)	*r*	-.03
Frequency of medication use		
Frequency of pain-relieving medication use	*r*	.09
Frequency of itch-relieving medication use	*r*	.11*
Medication attitude		
Beliefs about medication - general harm (BMQ)	*r*	-.11*
Beliefs about medication - general overuse (BMQ)	*r*	-.16***
Health care employee (past or present)	η_G^2	.02**
If health care employee (*n* = 76): prescribed medication (past or present)	η_G^2	.05
Personality characteristics		
Optimism (LOT-R)	*r*	.08
Neuroticism (EPQ-RSS)	*r*	-.01

Note. [a] *r* = Pearson correlation coefficient (for continuous variables); η_G^2 = generalized eta squared (for categorical variables). [b] The overall expected effectiveness is calculated across the different routes of medication administration and symptoms. [C] The overall expected characteristics are calculated across the different routes of medication administration. * p < .05, ** p < .01, *** p < .001; *p* values are unadjusted. Medium and large effect sizes are printed in bold.

relieving medication was expected to be most effective when administered topically (and least effective when administered orally).

Additional exploratory analyses showed that, irrespective of pain or itch symptoms, expectations about characteristics other than effectiveness also differed between the routes. Injections were expected to have the most rapid onset and long-lasting effects, and to be most frightening and expensive, while topical medication was expected to be the safest and easiest to use, and oral medication to have the most side effects. An exploration of the correlates of expected effectiveness of medication indicated that a higher expected effectiveness was moderately associated with expectations of medication having more long-lasting effects, a more rapid onset, and being more safe and easy to use. Expected effectiveness was not or only weakly associated with other expected characteristics of the routes (i.e., side effects, frightening, expensive) and the measured respondent characteristics (i.e., demographics, health, frequency of medication use, medication attitude, and personality characteristics).

The finding that expectations about the effectiveness of medication differed for different routes of administration is in line with previous research demonstrating differential placebo effects on pain for different routes of medication administration. However, the common belief that more invasive routes (such as injections) are more effective [150,177,265] is challenged by the finding that the expected effectiveness of medication administered via different routes depended on the targeted symptom. Although injections were indeed expected to be most effective for relieving pain, injections were second to topically administered medication for relieving itch. Also the finding that oral medication was expected to be more effective for relieving pain than topical medication could be interpreted as contradicting this idea, as the topical route is often believed to be more complex than the oral route [e.g., 87]. Moreover, previous research into pain relief also does not consistently support the idea of enhanced placebo effects for more invasive routes [18,71,87,192,203,221,265,323]. In addition, we found associations of a higher expected effectiveness with better expected safety and ease of use, but no substantial associations with side effects, being frightening, and c, which also does not support the importance of invasiveness. Especially the lack of an association with cost is surprising, as previous studies indicated larger placebo effects with expensive versus cheap placebos [82,308]. In sum, invasiveness cannot fully explain differential placebo effects for different routes.

A second explanatory factor for differential expectancies and placebo effects may be previous experiences, as learning accounts of placebo effects suggest they shape expectancies [59,222]. However, we found no or only small associations of expected

effectiveness with frequency of medication use, and with the presence and history of chronic pain and itch. Third, people might also expect medication to be most effective when administered via the most common route. Itch-relieving medications are indeed most commonly administered topically. However, pain-relieving medications are most commonly administered orally, rather than via injections. Fourth, the location of symptoms might play a role. Because itch is typically located on the skin, a topical medication seems an obvious choice, and since pain can occur at almost any location in the body, one might expect routes with systemic effects (injections or oral medications) to be more effective for relieving pain. Last, respondent characteristics, particularly personality characteristics that pertain to expectancies (i.e., optimism and neuroticism), have frequently been considered as possible moderators of placebo effects and several studies support this [135,311]. However, current associations of expected effectiveness with the measured demographics, health, medication attitude, and personality characteristics were statistically small or non-significant. In sum, multiple factors together, not just invasiveness, appear to underlie differential expectations about effectiveness of medication administered via different routes.

Several limitations of our study need to be acknowledged. First, we did not specify the nature of pain and itch (e.g., duration, location, intensity), nor a specific medication (e.g., over-the-counter vs. prescription drug). This allowed us to draw general inferences, but expectations about the different routes might also depend on these specifics. Second, although the current study design allowed us to measure numerous forms of medication administration and possible correlates of expected effectiveness, our assessments are by no means complete. Comparisons with other forms of administration (e.g., rectal) and other types of treatment (e.g., surgery), and associations with other respondent characteristics (e.g., generalized self-efficacy, genetic variations) might be considered for future research. Also, we did not ask respondents about the quality of their previous experiences with pain- and itch-relieving medication, e.g., whether they had experienced successful pain or itch relief, but this may significantly influence respondents' expectancies and should be considered in future research. Third, we consider it a strength of our study that we used a large sample representative of the Dutch population in terms of age, sex, and province of residence. Nonetheless, it should be noted that the sample is limited to people who registered to commercial online research panels and our findings may not fully generalize to the whole population or specific patient samples.

The current finding that the expected effectiveness of medication depends on the route of medication administration and the targeted symptom, has important implications for clinical research and practice, as patients' expectations are important

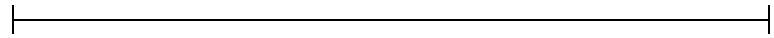
predictors of placebo effects and hence treatment outcome [222]. It challenges the classic interpretation of placebo-controlled trials, as their results do not only depend on responses to the active medication but also on responses to the placebo. As illustrated by the efficacy paradox [310], differential placebo effects imply that the medication with the greatest effect compared with its placebo control is not necessarily the most effective. This emphasizes the importance of direct head-to-head comparisons to find the medication and route of administration that is most effective for a specific symptom or disease. Furthermore, the differential results for pain and itch indicate that research showing placebo effects on pain cannot directly be generalized to other symptoms, even when underlying mechanisms largely overlap, as with itch. In clinical practice, it is important to take patients' and doctors' expectations into account. Keeping in mind the influence of the information a physician provides when administering medication on expectancies and consequently treatment outcome [221], the effectiveness of medication, as well as treatment adherence, might be enhanced by actively discussing a patients' expectations about the available or preferred route of administration. For example, when a physician prescribes topical medication for pain, relatively low effectiveness expectancies can be enhanced by expressing the intended positive outcomes, and might possibly also be enhanced by highlighting associated characteristics of the route such as safety and ease of use. Alternatively, on some occasions when several equally effective routes are available, it may be possible to select the route the patient expects to be most effective for administering a particular medication, or to switch to a different route if a patient's previous experiences were negative [131].

In conclusion, we found that the expected effectiveness of medication depended on both the route of administration (oral, injection, or topical) and the targeted symptom (pain or itch). In addition, the expected effectiveness was found to be associated with expectations about other characteristics of the routes (onset, duration, safety, and ease of use). Most importantly, our results indicate that findings from pain research cannot readily be translated to other symptoms. Instead, the findings suggest that differential placebo effects exist, and multiple factors, not merely invasiveness of the route of administration, are at play. The current findings have important implications for the interpretation of placebo-controlled trials and suggest that medication effects may be enhanced when taking the route of administration into account in clinical practice.

Supplementary materials Chapter 6

Supplementary Section 6.1. Questionnaire Expectations about Medication (English translation)

Questions on expectations about medication
In this questionnaire, you will be asked what you expect about different forms of medication, such as a pill or cream.
You can answer each question on a scale of *not at all* to *very much.* You can see an example of this scale below. Answer by moving the bar to a location that fits best with your opinion. You can do so by clicking on the bar and dragging it to the desired location on the scale. You can also directly click on the desired location.
At each question, the bar is automatically located in the middle of the scale. If this position matches with your answer, could you then still click on the bar? Otherwise, the software will consider the question as unanswered.
There are no right or wrong answers. We are interested in your personal opinion.

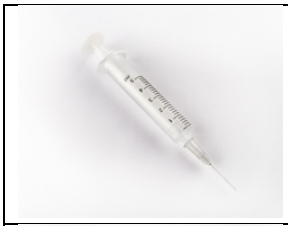


Not at all Very much

Description of the forms of medication
The questionnaire is about 6 forms of medication. Below you can find a brief description of each form.

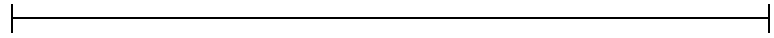
[presented in random order]

	**Tablet** A tablet is a round, flat pill. The medication is contained as a powder in this pill. A tablet is taken via the mouth.
	**Capsule** A capsule is an oval container. The medication is contained as a powder in this container. A capsule is taken via the mouth.

	**Syringe** A syringe is a vial with a hollow needle attached to it. The medication is dissolved in a fluid and is contained in the vial. The fluid is injected into the body via the needle.
	**Infusion** An infusion consists of a small bag that is connected to a hollow needle via a tube. The medication is dissolved in a fluid and is contained in the bag. The fluid enters the body via the needle.
	**Cream** Cream is a fatty spreadable substance. The medication is dissolved in this substance. Cream is applied to the skin.
	**Gel** Gel is a transparent spreadable substance. The medication is dissolved in this substance. Gel is applied to the skin.

Effective against pain/itch
How effective do you think **[pain-relieving/itch-relieving] medications** are when they are used in the following forms?

- tablet
- capsule
- syringe
- infusion
- cream
- gel

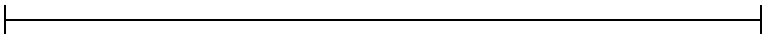


[Symptoms and forms (always accompanied by photo) are presented in random order.]

General characteristics

To what extent do you think each of the following characteristics applies to a [**form**]?

- side effects
- long-lasting effect
- rapid onset
- safe
- frightening
- expensive
- easy to use



Not applicable at all

Very much applicable

[Forms (always accompanied by photo) and characteristics are presented in random order.]

Supplementary Table 6.1. Confirmatory principal components analysis of the expected effectiveness of the six forms of medication administration for relieving pain

	Component		
	1	2	3
Tablet	-0.06	0.02	**-0.96**
Capsule	0.12	-0.02	**-0.87**
Syringe	**0.91**	-0.01	-0.04
Infusion	**0.93**	0.02	0.01
Cream	-0.08	**0.92**	-0.11
Gel	0.08	**0.96**	0.09

Note. Pattern matrix of the oblimin rotation with Kaiser normalization.

Supplementary Table 6.2. Confirmatory principal components analysis of the expected effectiveness of the six forms of medication administration for relieving itch

	Component		
	1	2	3
Tablet	-0.06	0.01	**-1.00**
Capsule	0.09	-0.02	**-0.90**
Syringe	**0.92**	-0.02	-0.03
Infusion	**0.97**	0.02	0.02
Cream	≈-0.01	**0.95**	0.02
Gel	<0.01	**0.95**	-0.02

Note. Pattern matrix of the oblimin rotation with Kaiser normalization.

Supplementary Table 6.3. Means (± standard deviations) of expected effectiveness of medication and expectations about other characteristics of the routes, as rated on 0-100 visual analogue scales

Characteristics	**Overall**		**Oral**		**Injection**		**Topical**	
Effectiveness								
Pain relief	67.9	(13.4)	73.0	(15.6)	81.8	(16.8)	48.8	(22.0)
Itch relief	63.0	(15.4)	58.3	(21.7)	60.9	(24.6)	69.9	(19.4)
Side effects	48.2	(12.6)	53.7	(15.8)	51.6	(16.3)	39.3	(17.6)
Long-lasting effect	57.4	(12.0)	59.0	(14.8)	66.3	(16.2)	46.8	(18.2)
Rapid onset	64.5	(10.7)	61.0	(14.7)	77.9	(15.6)	54.4	(18.1)
Safe	64.0	(12.8)	63.8	(16.3)	58.8	(17.8)	69.3	(15.9)
Frightening	32.2	(16.1)	26.1	(19.7)	52.7	(26.9)	17.9	(18.4)
Expensive	56.9	(12.5)	50.7	(16.8)	69.7	(16.3)	50.2	(17.6)
Easy to use	65.0	(12.7)	76.8	(16.7)	38.6	(25.3)	79.7	(16.5)

Supplementary Table 6.4. Comparisons of expected effectiveness of medication and of expectations about other characteristics of the routes

Characteristics	Main effect route of administration	Oral vs Injection	Oral vs Topical	Injection vs Topical
Effectiveness				
Pain relief	F (1.66, 839.37) = 628.29, p < .001, η_G^2 = **.47** [a]	F (1, 507) = 148.61, p < .001, η_G^2 = **.11** [b]	F (1, 507) = 572.39, p < .001, η_G^2 = **.37** [b]	F (1, 507) = 875.34, p < .001, η_G^2 = **.50** [b]
Itch relief	F (1.50, 761.86) = 50.12, p < .001, η_G^2 = **.07** [a]	F (1, 507) = 10.25, p = .006, η_G^2 = .01 [b]	F (1, 507) = 80.28, p < .001, η_G^2 = **.10** [b]	F (1, 507) = 38.58, p < .001, η_G^2 = .05 [b]
Side effects [c]	F (1.88, 953.10) = 178.58, p < .001, η_G^2 = **.19**	F (1, 507) = 9.17, p = .003, η_G^2 = .01	F (1, 507) = 275.16, p < .001, η_G^2 = **.22**	F (1, 507) = 194.10, p < .001, η_G^2 = **.16**
Long-lasting effect [c]	F (1.74, 880.62) = 260.79, p < .001, η_G^2 = **.27**	F (1, 507) = 93.01, p < .001, η_G^2 = **.08**	F (1, 507) = 240.05, p < .001, η_G^2 = **.17**	F (1, 507) = 367.04, p < .001, η_G^2 = **.31**
Rapid onset [c]	F (1.84, 934.86) = 337.31, p < .001, η_G^2 = **.35**	F (1, 507) = 421.48, p < .001, η_G^2 = **.31**	F (1, 507) = 53.33, p < .001, η_G^2 = .05	F (1, 507) = 494.71, p < .001, η_G^2 = **.39**
Safe [c]	F (1.88, 951.07) = 82.37, p < .001, η_G^2 = **.10**	F (1, 507) = 36.71, p < .001, η_G^2 = .03	F (1, 507) = 59.17, p < .001, η_G^2 = .04	F (1, 507) = 135.01, p < .001, η_G^2 = **.12**
Frightening [c]	F (1.47, 743.07) = 499.74, p < .001, η_G^2 = **.42**	F (1, 507) = 437.48, p < .001, η_G^2 = **.32**	F (1, 507) = 125.33, p < .001, η_G^2 = **.07**	F (1, 507) = 664.77, p < .001, η_G^2 = **.44**
Expensive [c]	F (1.81, 919.59) = 319.81, p < .001, η_G^2 = **.31**	F (1, 507) = 443.51, p < .001, η_G^2 = **.32**	F (1, 507) = 0.41, p = .53, η_G^2 < .01	F (1, 507) = 392.69, p < .001, η_G^2 = **.32**
Easy to use [c]	F (1.57, 795.84) = 751.18, p < .001, η_G^2 = **.55**	F (1, 507) = 829.36, p < .001, η_G^2 = **.52**	F (1, 507) = 12.75, p < .001, η_G^2 = .01	F (1, 507) = 948.99, p < .001, η_G^2 = **.55**

Note. [a] p values of these repeated measures analysis of variance are corrected according to inheritance procedure (p / ⅗ [104]); [b] p values of these repeated measures analysis of variance are corrected according to inheritance procedure (p x 4 [104]); [c] p values are unadjusted. Medium and large effect sizes are printed in bold.

Supplementary Table 6.5. Associations of the expected effectiveness of medication with expectations about other characteristics of the routes and with respondent characteristics, both across routes of administration and symptoms (overall) and separately per route of administration and symptom

		Expected effectiveness						
		Overall	Pain			Itch		
	[a]		Oral	Injection	Topical	Oral	Injection	Topical
Other characteristics of the routes [b]								
Side effects	*r*	-.06	-.10*	-.03	.05	-.03	-.02	<.01
Long-lasting effect	*r*	**.44*****	**.42*****	**.36*****	**.39*****	**.31*****	.26***	.26***
Rapid onset	*r*	**.49*****	**.43*****	**.57*****	**.36*****	.24***	.25***	**.37*****
Safe	*r*	**.42*****	**.37*****	.27***	.17***	.18***	.26***	.26***
Frightening	*r*	-.20***	-.23***	-.05	.05	-.11*	-.19***	-.20***
Expensive	*r*	.05	-.03	.23***	-.03	.06	.03	-.06
Easy to use	*r*	**.31*****	**.31*****	.02	.04	.12**	.23***	.27***
Demographics								
Age	*r*	.04	-.01	-.02	.01	.07	.10*	-.05
Sex	η_G^2	< .01	< .01	< .01	< .01	< .01	< .01	.01*
Educational level	η_G^2	< .01	< .01	< .01	< .01	.02*	.02*	.01
Religious or ideological affiliation	η_G^2	< .01	< .01	< .01	< .01	< .01	< .01	< .01
Marital status	η_G^2	< .01	< .01	< .01	< .01	< .01	< .01	< .01
Health								
Currently in treatment for long-lasting medical or psychological complaints or diseases	η_G^2	< .01	< .01	< .01	< .01	.01	< .01	< .01
Chronic pain past	η_G^2	.01*	< .01	.01	< .01	-	-	-
Chronic itch past	η_G^2	< .01	-	-	-	< .01	< .01	< .01
Chronic pain present	η_G^2	.01	< .01	.01	< .01	-	-	-
Chronic itch present	η_G^2	< .01	-	-	-	< .01	< .01	< .01
Current pain intensity	*r*	.05	.04	.07	-.04	-	-	-
Current itch intensity	*r*	-.01	-	-	-	.01	-.02	-.01
Physical health status (SF-12)	*r*	-.06	-.01	-.07	.07	-.13**	-.11*	.04
Mental health status (SF-12)	*r*	-.02	-.01	-.04	.04	-.01	-.01	-.06
Frequency of medication use [b]								
Frequency of pain-relieving medication use	*r*	.09	.05	.10*	.10*	-	-	-
Frequency of itch-relieving medication use	*r*	.11*	-	-	-	.19***	.02	.15**

Continues on next page

Supplementary Table 6.5. *continued*

		Expected effectiveness						
		Overall	Pain			Itch		
	[a]		Oral	Injection	Topical	Oral	Injection	Topical
Health care employee (past or present)	η_G^2	.02**	< .01	.01**	< .01	.02**	.02**	< .01
If health care employee (*n* = 76): prescribed medication (past or present)	η_G^2	.05	.01	.03	**.11****	.03	.01	.04
Personality characteristics								
Optimism (LOT-R)	*r*	.08	.09	.09*	.07	.01	-.02	.11*
Neuroticism (EPQ-RSS)	*r*	-.01	< .01	< .01	-.02	-.02	-.03	.04

Note. [a] *r* = Pearson correlation coefficient (for continuous variables); η_G^2 = generalized eta squared (for categorical variables). [b] correlations between corresponding routes are reported (i.e., oral *vs.* oral; injection *vs.* injection, and topical *vs.* topical). * $p < .05$, ** $p < .01$, *** $p < .001$; *p* values are unadjusted. Medium and large effect sizes are printed in bold.

CHAPTER 7

SUMMARY & GENERAL DISCUSSION

SUMMARY

Placebo effects are health improvements following the administration of an inert treatment (i.e., placebo). These effects are typically ascribed to a person's expectations about the beneficial outcomes of taking the placebo. Particularly pain has reliably been found to be prone to placebo effects, as well as to placebo-like effects that can occur due to expectations about an active treatment or no treatment at all. Also other physical symptoms, such as itch and fatigue, have been found to be prone to these effects, although more incidentally. Treatment of physical symptoms may be enhanced by harnessing placebo-and placebo-like effects in clinical practice. To do so effectively, a deeper understanding of placebo and placebo-like effects and the role of expectancies herein is crucial for both researchers and clinicians.

The main aim of the current thesis was to address ways of harnessing placebo effects for relieving pain and other physical symptoms by targeting expectancies. Most importantly, we studied several expectation inductions (i.e., verbal suggestion, conditioning, and mental imagery) to assess their individual, comparative, and combined effectiveness for relieving physical symptoms, primarily pain. We additionally investigated the role of treatment characteristics (i.e., route of medication administration) and individual characteristics (e.g., personality characteristics) in placebo and placebo-like effects.

In **Chapter 2**, we reviewed the theoretical and empirical literature on the influence of expectancies on pain. In the dominant psychological learning theories, expectancies were found to play a key role. Three kinds of expectancies could be distinguished: stimulus expectancies (pertaining to external stimuli or events, like receiving a prescription for medication), response expectancies (pertaining to internal, nonvolitional experiences, like pain), and self-efficacy expectancies (pertaining to the ability to perform behavior, like to engage in physical activity despite pain). Of these, response expectancies are typically considered to be the core mechanism of placebo and placebo-like effects, and to exert the largest influence on pain, as they directly pertain to the experience itself. Three learning processes of expectancies are generally theorized: instructional learning (e.g., verbal suggestion), conditioning, and observational learning. In addition, expectancies may be learned via mental imagery. We also discussed multifaceted expectancy constructs (e.g., optimism), in which the co-occurrence of expectancies with related emotions and cognitions is captured. Particularly optimism and pain catastrophizing were found to be associated with pain, but also trust, worry, and neuroticism appeared influential, although research is more

limited. In sum, our review underlined the important influence of expectancies on pain, while also providing some understanding of the complexity of expectancies. Modifying expectancies by addressing the different learning processes appears promising for harnessing placebo and placebo-like effects.

In **Chapter 3**, we systematically investigated the available empirical literature on the magnitude of the effects of brief expectation interventions on patients' pain in a meta-analysis. We found that verbal suggestion, conditioning, and mental imagery relieved pain in clinical samples. The evidence that verbal suggestions of the analgesic qualities of a treatment (placebo or active) can induce placebo and placebo-like effects on patients' pain was particularly strong; a substantial number of studies indicated effects that were on average statistically medium to large. Only few studies assessed conditioning procedures, which were always reinforced by verbal suggestions. Surprisingly, their effects were not larger than those of verbal suggestion alone. Brief imagery exercises (e.g., using images of pain reduction due to numbness) had relatively small, though promising, effects on patients' pain. We explored several factors that might moderate the effects of the expectation inductions. Notably, we observed that the effects of verbal suggestion on experimental and, especially, acute procedural pain (e.g., post-surgery pain) were substantially larger than the effects on chronic pain (e.g., ongoing neuropathic pain). We further found indications that verbal suggestions were more effective when they referred to injected placebos rather than orally or topically administered placebos. Taking everything together, our meta-analysis suggests that findings from experimental research generalize to clinical settings in the case of acute procedural pain, although less so in case of chronic pain. Expectation interventions, especially verbal suggestions, are thus promising methods for optimizing the effectiveness of regular analgesic treatment in clinical practice, at least in acute situations.

In **Chapter 4**, we studied the effects of both verbal suggestion and mental imagery on pain, itch, and fatigue as indicators of physical sensitivity. This experimental study in a healthy sample showed that a verbal suggestion stating that a (placebo) capsule can reduce sensitivity to physical sensations, such as pain, itch, and fatigue, strongly affected participants' expectations about the effects of the capsule. Also, a newly developed mental imagery exercise of a best possible health affected participants' positive and negative future expectancies. However, neither the verbal suggestion, nor the imagery exercise, nor their combination affected physical sensitivity, as indicated by the self-reported and physiological responses to the experimentally evoked pain, itch, and fatigue. We also found no evidence that individual differences, such as in participants' tendency to be more or less optimistic, predicted participants' responses. These findings

indicate that expectancy effects do not always occur. Possibly, they depend, among others, on their level of specificity, with a focus on multiple sensations at once or health in general being less effective than a focus on a specific response.

In **Chapter 5**, we investigated a newly developed imagery exercise that specifically focused on pain to study placebo-like effects. In the first of two experimental studies, healthy participants imagined that they would experience reduced pain during a subsequent pain evoking cold pressor task. They did so using the image of a warm and impermeable glove. Results showed, for the first time, that imagery of reduced pain (i.e., response imagery) could reduce subsequent pain. Importantly, these effects were mediated by the participants' expectations of the upcoming pain (i.e., response expectancies). The effects were however not accompanied by corresponding physiological responses. The second study replicated these findings. In this study, we furthermore found that an additional verbal suggestion regarding the effectiveness of the imagery exercise did not or only marginally enhance the pain reducing effects. Moreover, also in these two studies, individual differences did not appear to predict the observed effects. Together, these studies show that placebo-like effects on pain can be induced via response imagery. Response imagery thus appears to be a promising method for treating pain, even before its onset.

In **Chapter 6**, we further explored the differential placebo effects of different routes of medication administration that we observed in Chapter 2, by assessing underlying expectancies in a survey. A large sample representative of the Dutch population rated the expected effectiveness of both pain- and itch-relieving mediation when administered via different routes: oral, injection, and topical. In line with our previous findings, respondents expected injections to be most effective for relieving pain. In contrast, respondents expected topical medication to be most effective for relieving itch. These findings indicate that the expected effectiveness of medication, and hence placebo and placebo-like effects, depends on both the route of medication administration and the targeted symptom. Additional correlational analyses showed that a higher expected effectiveness was associated with expectations of medication having longer-lasting effects, a more rapid onset, and being safer and easier to use. The expected effectiveness was not or only weakly associated with expected side effects, cost, and being frightening. Also, individual differences in demographic characteristics, health, frequency of medication use, medication attitude, and personality characteristics were not or only weakly associated. Together, these findings indicate that the commonly held belief that more invasive treatments are more potent does not hold. Instead, other factors play a role as well, such as the type of targeted symptom,

and possibly the location of the symptom and the commonness of a route of medication administration for the symptom.

Taken together, the findings of the research presented in this thesis underscore the influence of expectancies on pain and the potential of using expectation interventions for enhancing the treatment of pain and other physical symptoms. We found that placebo and placebo-like effects can be induced via verbal suggestion, conditioning, and mental imagery. Most notably, our findings show that particularly verbal suggestions may enhance the short-term outcomes of analgesic treatments in patients. Moreover, we found, for the first time, that mental imagery of reduced pain (i.e., response imagery) can induce analgesia via its effects on response expectancies. Furthermore, people's expectations about the effectiveness of treatments also depended on the route of medication administration and targeted symptom. In conclusion, harnessing placebo effects by targeting expectancies is promising for enhancing standard clinical care of physical symptoms, such as pain.

GENERAL DISCUSSION

Research into placebo effects suggests that expectancies, the putative core mechanism, are important determinants of treatment outcomes. Hence, optimizing patients' expectancies is promising for enhancing treatment of physical symptoms such as pain. The main aim of the current thesis was to address ways of harnessing placebo effects for relieving pain and other physical symptoms by targeting expectancies. Most importantly, we studied the individual, comparative, and combined effectiveness of expectation inductions (i.e., verbal suggestion, conditioning, and mental imagery). We hereby studied placebo and placebo-like effects on pain and other physical symptoms, in both healthy and clinical samples. We also explored psychological and physiological mechanisms involved. Additionally, we investigated the role of treatment and individual characteristics. In this closing chapter, we summarize and discuss the findings of the research in this thesis in relation to the literature. We also address the limitations of the work, and highlight directions for future research and implications for clinical practice.

Role of expectancies in pain and other physical symptoms

In Chapter 2, we integrated theoretical and empirical literature on the influence of expectancies on pain. We showed that expectancies are a central factor in psychological learning theories, including accounts of classical conditioning and social learning theories [17,38,158,159,161,217,244,280]. In these theories, different kinds of expectancies can be distinguished: response expectancies (i.e., pertaining to internal, nonvolitional experiences), stimulus expectancies (i.e., pertaining to external stimuli or events), and self-efficacy expectancies (i.e., pertaining to the ability to perform behavior) [158,159]. These expectancies are theorized to be important determinants of behavior, events, and experiences. An examination of the empirical literature indicated that each of these kinds of expectancies can independently influence pain [15,56,141,145,160,184,234,262,297]. The most extensive evidence has been found for the influence of response expectancies on pain, which is in line with their theorized direct effect on nonvolitional responses like pain and other physical symptoms [158,159]. Theoretical views and empirical research regarding the interplay between different kinds of expectancies and related multifaceted expectancy constructs (e.g., pain catastrophizing, trust) is relatively limited [17,297].

To make use of the influence of expectancies on pain as well as other symptoms, it is important to understand how expectancies are formed. In Chapter 2 we saw that the psychological learning theories describe three processes via which expectancies can be learned: instructional learning (e.g., verbal suggestion), conditioning, and observational learning [17,38,158]. Inducing expectancies by addressing these learning processes is promising for enhancing treatment outcomes. In addition, we posed in this thesis that expectancies can also be learned via mental imagery, i.e., simulation of experiences, and that imagery exercises may be potent expectation interventions.

Effects of expectation inductions on pain and other symptoms

In the current thesis, we investigated the effects of three methods of inducing expectancies on pain and other physical symptoms (Chapter 3, 4, and 5). Specifically, we assessed placebo and placebo-like effects induced by verbal suggestion, conditioning, and mental imagery, as well as combinations of expectation inductions.

Verbal suggestion

Previous research has provided robust evidence for the influence of verbal suggestion on experimentally evoked pain in healthy samples [16,189,266,299]. An objective of the current thesis was to assess if these effects also generalize to clinical samples and to physical symptoms other than pain.

Our meta-analysis in Chapter 3 provided compelling evidence that verbal suggestion of the analgesic qualities of a placebo or active treatment can induce placebo and placebo-like effects on patients' pain. The effects were found to be especially strong for acute procedural pain (e.g., post-surgery pain). Effects on experimentally evoked pain were also substantial. This suggests that findings from experimental research in healthy samples extrapolate quite well to clinical samples when it comes to acute pain. However, verbal suggestion could only elicit modest relief from chronic pain (e.g., neuropathic pain or migraine). This is in line with a recent finding that long-term exposure to fibromyalgia pain was associated with reduced placebo analgesia [170], and might possibly be due to repeated negative treatment experiences in the past and/or the multitude of determinants of symptom chronicity [233,320]. It should be noted however that previous within-study comparisons did not indicate chronic pain to be less sensitive than experimental pain to placebo and placebo-like effects [52,226,227]. Further research is warranted. Regarding expectancies, the included studies indicated that the

effects of verbal suggestion on the different types of pain could be ascribed to expectancy modifications [52,226,261,300,301].

In Chapter 4, we assessed in a healthy sample if a verbal suggestion might be effective for not only reducing pain, but also for reducing itch and fatigue, as these symptoms frequently co-occur [2,41,54,94,185,305]. We found that a verbal suggestion stating that a (placebo) capsule can reduce sensitivity to physical sensations, such as pain, itch, and fatigue, in the majority of users strongly affected participants' expectations about the effects of the capsule. However, it did not affect self-reported pain, itch, or fatigue during the subsequent sensitivity tests. This contrasts previous findings that verbal suggestions about one specific sensation (e.g., pain, itch, or fatigue) can reduce that sensation [20,47,68,79,295]. Possibly, focusing on physical sensitivity in general, rather than on one specific sensation, might have made it difficult for participants to form a clear picture of the suggested outcome. Also, since most theories implicitly assume that an expectation that matches the level of specificity of the outcome is most predictive [17,38,159,244,257] [see also 132], we might infer that general verbal suggestions are less effective than specific suggestions, but further research is required.

Conditioning

The meta-analysis in Chapter 3 showed that conditioning procedures have infrequently been used to induce placebo analgesic effects in clinical samples. The few studies that could be included in our analyses, used conditioning procedures in which the pairings of the conditioned stimulus (e.g., placebo cream) and unconditioned stimulus (e.g., reduced pain stimulation) were always reinforced by verbal suggestion, and in which effects on experimentally evoked pain were assessed. Effects on expectancies were never assessed. Surprisingly, we found in our meta-analysis that this combination of conditioning with verbal suggestion did not exert larger effects on pain than verbal suggestion alone. This finding contrasts previous research in healthy samples, where such a combined procedure is typically found to have more robust effects than verbal suggestion alone [20,166,197]. However, the paucity of research prevents us from drawing firm conclusions about the size of conditioning effects in clinical samples and more direct comparisons of the individual and combined expectation inductions are required [166]. Furthermore, more ecologically valid conditioning paradigms, e.g., assessing the influence of effective prior treatments on current treatment outcomes [6,178], may be promising for placebo research in clinical samples.

Mental imagery

We further investigated if mental imagery could provide an additional method through which expectancies can be induced and, consequently, through which pain and other symptoms can be relieved (i.e., induction of placebo-like effects).

Our meta-analysis (Chapter 3) indicated that the effects of brief imagery exercises (e.g., imagery of pain reduction due to numbness) on patients' pain were relatively small, but nonetheless promising. Notably, these interventions were never explicitly defined as expectation interventions and expectancies were not assessed. To more systematically study imagery as a method to induce expectancies, we conducted several experimental studies.

In Chapter 4, we found that our newly developed imagery exercise, in which participants were instructed to imagine their best possible health, did not affect physical sensitivity, as indicated by the absence of effects on self-reported pain, itch, and fatigue during the sensitivity tests. Participants did report more positive and less negative general expectancies. As with the verbal suggestion of reduced physical sensitivity, this finding might be partially explained by the broad focus of the image, i.e., on health in general rather than on one specific symptom [132,257]. Furthermore, because health is often conceptualized in negative terms (e.g., absence of symptoms), an image of health might have been too abstract for participants. This might be especially critical because the participants were already healthy and, consequently, their image of optimal health might not have differed substantially from their current state.

Building on these findings, we developed an imagery exercise that was specifically focused on one sensation (i.e., response imagery). In Chapter 5, we presented the results of two studies into the effects of this response imagery exercise on pain. In both studies, participants who had first experienced pain evoked by a cold pressor task, imagined pain reduction using the image of a glove, which was described as being warm and water-impermeable. In the first study, we found that participants experienced less pain during a subsequent cold pressor test than participants who merely imagined their hand. In Study 2, we further improved the instructions of the imagery exercise and used a no treatment control condition that could more confidently be described as neutral. We again found that response imagery could induce placebo-like analgesia, with larger effects than in the first study. These findings are in line with previous findings that imagery can reduce pain [231,232,291]. Moreover, they extend these findings by showing for the first time that imagery of pain relief can affect future pain and that these effects were mediated by response expectancies.

Comparisons and combinations of expectation inductions

From our and previous research, we can infer that verbal suggestion, conditioning, and mental imagery can each, independently, induce placebo and/or placebo-like effects. A comparison of the expectation inductions in our meta-analysis in clinical samples (Chapter 3) showed that the evidence for the effectiveness of verbal suggestion was most extensive. It should be noted however that this comparison was hampered by the limited number of studies on conditioning and mental imagery, the reinforcement of conditioning by verbal suggestion, and the indirect nature of the comparison (i.e., between studies rather than within). Notably, our direct comparison of a general verbal suggestion with imagery of a best possible health in Chapter 4 showed neither one of these expectation inductions to be effective. We furthermore observed relatively large effects of response imagery on pain in a healthy sample (Chapter 5). Further comparative research could provide more information on the relative effects of the different expectation inductions in both experimental and clinical settings.

Combining different methods of inducing expectancies, each tapping into different learning processes, may be especially effective. Surprisingly however, we found no evidence for this in the current thesis. As mentioned above, our meta-analysis (Chapter 3) did not provide evidence that conditioning reinforced by verbal suggestion was more effective than verbal suggestion alone. In Chapter 4, we found that also when participants received both the positive verbal suggestion and imagery exercise, physical sensitivity (i.e., pain, itch, and fatigue) was not affected, possibly because we did not present them as connected interventions. Furthermore, we found that the pain-reducing effects of response imagery were not or only marginally enhanced when it was preceded by an additional verbal suggestion that described the effectiveness of the exercise (Chapter 5, Study 2). Perhaps this can be explained by a ceiling effect, where the verbal suggestion could not elicit significant analgesia above response imagery. Thus, our research does not provide direct evidence for enhanced benefits of combining expectation inductions, which is in contrast to previous research [20,76,166,197,207]. Our contradictory findings might imply that combining different expectation inductions may be beneficial only under specific circumstances. Further research into optimal combinations for maximizing placebo and placebo-like effects is warranted.

Psychological mechanisms of placebo and placebo-like effects

In this thesis, we focused on expectancy as the core psychological mechanism of placebo and placebo-like effects and accordingly investigated methods that could

modify expectancies and thereby reduce pain and other physical symptoms. As discussed above, we found that verbal suggestion and mental imagery indeed modified expectancies (Chapters 3 and 4), and that response expectancies mediated the effects of response imagery on pain (Chapter 5). However, expectancies were not always related with the outcome (Chapter 4) [see also 277,325]. In addition, expectancies do not explain all variance in placebo and placebo-like effects [52,226,300,301]. This suggests that additional psychological mechanisms are likely to be involved.

Most importantly, theoretical work and psychological and neurobiological data suggest that affective processes may play a role [14,91]. It has been theorized that expectations of positive treatment outcomes reduce pain and other symptoms by reducing negative affect, particularly anxiety [91]. Supporting this, several previous studies, in healthy samples, found placebo analgesia to be associated with lowered subjective stress [8,9,11] [but see 90]. In line, neuroimaging research indicates that placebo and placebo-like effects are associated with brain processes known to represent affective processes, next to sensory and expectancy processes [14,213]. However, in our meta-analysis, we did not observe an effect of the expectation inductions on anxiety in clinical samples, with the exception of one study in which large effects of imagery on anxiety were observed (Chapter 3). In addition, our experimental studies (Chapters 4 and 5), did not indicate an effect of verbal suggestion or response imagery on anxiety, and we even found indications of increased anxiety after best possible health imagery. At a more specific level, previous research found placebo analgesia to be related to reduced pain anxiety [72,301], but we could not determine this in our own work (Chapter 5, Study 2), due to generally low levels of pain anxiety (i.e., floor effects). Last, positive affect was not observed to be influenced by verbal suggestion and imagery (Chapters 4 and 5) [227].

Taken together, research supports the important role of expectancies in placebo and placebo-like effects, but does not provide consistent support for the involvement of affective processes. The involvement of these affective, and of related cognitive processes (e.g., attentional processing [45,101,188]), may be further investigated by modifying them in experimental research designs [e.g., 246].

Physiological mechanisms of placebo and placebo-like effects

The effects of the expectation inductions on the self-reported intensity of pain and other symptoms were our primary focus in this thesis. In addition, we investigated physiological responses to obtain a more comprehensive understanding of placebo and

placebo-like effects. More specifically, we assessed responses of the autonomic nervous system (i.e., heart rate, skin conductance, and alpha-amylase) and the endocrine system (i.e., cortisol) since these are known correlates of placebo and placebo-like effects [28,81,103,212,230], in addition to physical sensations such as pain [63,110,175,186,285].

Regarding the involvement of the autonomic nervous system, several clinical studies included in our meta-analysis (Chapter 3) showed reduced heart rate due to verbal suggestion of analgesia [28,230]. The only included study that examined physiological responses to imagery, found no evidence for effects on heart rate [92]. In Chapter 4, we found that neither the verbal suggestion of reduced physical sensitivity by the placebo pill nor imagery of a best possible health affected heart rate or skin conductance responses during the physical sensitivity tests, which is in line with the absence of effects on self-reported physical sensitivity. In Chapter 5, the observed effects of response imagery on pain were not paralleled by effects on heart rate and skin conductance (Study 1 and 2), nor alpha-amylase (Study 1). In contrast to these mostly negative findings, previous research in healthy samples did provide some evidence for the involvement of the autonomic nervous system in placebo and placebo-like analgesic effects [28,81,103,212,230], although various other studies could not confirm this [9,72,100,198].

Regarding cortisol, the research in the current thesis does not provide evidence for its involvement in placebo and placebo-like effects. Both the clinical studies included in our meta-analysis (Chapter 3) [122,129,261] and our own experimental work (Chapter 5, Study 1) did not show the effects of the expectation inductions on pain to be paralleled by effects on cortisol levels. Also previous research in healthy samples did not provide evidence for its involvement in placebo analgesia [90,146].

In sum, there is some evidence in the literature for placebo and placebo-like effects on physiological responses, but this is inconsistent, and these effects were not found in the experimental studies reported in this thesis. These inconsistencies may partly be explained by large inter- and intra-individual variability. Particularly cortisol and alpha-amylase levels, but also heart rate and skin conductance are known to vary considerably over time, as they are affected by many factors including a circadian rhythm, physical activity, and stress [63,163,186,249]. It might be that autonomic and endocrine measures can only reliably reflect relatively large effects [186,285], and that the effects in experimental placebo and placebo-like research are frequently too small and/or the studies insufficiently powered to observe such effects. Last, it is possible that cortisol is particularly involved in nocebo effects, due to induced stress responses [26,146], but that it plays a less prominent role in placebo and placebo-like effects.

Treatment characteristics

In Chapters 3 and 6, we found that people's expectancies and placebo and placebo-like effects also depend on treatment characteristics, specifically the route of medication administration. In our meta-analysis (Chapter 3), subset analyses indicated that the effects of verbal suggestion and conditioning on patients' pain were larger when they pertained to injections than when they pertained to orally or topically administered treatments. This is in line with the common belief that more invasive treatments have more powerful placebo effects [150,177,265]. We investigated this further in Chapter 6, looking into the underlying expectations about the effectiveness of medication administered orally, via injection, or topically for relieving both pain and itch. Our survey, in a large sample representative of the Dutch population, provides further support, albeit indirect, for the existence of differential placebo effects depending on treatment characteristics, and suggests that they also depend on the targeted symptom. Specifically, the finding that injections were expected to be most effective for pain relief is in line with our findings in Chapter 3 and again confirms the common belief that more invasive treatments can elicit more powerful placebo effects, as has also been observed in several previous studies [29,71,323]. Importantly however, for itch-relief topical medication was expected to be most effective, while injections came second, which implies symptom-specificity. Moreover, we found in Chapter 6 that a higher expected effectiveness of the pain- and itch-relieving medication administered via the different routes was significantly associated with expected safety and ease of use, but not or not substantially with side effects, being frightening, and cost. Together with previous research [18,87,152,169,192,203,265,294,323], our findings imply that expectancies are multiple-determined. That is, not just the invasiveness of the route of administration, but also other factors such as the type of targeted symptom, the primary symptom location, and the commonness of a route for the symptom, are likely to underlie the expectations that people hold about medication effectiveness and hence differential placebo and placebo-like effects.

Individual differences

Placebo and placebo-like effects are generally associated with substantial interindividual variability [135,236]. Throughout this thesis, we explored a variety of individual characteristics that might be associated with expectancies and variable effects of the expectation inductions. Regarding personality characteristics, particularly those that pertain to expectancies such as optimism and neuroticism, we did not find support

that they moderate the effects of verbal suggestion or imagery on pain, itch, or fatigue (Chapters 4 and 5). We also did not find these personality characteristics nor demographic characteristics, such as age, sex, educational level, and religious or ideological affiliation, to be associated with the expected effectiveness of pain- and itch-relieving medication administered via different routes (Chapter 6). Also, health characteristics, such as the presence of chronic pain or itch and the frequency of medication use were not substantially correlated with the expected effectiveness of medication in our survey (Chapter 6). Overall, the current thesis does not provide evidence that certain individual characteristics can reliably predict placebo and placebo-like effects. This is generally in line with the literature, in which a broad spectrum of possible predictors has been investigated in efforts to identify placebo responders, but in which no consistent predictors emerged [135,311]. Although methodological limitations of our and previous research should be considered (particularly relatively small, homogenous, and healthy samples), it seems unlikely at this point that a single individual characteristic can consistently predict placebo and placebo-like effects. It appears more probable that interactions between various stable and situational variables are at work. That is, the influence of personality and demographic characteristics might depend on situational variables like the targeted symptom or condition (e.g., type and chronicity) and specifics of an intervention (e.g., method of expectation induction and route of treatment administration) (Chapters 3 and 6). Furthermore, other individual characteristics that vary across contexts and that have previously been associated with placebo and placebo-like effects may be investigated further, such as patients' desire and/or motivation for symptom relief [144,236,237,300], baseline symptom severity [311], baseline mood and stress [10,189-191,246], and psychopathology [170,179]. Last, biomarkers such as genetic variations have been found to be predictive [117].

Limitations

The work presented in this thesis naturally has several limitations. Here we expand on those limitations that are most important for the interpretation of our findings.

First, we acknowledge that the effects observed in the current work were variable and not always statistically large (Chapters 3, 4, and 5). A comparison across the research presented in this thesis suggests that the method of inducing expectancies, the specificity and phrasing of the instructions, and the characteristics of the targeted symptoms might contribute to this variability. Further research is required to gain more

insight into how these factors can be utilized independently and interactively for maximizing placebo and placebo-like effects.

Second, the generalizability of the current findings might be limited by the samples and methods included in the different studies. Especially the inclusion of healthy participants (young, mostly female students) and the use of short-lasting experimental sensations of moderate intensity in our experimental studies (Chapters 4 and 5) has limitations. Experimental research in healthy samples is highly suitable for research of new interventions and their mechanisms, but findings are not directly generalizable to clinical contexts. Our results from Chapter 3 do suggest that findings from experimental research in healthy participants might translate well to samples of patients who experience acute procedural pain. Also, within-study comparisons of placebo effects on experimentally evoked pain do not suggest differences between patients and healthy controls [166,179]. However, the effects on chronic pain were substantially smaller. Among others, the psychological mechanisms involved may differ between healthy participants and patients with acute or chronic symptoms [121,170], and may depend also on the type and intensity of the sensations. For example, anxiety, particularly anxiety about a specific symptom, may play a larger role in patients, especially when the symptom is intense and possibly indicative of a severe condition [183,321]. In this vein, studies directly comparing the effects between healthy and patient samples [166,179], and between experimental versus clinical pain are of great value [52,226,227]. In Chapter 6 we were able to study a general sample, but also these findings may not directly translate to clinical practice, even though a substantial proportion of the sample experienced chronic pain and/or itch.

Third, blinding is typically infeasible when studying psychological interventions. In our experimental studies and the studies included in the meta-analysis (Chapters 3, 4, and 5), participants were necessarily aware of the intervention they received. Even though we tried to maximize blinding, for example, by not informing participants about the existence or characteristics of different conditions and by including control conditions that might not have been recognized as such (e.g., imagery of hand in Chapter 5, Study 1), performance bias might have occurred. It was also infeasible to blind outcome assessors of the primary outcomes since the participants rated these using self-report measures. This possibly caused detection bias. Consequently, it cannot be excluded that participants were aware of the research aims or formed their own hypotheses about the research, and that they responded in a manner that they thought was expected from them (i.e., socially desirable responding). This could possibly be related to the absence of effects on corresponding physiological parameters in Chapter 5, although that might be attributed chiefly to other factors, such as high inter- and intra-

individual variability and/or sensitivity to relatively large effects only, as discussed above. Also, previous research did not find social desirability, assessed with questionnaires, to play a role in placebo and placebo-like effects [102,209,295]. Nonetheless, the involvement of response biases cannot be ruled out and may even be inherently involved in placebo and placebo-like effects [309].

Last, as the primary aim of our experimental studies (Chapters 4 and 5) was to assess the effects of the expectation inductions on the experienced intensity of pain and other symptoms, these studies might have not been sufficiently powered for our exploratory investigations of psychological mechanisms other than expectancies, physiological mechanisms, and individual differences. Therefore, these results should be interpreted carefully and adequately powered future research specifically focused on these factors is required to obtain more conclusive results.

Future research directions

Building on the placebo literature, the current thesis contributed to the knowledge on the influence of expectancies and expectation inductions on pain and other symptoms. Several promising directions for future research are highlighted in this section.

Characteristics of expectation inductions

First and foremost, further research into the different expectation inductions, particularly into the characteristics that determine their effectiveness, is warranted.

Evidence for the effects of verbal suggestions about placebo and active treatments on patients' pain relief is robust, but some open questions remain about how optimal effects can be achieved. There are indications that the induction of specific response expectancies might be more effective for relieving physical symptoms than general expectation inductions targeting multiple symptoms at once (Chapter 4) [132,257]. To study this further, direct head-to-head comparisons of more versus less specific inductions are required. Further research might also investigate the differential effects of precise phrasings of instructions. For example, short verbal suggestions merely about the outcome might be compared to more extensive suggestions also providing information about mechanisms or its common use. Also, the potential benefits of tailoring suggestions to the specific patient and situation might be a matter for future investigation.

Chapter 3 indicated that particularly placebo research of conditioning in clinical contexts is still in its infancy. To better understand the characteristics that determine the effects of conditioning procedures, additional experimental research should assess not only the effects of conditioning reinforced by verbal suggestion, but also those of conditioning alone. Future research, could additionally focus on to what extent previous treatment experiences transfer to current and future treatment outcomes using more ecologically valid designs, e.g., by comparing placebo effects between groups of patients who previously received medication at doses known to be differentially effective [6,178]. Furthermore, placebo-controlled drug reduction offers a promising possibility for utilizing conditioning processes in clinical practice [1,77,254], but further research into the potential and limitations of such procedures is required.

Our findings provide initial evidence for using mental imagery to induce expectancies and thereby relieve physical symptoms. Future studies might replicate these findings and provide a better understanding of the characteristics of effective imagery interventions. As with suggestions, the influence of specificity and precise phrasings of instructions could be investigated. Furthermore, the potential benefits of creating personalized instead of standard images could be examined. This might be especially beneficial for rescripting the spontaneous dysfunctional images that many patients with chronic symptoms experience frequently [34,228].

Observational learning also plays a central role in the psychological learning theories [17,158,159], but it has scarcely been studied and, to our knowledge, only using experimental designs in healthy samples [58,139,307]. It does have clear clinical relevance as, among others, patients regularly consult other patients (e.g., via online fora). Future research could, for example, study how learning about other patients' experiences, e.g., via written or recorded testimonies or via participation in patient associations, can affect treatment outcomes and how this can be addressed for maximizing these outcomes.

Furthermore, future research might provide more clear insight into when and how the combination of multiple expectation inductions, each tapping into different learning processes, could maximize expectancy effects. As described above, certain circumstances such as the connection between the interventions are likely to be of importance and might be investigated further. Furthermore, next to the previously investigated combinations, reinforcing verbal suggestion by imagery of the suggested treatment outcome might be promising for maximizing placebo and placebo-like effects. Also, conditioning procedures using imagined rather than real-life stimuli might offer new options for eliciting placebo and placebo-like effects. For example, imagined pain relief might be used as an unconditioned stimulus instead of the commonly used reduction of experimental pain stimulation [65]. Alternatively, personalized images

associated with pain relief as conditioned stimuli might fit into more ecologically valid experimental conditioning paradigms as compared to commonly used abstract stimuli like specific colors. Notably, research into the combination of expectation interventions is particularly important for patients with chronic symptoms, given the likely long-term exposure to a multitude of factors that determine negative expectancies and possibly in turn symptom chronicity [233,320].

In addition, the need for the use of a placebo and deception to establish expectancy effects deserves further attention. In our meta-analysis (Chapter 3), we saw that also suggestions about active treatments can enhance outcomes. And we found in two experimental studies (Chapter 5) that mere imagery of a response, without reference to a placebo or active treatment, could induce placebo-like effects. These findings indicate that administering a placebo is not necessary for harnessing placebo effects. Moreover, placebos are commonly administered in a deceptive manner, but this raises ethical issues in clinical practice [7] and is not necessary. One way in which placebos may be prescribed nondeceptively, is by openly informing patients that they are receiving a placebo and by teaching them about placebo effects. Several studies provide promising evidence that such open-label placebos can relieve irritable bowel syndrome symptoms [149], chronic low back pain [49], and allergic rhinitis symptoms [255]. Further mechanistic laboratory research, as well as large scale and longitudinal research into the induction of expectancies without a placebo and/or deception is required. Especially methods that involve neither a placebo nor deception, such as response imagery (Chapter 5) and adequately informing patients about the likely outcomes of active treatments, appear promising for implementation in clinical practice.

Last, the influence of how and in which context an intervention is given is of interest. Especially the communication style of a clinician is important; attending to a patient in a warm and empathic manner and demonstrating competence has been found to enhance placebo and placebo-like effects [138,147,151,154,303]. Future research might additionally investigate the influence of context factors like being in a medical setting, the status of the clinician, the clinician's own expectancies, and patient-clinician similarity e.g., in terms of sex, age, and cultural background [75,107,187].

Mechanisms of expectation inductions

Knowledge on the psychological and physiological mechanisms could inform theoretical developments and might suggest ways for optimally utilizing placebo and placebo-like effects in clinical practice.

To begin with, future research may provide a more comprehensive understanding of the involvement of expectancies in placebo and placebo-like effects. To achieve this,

not only the assessment and modification of response expectancies is of relevance, but also that of stimulus and self-efficacy expectancies (Chapter 2). These kinds of expectancies are likely to play only a minimal role in laboratory settings, but may be important in clinical settings where patients can exert more control over their treatment and pain (e.g., taking a higher dose or refraining from painful movements). More extensive assessments could entail adding scales about the expected characteristics of a treatment (stimulus expectancy) or about the expected ability to tolerate the pain (self-efficacy expectancy). Next to expectancies, other psychological mechanisms, such as affect, might be investigated. This could, for example, be done using additive research designs, in which negative affect is concomitantly reduced (e.g., via relaxation [195]) or increased (e.g., via a social stress task [246]).

The physiological mechanisms of placebo and placebo-like effects may become clearer when the inter- and intra-individual variability of autonomic and endocrine responses is better taken into account, as discussed above. Also other physiological mechanisms can be explored further, such as the involvement of endogenous opioids and dopamine [24]. Especially neuroimaging research appears promising; brain areas known to be involved in pain, expectancy, and affect processing have been found to be reliably involved in placebo and placebo-like analgesic effects [14]. Further research may, for example, examine the common and unique processes involved in the formation of expectancies via the different learning processes and in their effects on different symptoms and other outcomes.

Generalization across symptoms and time frames

As previously discussed, research into placebo and placebo-like effects has predominantly focused on pain. However, in Chapter 6 we saw that findings for pain do not directly generalize to other symptoms, even when underlying mechanisms largely overlap, as with itch [260,279]. Although placebo and placebo-like effects appear to be a general phenomenon [24], different outcomes may be differentially sensitive to the learning processes, and different psychological and physiological mechanisms may be involved. Thus, further research specifically looking into the influence of expectancies and the effects of expectation inductions on physical symptoms other than pain (e.g., itch and fatigue as studied in Chapters 3 and 6, and e.g., gastrointestinal and Parkinson symptoms [182,281]) is essential. It could be studied, for example, if response imagery might reduce itch when images of a cooling glove or of the application of menthol or other itch-relieving substance are used [216]. Also, head-to-head comparisons between the effects of expectation inductions on different physical symptoms would further

strengthen the knowledge on the generalizability of placebo and placebo-like effects across outcomes.

Furthermore, the research in the current thesis, as well as the majority of previous research, only allows conclusions about the immediate effects of the expectation inductions. There are indications that expectancy effects can remain for an extended period of time [247], and that outcome expectancies can predict pain up to half a year later in prospective research [111], but more longitudinal research into the long-term effects of expectation interventions is required.

Negative effects of expectancies

In the current thesis, we focused on placebo and placebo-like effects, that is, on the positive effects of positive expectancies. However, people can also hold negative expectancies, for example about harmful side effects of a treatment or of symptom worsening over time. Although research is relatively limited, it has been shown that the effects of such negative expectancies, i.e., nocebo or nocebo-like effects, can be as large as or larger than placebo and placebo-like effects [61,225], and the same learning processes are putatively involved [59].

Moreover, it has been theorized that positive expectancies may sometimes backfire when they are overly positive. The Affective Expectancy Model [318] poses that if there is a large discrepancy between one's expectation (e.g., no pain) and the actual sensation (e.g., intense pain), and if one is aware of this, the experience may contrast away from the expectation (e.g., increased pain). Empirical evidence for these contrast effects exists in various fields (e.g., affect, social priming) [37,44,97,98], but is scarce in the context of physical symptoms. Unfulfilled positive expectancies may also have detrimental effects on the long run, e.g., by harming trust in one's own expectations and in the clinician who gave the instructions, or even in health care in general [270,322]. Further research into the existence and determining factors of contrast effects and the long-term effects of unfulfilled expectancies might provide a clearer view of the limits of expectation inductions for relieving pain and other physical symptoms.

Implications for clinical practice

The research in the present thesis suggests that harnessing placebo and placebo-like effects via expectation interventions is promising for enhancing outcomes of standard treatments in clinical practice, especially for pain treatments. Although further

empirical support is required, several practical recommendations can tentatively be made based on the current findings and literature.

Given the important influence of expectancies on physical symptoms, clinicians might routinely assess patients' expectations about their symptoms and about the effectiveness of the available treatment options. When a patient's expectancies appear to be unrealistic (e.g., overly negative about possible treatment outcomes) or when a patient does not know what to expect, it may be advisable to use an expectation intervention to modify the patient's expectancies and thereby improve the actual treatment outcomes.

Our review of the literature (Chapter 3) showed that verbal suggestions are potentially the most effective for relieving pain, at least in the short term. This underlines the importance for clinicians to carefully consider the information they provide when administering a treatment. A clinician should clearly inform patients about, and emphasize, intended and expected positive outcomes of treatments. These suggestions are possibly most effective when they are specific, focusing on the primary symptom a patient is suffering from (Chapter 4) [132,257], but further evidence is required to determine the influence of specificity and other details of the phrasings of suggestions.

The research described in Chapters 3, 4, and 5 suggests that also mental imagery can induce expectancies and thereby relieve pain, particularly imagery of the desired response might be beneficial. Although research into imagery as an expectation intervention is still in its infancy, imagery interventions are already used in clinical practice, generally with the purpose of relaxation and anxiety reduction during pain [231,232,291]. Imagery of future pain relief may be beneficial for (partly) preventing procedural pain, e.g., surgery pain. Imagery of pain relief may also provide a good alternative when other treatments during pain may be insufficient, infeasible, or undesirable. A strength of imagery is that it entails relatively active experiences, on which patients have a great deal of control, i.e., they can shape the image that is most fitting to the outcome they desire [228]. Furthermore, patients can use it independently at home, with possibly larger effects when practiced repeatedly [291]. This might potentially be facilitated via internet-based treatment with support of a therapist, as has been previously found to be effective for cognitive behavioral therapy for patients with chronic physical conditions [288].

Next to expectation interventions tapping into the learning processes of expectancies, we observed in Chapters 3 and 6 that the route of medication administration is associated with differential expectancies. Combined with previous literature, this suggests that when multiple treatment options are available, treatment

outcome might be improved by selecting or letting the patient choose the treatment about which the patient holds the most positive expectations [131,250] [but see 325]. In such a case, practical and ethical constraints such as differential costs and risks of the routes should be taken into consideration.

The current thesis, in line with previous literature, does not suggest additional benefits for tailoring treatments based on personality or other individual characteristics, as no consistent predictors of outcomes were found. This might imply that everyone may in principle be able to profit from expectation interventions.

In sum, patients may benefit when expectancies are taken into account in clinical practice, and, when appropriate, actively modified with expectation interventions. Notably, addressing patients' expectancies does not need to cost extra time or financial resources, especially verbal suggestions are easily incorporated in regular practice. This might even reduce costs in the long term. In addition, teaching patients about the influences and mechanisms of placebo and placebo-like effects is important in view of raising awareness that expectancies significantly influence experiences. To successfully implement these approaches in everyday clinical practice, clinicians need to be trained in placebo and placebo-like effects and in methods for harnessing these effects optimally [e.g., 239]. These strategies will ideally be embedded in clinical guidelines [e.g., 165].

Conclusion

Taken together, the research into placebo and placebo-like effects presented in the current thesis provides further evidence for the effects of expectancies and expectation inductions on pain. Most notably, the current findings show that particularly verbal suggestion is promising for enhancing analgesic treatments, next to conditioning and mental imagery. Moreover, we found that mental imagery of pain reduction can induce expectancies and consequently analgesia. We additionally showed that people hold different expectations about the effectiveness of medication depending on the route of administration and targeted symptom, which can be associated with differential placebo effects. In conclusion, harnessing placebo effects by targeting expectancies is promising for enhancing standard clinical care of physical symptoms such as pain.

REFERENCES

1 Ader, R., Mercurio, M.G., Walton, J., James, D., Davis, M., Ojha, V., Kimball, A.B., & Fiorentino, D. (2010). Conditioned pharmacotherapeutic effects: A preliminary study. *Psychosomatic Medicine*, *72,* 192-197.

2 Aktas, A., Walsh, D., & Rybicki, L. (2010). Symptom clusters: Myth or reality? *Palliative Medicine*, *24,* 373-385.

3 Aldrich, S., Eccleston, C., & Crombez, G. (2000). Worrying about chronic pain: Vigilance to threat and misdirected problem solving. *Behaviour Research and Therapy*, *38,* 457-470.

4 Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *The Journal of Neuroscience*, *19,* 484-494.

5 Amanzio, M., Pollo, A., Maggi, G., & Benedetti, F. (2001). Response variability to analgesics: A role for non-specific activation of endogenous opioids. *PAIN*, *90,* 205-215.

6 Andre-Obadia, N., Magnin, M., & Garcia-Larrea, L. (2011). On the importance of placebo timing in rTMS studies for pain relief. *Pain*, *152,* 1233-7.

7 Annoni, M., & Miller, F. (2014). Placebos in clinical practice: An ethical overview. *Douleur et Analgésie*, *27,* 215-220.

8 Aslaksen, P.M., Bystad, M., Vambheim, S.M., & Flaten, M.A. (2011). Gender differences in placebo analgesia: Event-related potentials and emotional modulation. *Psychosomatic Medicine*, *73,* 193-199.

9 Aslaksen, P.M., & Flaten, M.A. (2008). The roles of physiological and subjective stress in the effectiveness of a placebo on experimentally induced pain. *Psychosomatic Medicine*, *70,* 811-818.

10 Aslaksen, P.M., & Lyby, P.S. (2015). Fear of pain potentiates nocebo hyperalgesia. *Journal of Pain Research*, *8,* 703-710.

11 Aslaksen, P.M., Zwarg, M.L., Eilertsen, H.I.H., Gorecka, M.M., & Bjørkedal, E. (2015). Opposite effects of the same drug: Reversal of topical analgesia by nocebo information. *PAIN*, *156,* 39-46.

12 Astrand, P.O., & Ryhming, I. (1954). A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *Journal of Applied Physiology*, *7,* 218-221.

13 Atlas, L.Y., & Wager, T.D. (2012). How expectations shape pain. *Neuroscience Letters*, *520,* 140-148.

14 Atlas, L.Y., & Wager, T.D. (2014). A meta-analysis of brain mechanisms of placebo analgesia: Consistent findings and unanswered questions. In. *Handbook of Experimental Pharmacology* (pp. 37-69). *Springer*.

15 Atlas, L.Y., Whittington, R.A., Lindquist, M.A., Wielgosz, J., Sonty, N., & Wager, T.D. (2012). Dissociable influences of opiates and expectations on pain. *The Journal of Neuroscience*, *32,* 8053-8064.

16 Atlas, L.Y., Wielgosz, J., Whittington, R.A., & Wager, T.D. (2014). Specifying the non-specific factors underlying opioid analgesia: Expectancy, attention, and affect. *Psychopharmacology*, *231,* 813-823.

17 Bandura, A. (1977). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review*, *84,* 191-215.

18 Bannuru, R.R., McAlindon, T.E., Sullivan, M.C., Wong, J.B., Kent, D.M., & Schmid, C.H. (2015). Effectiveness and implications of alternative placebo treatments: A systematic review and network meta-analysis of osteoarthritis trials. *Annals of Internal Medicine*, *163,* 365-372.

19 Bantick, S.J., Wise, R.G., Ploghaus, A., Clare, S., Smith, S.M., & Tracey, I. (2002). Imaging how attention modulates pain in humans using functional MRI. *Brain*, *125,* 310-319.

20 Bartels, D.J.P., van Laarhoven, A.I.M., Haverkamp, E.A., Wilder-Smith, O.H.,

Donders, A.R.T., van Middendorp, H., van de Kerkhof, P.C.M., & Evers, A.W.M. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLOS ONE*, *9,* e91727.

21 Baumeister, R.F., Bratslavsky, E., Finkenauer, C., & Vohs, K.D. (2001). Bad is stronger than good. *Review of General Psychology*, *5,* 323-370.

22 Beers, T.M., Jr., & Karoly, P. (1979). Cognitive strategies, expectancy, and coping style in the control of pain. *Journal of Consulting and Clinical Psychology*, *47,* 179-180.

23 Benedetti, F. (2008). Placebo effects. Understanding the mechanisms in health and disease. *Oxford University Press*.

24 Benedetti, F. (2014). Placebo effects. 2nd edition. *Oxford University Press*.

25 Benedetti, F., Amanzio, M., & Maggi, G. (1995). Potentiation of placebo analgesia by proglumide. *The Lancet*, *346,* 1231.

26 Benedetti, F., Amanzio, M., Vighetti, S., & Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *The Journal of Neuroscience*, *26,* 12014-12022.

27 Benedetti, F., Arduino, C., & Amanzio, M. (1999). Somatotopic activation of opioid systems by target-directed expectations of analgesia. *The Journal of Neuroscience*, *19,* 3639-3648.

28 Benedetti, F., Arduino, C., Costa, S., Vighetti, S., Tarenzi, L., Rainero, I., & Asteggiano, G. (2006). Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *PAIN*, *121,* 133-144.

29 Benedetti, F., & Dogue, S. (2015). Different placebos, different mechanisms, different outcomes: Lessons for clinical trials. *PLOS ONE*, *10,* e0140967.

30 Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., & Pollo, A. (2003). Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment*, *6,* 1a.

31 Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *The Journal of Neuroscience*, *23,* 4315-4323.

32 Berg, C.J., Snyder, C.R., & Hamilton, N. (2008). The effectiveness of a hope intervention in coping with cold pressor pain. *Journal of Health Psychology*, *13,* 804-809.

33 Berna, C., Kirsch, I., Zion, S.R., Lee, Y.C., Jensen, K.B., Sadler, P., Kaptchuk, T.J., & Edwards, R.R. (2017). Side effects can enhance treatment response through expectancy effects: An experimental analgesic randomized controlled trial. *PAIN*, *158,* 1014-1020.

34 Berna, C., Tracey, I., & Holmes, E.A. (2012). How a better understanding of spontaneous mental imagery linked to pain could enhance imagery-based therapy in chronic pain. *Journal of Experimental Psychopathology*, *3,* 258-273.

35 Bialosky, J.E., George, S.Z., Horn, M.E., Price, D.D., Staud, R., & Robinson, M.E. (2014). Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain. *The Journal of Pain*, *15,* 136-148.

36 Blackwell, B., Bloomfield, S.S., & Buncher, C.R. (1972). Demonstration to medical students of placebo responses and non-drug factors. *The Lancet*, *299,* 1279-1282.

37 Bless, H., & Burger, A.M. (2016). Assimilation and contrast in social priming. *Current Opinion in Psychology*, *12,* 26–31.

38 Bolles, R.C. (1972). Reinforcement, expectancy, and learning. *Psychological Review*, *79,* 394-409.

39 Borkovec, T.D., Robinson, E., Pruzinsky, T., & Depree, J.A. (1983). Preliminary exploration of worry: Some characteristics and processes. *Behaviour Research and Therapy*, *21,* 9-16.

40 Boselie, J.J.L.M., Vancleef, L.M.G.,

Smeets, T., & Peters, M.L. (2014). Increasing optimism abolishes pain-induced impairments in executive task performance. *PAIN*, *155,* 334–340.

41 Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *European Journal of Pain*, *10,* 287-333.

42 Brosschot, J.F., & van der Doef, M. (2006). Daily worrying and somatic health complaints: Testing the effectiveness of a simple worry reduction intervention. *Psychology & Health*, *21,* 19-31.

43 Brown, G.P., Macleod, A.K., Tata, P., & Goddard, L. (2002). Worry and the simulation of future outcomes. *Anxiety Stress and Coping*, *15,* 1-17.

44 Buckingham, G., & Goodale, M.A. (2013). When the predictive brain gets it really wrong. *Behavioral and Brain Sciences*, *36,* 208-209.

45 Buhle, J.T., Stevens, B.L., Friedman, J.J., & Wager, T.D. (2012). Distraction and placebo: Two separate routes to pain control. *Psychological Science*, *23,* 246-253.

46 Butler, G., & Mathews, A. (1983). Cognitive-processes in anxiety. *Advances in Behaviour Research and Therapy*, *5,* 51-62.

47 Carlino, E., Benedetti, F., & Pollo, A. (2014). The effects of manipulating verbal suggestions on physical performance. *Zeitschrift Fur Psychologie-Journal of Psychology*, *222,* 154-164.

48 Carroll, J.S. (1978). The effect of imagining an event on expectations for the event: An interpretation in terms of the availability heuristic. *Journal of Experimental Social Psychology*, *14,* 88-96.

49 Carvalho, C., Caetano, J.M., Cunha, L., Rebouta, P., Kaptchuk, T.J., & Kirsch, I. (2016). Open-label placebo treatment in chronic low back pain: A randomized controlled trial. *PAIN*, *157,* 2766-2772.

50 Caterinicchio, R.P. (1979). Testing plausible path models of interpersonal-trust in patient-physician treatment relationships. *Social Science & Medicine Part A: Medical Psychology & Medical Sociology*, *13a,* 81-99.

51 Centraal Bureau voor de Statistiek (2015). Bevolking; geslacht, leeftijd, burgerlijke staat en regio.

52 Charron, J., Rainville, P., & Marchand, S. (2006). Direct comparison of placebo effects on clinical and experimental pain. *Clinical Journal of Pain*, *22,* 204-211.

53 Chaves, J.F., & Barber, T.X. (1974). Cognitive strategies, experimenter modeling, and expectation in the attenuation of pain. *Journal of Abnormal Psychology*, *83,* 356-363.

54 Clauw, D.J., & Chrousos, G.P. (1997). Chronic pain and fatigue syndromes: Overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation*, *4,* 134-153.

55 Cohen, J. (1988). Statistical power analysis for the behavioral sciences. 2nd edition. *Lawrence Erlbaum Associates*.

56 Colagiuri, B., Quinn, V.F., & Colloca, L. (2015). Nocebo hyperalgesia, partial reinforcement, and extinction. *The Journal of Pain*, *16,* 995-1004.

57 Colagiuri, B., Schenk, L.A., Kessler, M.D., Dorsey, S.G., & Colloca, L. (2015). The placebo effect: From concepts to genes. *Neuroscience*, *307,* 171-190.

58 Colloca, L., & Benedetti, F. (2009). Placebo analgesia induced by social observational learning. *PAIN*, *144,* 28-34.

59 Colloca, L., & Miller, F.G. (2011). How placebo responses are formed: A learning perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366,* 1859-1869.

60 Colloca, L., Petrovic, P., Wager, T.D., Ingvar, M., & Benedetti, F. (2010). How the number of learning trials affects placebo and nocebo responses. *PAIN*, *151,* 430-439.

61 Colloca, L., Sigaudo, M., & Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *PAIN*, *136,* 211-218.

62 Cormier, S., Lavigne, G.L., Choiniere, M., & Rainville, P. (2016). Expectations

predict chronic pain treatment outcomes. *PAIN*, *157,* 329-338.

63 Cowen, R., Stasiowska, M.K., Laycock, H., & Bantel, C. (2015). Assessing pain objectively: The use of physiological markers. *Anaesthesia*, *70,* 828-847.

64 Craig, C.L., Marshall, A.L., Sjöström, M., Bauman, A.E., Booth, M.L., Ainsworth, B.E., Pratt, M., Ekelund, U., Yngve, A., Sallis, J.F., & Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise*, *35,* 1381-1395.

65 Dadds, M.R., Bovbjerg, D.H., Redd, W.H., & Cutmore, T.R.H. (1997). Imagery in human classical conditioning. *Psychological Bulletin*, *122,* 89-103.

66 Danhauer, S.C., Marler, B., Rutherford, C.A., Lovato, J.F., Asbury, D.Y., McQuellon, R.P., & Miller, B.E. (2007). Music or guided imagery for women undergoing colposcopy: A randomized controlled study of effects on anxiety, perceived pain, and patient satisfaction. *Journal of Lower Genital Tract Disease*, *11,* 39-45.

67 Darragh, M., Booth, R.J., & Consedine, N.S. (2014). Investigating the 'placebo personality' outside the pain paradigm. *Journal of Psychosomatic Research*, *76,* 414-421.

68 Darragh, M., Chang, J.W.-H., Booth, R.J., & Consedine, N.S. (2015). The placebo effect in inflammatory skin reactions: The influence of verbal suggestion on itch and weal size. *Journal of Psychosomatic Research*, *78,* 489-494.

69 Davis, C.E., Stockstill, J.W., Stanley, W.D., & Wu, Q. (2014). Pain-related worry in patients with chronic orofacial pain. *Journal of the American Dental Association*, *145,* 722-730.

70 de Craen, A.J.M., Lampe-Schoenmaeckers, A.J.E.M., Kraal, J.W., Tijssen, J.G.P., & Kleijnen, J. (2001). Impact of experimentally-induced expectancy on the analgesic efficacy of tramadol in chronic pain patients: A 2 x 2 factorial, randomized, placebo-controlled, double-blind trial. *Journal of Pain and Symptom Management*, *21,* 210-217.

71 de Craen, A.J.M., Tijssen, J.G.P., de Gans, J., & Kleijnen, J. (2000). Placebo effect in the acute treatment of migraine: Subcutaneous placebos are better than oral placebos. *The Journal of Neurology*, *247,* 183-188.

72 de Jong, P.J., van Baast, R., Arntz, A., & Merckelbach, H. (1996). The placebo effect in pain reduction: The influence of conditioning experiences and response expectancies. *International Journal of Behavioral Medicine*, *3,* 14-29.

73 Desimone, J.A., Harms, P.D., & Desimone, A.J. (2015). Best practice recommendations for data screening. *Journal of Organizational Behavior*, *36,* 171-181.

74 Devine, D.P., & Spanos, N.P. (1990). Effectiveness of maximally different cognitive strategies and expectancy in attenuation of reported pain. *Journal of Personality and Social Psychology*, *58,* 672-678.

75 Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *The Lancet*, *357,* 757-762.

76 Dillworth, T., & Jensen, M.P. (2010). The role of suggestions in hypnosis for chronic pain: A review of the literature. *The Open Pain Journal*, *3,* 39-51.

77 Doering, B.K., & Rief, W. (2012). Utilizing placebo mechanisms for dose reduction in pharmacotherapy. *Trends in Pharmacological Sciences*, *33,* 165-172.

78 Drury, D.G., Stuempfle, K.J., Shannon, R., & Miller, J. (2004). An investigation of exercise-induced hypoalgesia after isometric and cardiovascular exercise. *Journal of Exercise Physiology online*, *7,* 1-5.

79 Duncan, M.J. (2010). Placebo effects of caffeine on anaerobic performance in moderately trained adults. *Serbian Journal of Sports Sciences*, *4,* 99-106.

80 Eccleston, C., & Crombez, G. (1999). Pain

demands attention: A cognitive-affective model of the interruptive function of pain. *Psychological Bulletin*, *125,* 356-366.

81 Eippert, F., Bingel, U., Schoell, E.D., Yacubian, J., Klinger, R., Lorenz, J., & Büchel, C. (2009). Activation of the opioidergic descending pain control system underlies placebo analgesia. *Neuron*, *63,* 533-543.

82 Espay, A.J., Norris, M.M., Eliassen, J.C., Dwivedi, A., Smith, M.S., Banks, C., Allendorfer, J.B., Lang, A.E., Fleck, D.E., Linke, M.J., & Szaflarski, J.P. (2015). Placebo effect of medication cost in Parkinson disease: A randomized double-blind study. *Neurology*, *84,* 794-802.

83 Evers, A.W.M., Peerdeman, K.J., Bartels, D.J.P., & van Laarhoven, A.I.M. (2016). Placebo and nocebo effects on itch: Methodological and clinical implications. In: Misery, L., & Ständer, S. (Eds.). *Pruritus* (pp. 103-110). *Springer International Publishing*.

84 Faasse, K., Cundy, T., Gamble, G., & Petrie, K.J. (2013). The effect of an apparent change to a branded or generic medication on drug effectiveness and side effects. *Psychosomatic Medicine*, *75,* 90-96.

85 Fairchild, A.J., & MacKinnon, D.P. (2009). A general model for testing mediation and moderation effects. *Prevention Science*, *10,* 87-99.

86 Fardo, F., Allen, M., Jegindo, E.E., Angrilli, A., & Roepstorff, A. (2015). Neurocognitive evidence for mental imagery-driven hypoalgesic and hyperalgesic pain regulation. *NeuroImage*, *120,* 350-361.

87 Fassler, M., Meissner, K., Kleijnen, J., Hrobjartsson, A., & Linde, K. (2015). A systematic review found no consistent difference in effect between more and less intensive placebo interventions. *Journal of Clinical Epidemiology*, *68,* 442-451.

88 Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41,* 1149-1160.

89 Fazio, R.H., Chen, J., Mcdonel, E.C., & Sherman, S.J. (1982). Attitude accessibility, attitude behavior consistency, and the strength of the object evaluation association. *Journal of Experimental Social Psychology*, *18,* 339-357.

90 Flaten, M.A., Aslaksen, P.M., Finset, A., Simonsen, T., & Johansen, O. (2006). Cognitive and emotional factors in placebo analgesia. *Journal of Psychosomatic Research*, *61,* 81-89.

91 Flaten, M.A., Aslaksen, P.M., Lyby, P.S., & Bjorkedal, E. (2011). The relation of emotions to placebo responses. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *366,* 1818-1827.

92 Foji, S., Tadayonfar, M.A., Mohsenpour, M., & Rakhshani, M.H. (2015). The study of the effect of guided imagery on pain, anxiety and some other hemodynamic factors in patients undergoing coronary angiography. *Complementary Therapies in Clinical Practice*, *21,* 119-123.

93 Freeman, S., Yu, R., Egorova, N., Chen, X., Kirsch, I., Claggett, B., Kaptchuk, T.J., Gollub, R.L., & Kong, J. (2015). Distinct neural representations of placebo and nocebo effects. *NeuroImage*, *112,* 197-207.

94 Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G., Komaroff, A., & the International Chronic Fatigue Syndrome Study Group (1994). The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Annals of Internal Medicine*, *121,* 953-959.

95 Geers, A.L., Fowler, S.L., Wellman, J.A., Helfer, S.G., Close, S., & France, C.R. (2015). Prior experience with a pain stimulus as a predictor of placebo analgesia. *Journal of Behavioral Medicine*, *38,* 136-142.

96 Geers, A.L., Kosbab, K., Helfer, S.G., Weiland, P.E., & Wellman, J.A. (2007). Further evidence for individual differences in placebo responding: An

interactionist perspective. *Journal of Psychosomatic Research*, *62,* 563-570.
97 Geers, A.L., & Lassiter, G.D. (1999). Affective expectations and information gain: Evidence for assimilation and contrast effects in affective experience. *Journal of Experimental Social Psychology*, *35,* 394-413.
98 Geers, A.L., & Lassiter, G.D. (2005). Affective assimilation and contrast: Effects of expectations and prior stimulus exposure. *Basic and Applied Social Psychology*, *27,* 143-154.
99 Geers, A.L., Weiland, P.E., Kosbab, K., Landry, S.J., & Helfer, S.G. (2005). Goal activation, expectations, and the placebo effect. *Journal of Personality and Social Psychology*, *89,* 143-159.
100 Geers, A.L., Wellman, J.A., Fowler, S.L., Helfer, S.G., & France, C.R. (2010). Dispositional optimism predicts placebo analgesia. *The Journal of Pain*, *11,* 1165-1171.
101 Geers, A.L., Wellman, J.A., Fowler, S.L., Rasinski, H.M., & Helfer, S.G. (2011). Placebo expectations and the detection of somatic information. *Journal of Behavioral Medicine*, *34,* 208-217.
102 Geuter, S., & Büchel, C. (2013). Facilitation of pain in the human spinal cord by nocebo treatment. *The Journal of Neuroscience*, *33,* 13784-13790.
103 Geuter, S., Eippert, F., Hindi Attar, C., & Büchel, C. (2013). Cortical and subcortical responses to high and low effective placebo treatments. *NeuroImage*, *67,* 227-236.
104 Goeman, J.J., & Finos, L. (2012). The inheritance procedure: Multiple testing of tree-structured hypotheses. *Statistical Applications in Genetics and Molecular Biology*, *11,* 11.
105 Gonzales, E.A., Ledesma, R.J.A., McAllister, D.J., Perry, S.M., Dyer, C.A., & Maye, J.P. (2010). Effects of guided imagery on postoperative outcomes in patients undergoing same-day surgical procedures: A randomized, single-blind study. *AANA Journal*, *78,* 181-188.
106 Goodin, B.R., & Bulls, H.W. (2013). Optimism and the experience of pain: Benefits of seeing the glass as half full. *Current Pain and Headache Reports*, *17,* 329.
107 Gracely, R.H., Dubner, R., Deeter, W.R., & Wolskee, P.J. (1985). Clinicians' expectations influence placebo analgesia. *The Lancet*, *325,* 43.
108 Green, J.P., Barabasz, A.F., Barrett, D., & Montgomery, G.H. (2005). Forging ahead: The 2003 APA Division 30 definition of hypnosis. *International Journal of Clinical and Experimental Hypnosis*, *53,* 259-264.
109 Gregory, W.L., Burroughs, W.J., & Ainslie, F.M. (1985). Self-relevant scenarios as an indirect means of attitude-change. *Personality and Social Psychology Bulletin*, *11,* 435-444.
110 Greisen, J., Juhl, C.B., Grøfte, T., Vilstrup, H., Jensen, T.S., & Schmitz, O. (2001). Acute pain induces insulin resistance in humans. *Anesthesiology*, *95,* 578-584.
111 Groeneweg, R., Haanstra, T., Bolman, C.A.W., Oostendorp, R.A.B., van Tulder, M.W., & Ostelo, R.W.J.G. (2017). Treatment success in neck pain: The added predictive value of psychosocial variables in addition to clinical variables. *Scandinavian Journal of Pain*, *14,* 44-52.
112 Gryll, S.L., & Katahn, M. (1978). Situational factors contributing to placebo effect. *Psychopharmacology*, *57,* 253-261.
113 Haanstra, T.M., Kamper, S.J., Williams, C.M., Spriensma, A.S., Lin, C.W.C., Maher, C.G., de Vet, H.C.W., & Ostelo, R.W.J.G. (2015). Does adherence to treatment mediate the relationship between patients' treatment outcome expectancies and the outcomes of pain intensity and recovery from acute low back pain? *PAIN*, *156,* 1530-1536.
114 Haanstra, T.M., van den Berg, T., Ostelo, R.W., Poolman, R.W., Jansma, E.P., Cuijpers, P., & de Vet, H.C. (2012). Systematic review: Do patient expectations influence treatment outcomes in total knee and total hip arthroplasty? *Health Qual Life Outcomes*, *10,* 152.

115 Haase, O., Schwenk, W., Hermann, C., & Müller, J.M. (2005). Guided imagery and relaxation in conventional colorectal resections: A randomized, controlled, partially blinded trial. *Diseases of the Colon & Rectum*, *48,* 1955-1963.

116 Hackmann, A., Bennett-Levy, J., & Holmes, E.A. (2011). Oxford guide to imagery in cognitive therapy. *Oxford University Press*.

117 Hall, K.T., Loscalzo, J., & Kaptchuk, T.J. (2015). Genetics and the placebo effect: The placebome. *Trends in Molecular Medicine*, *21,* 285-294.

118 Hall, M.A., Dugan, E., Zheng, B.Y., & Mishra, A.K. (2001). Trust in physicians and medical institutions: What is it, can it be measured, and does it matter? *Milbank Quarterly*, *79,* 613-639.

119 Hanssen, M.M., Peters, M.L., Vlaeyen, J.W.S., Meevissen, Y.M.C., & Vancleef, L.M.G. (2013). Optimism lowers pain: Evidence of the causal status and underlying mechanisms. *PAIN*, *154,* 53-58.

120 Hanssen, M.M., Vancleef, L.M.G., Vlaeyen, J.W.S., & Peters, M.L. (2014). More optimism, less pain! The influence of generalized and pain-specific expectations on experienced cold-pressor pain. *Journal of Behavioral Medicine*, *37,* 47-58.

121 Harvie, D.S., Moseley, G.L., Hillier, S.L., & Meulders, A. (2017). Classical conditioning differences associated with chronic pain: A systematic review. *The Journal of Pain*, *18,* 889-898.

122 Hashish, I., Hai, H.K., Harvey, W., Feinmann, C., & Harris, M. (1988). Reduction of postoperative pain and swelling by ultrasound treatment: A placebo effect. *PAIN*, *33,* 303-311.

123 Hashmi, J.A., Kong, J., Spaeth, R., Khan, S., Kaptchuk, T.J., & Gollub, R.L. (2014). Functional network architecture predicts psychologically mediated analgesia related to treatment in chronic knee pain patients. *The Journal of Neuroscience*, *34,* 3924-3936.

124 Hassanlouei, H., Arendt-Nielsen, L., Kersting, U.G., & Falla, D. (2012). Effect of exercise-induced fatigue on postural control of the knee. *Journal of Electromyography and Kinesiology*, *22,* 342-347.

125 Hayano, J., Yamada, M., Sakakibara, Y., Fujinami, T., Yokoyama, K., Watanabe, Y., & Takata, K. (1990). Short- and long-term effects of cigarette smoking on heart rate variability. *The American Journal of Cardiology*, *65,* 84-88.

126 Hayes, A.F. (2013). Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. *Guilford Press*.

127 Higgins, J.P.T., & Green, S. (2011). Cochrane handbook for systematic reviews of interventions. *The Cochrane Collaboration*.

128 Higgins, J.P.T., Thompson, S.G., Deeks, J.J., & Altman, D.G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal*, *327,* 557-560.

129 Ho, K.H., Hashish, I., Salmon, P., Freeman, R., & Harvey, W. (1988). Reduction of post-operative swelling by a placebo effect. *Journal of psychosomatic research*, *32,* 197-205.

130 Hoffman, M.D., & Hoffman, D.R. (2007). Does aerobic exercise improve pain perception and mood? A review of the evidence related to healthy and chronic pain subjects. *Current Pain and Headache Reports*, *11,* 93-97.

131 Hofmann, M., Wrobel, N., Kessner, S., & Bingel, U. (2014). Minimizing carry-over effects after treatment failure and maximizing therapeutic outcome: Can changing the route of administration mitigate the influence of treatment history? *Zeitschrift Fur Psychologie-Journal of Psychology*, *222,* 171-178.

132 Hofstetter, C.R., Sallis, J.F., & Hovell, M.F. (1990). Some health dimensions of self-efficacy: Analysis of theoretical specificity. *Social Science & Medicine*, *31,* 1051-1056.

133 Holmes, E.A., Arntz, A., & Smucker, M.R. (2007). Imagery rescripting in cognitive behaviour therapy: Images, treatment

techniques and outcomes. *Journal of Behavior Therapy and Experimental Psychiatry*, *38,* 297-305.

134 Horan, J.J., Laying, F.C., & Pursell, C.H. (1976). Preliminary study of effects of "in vivo" emotive imagery on dental discomfort. *Perceptual and Motor Skills*, *42,* 105-106.

135 Horing, B., Weimer, K., Muth, E.R., & Enck, P. (2014). Prediction of placebo responses: A systematic review of the literature. *Frontiers in Psychology*, *5,* 1079.

136 Horing, B., Weimer, K., Schrade, D., Muth, E.R., Scisco, J.L., Enck, P., & Klosterhalfen, S. (2013). Reduction of motion sickness with an enhanced placebo instruction: An experimental study with healthy participants. *Psychosomatic Medicine*, *75,* 497-504.

137 Horne, R., Weinman, J., & Hankins, M. (1999). The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychology & Health*, *14,* 1-24.

138 Howe, L.C., Goyer, J.P., & Crum, A.J. (2017). Harnessing the placebo effect: Exploring the influence of physician characteristics on placebo response. *Health Psychology*.

139 Hunter, T., Siess, F., & Colloca, L. (2014). Socially induced placebo analgesia: A comparison of a pre-recorded versus live face-to-face observation. *European Journal of Pain*, *18,* 914-922.

140 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (1998). ICH harmonised tripartite guideline E9 statistical principles for clinical trials. *Federal Register*.

141 Jackson, T., Wang, Y.L., Wang, Y., & Fan, H.Y. (2014). Self-efficacy and chronic pain outcomes: A meta-analytic review. *The Journal of Pain*, *15,* 800-814.

142 Jacobson, A.F. (2006). Cognitive-behavioral interventions for IV insertion pain. *AORN Journal*, *84,* 1031-1048.

143 Jensen, K., Kirsch, I., Odmalm, S., Kaptchuk, T.J., & Ingvar, M. (2015). Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. *Proceedings of the National Academy of Sciences of the United States of America*, *112,* 7863-7867.

144 Jensen, M.P., & Karoly, P. (1991). Motivation and expectancy factors in symptom perception: A laboratory study of the placebo-effect. *Psychosomatic Medicine*, *53,* 144-152.

145 Jensen, M.P., Turner, J.A., & Romano, J.M. (1991). Self-efficacy and outcome expectancies: Relationship to chronic pain coping strategies and adjustment. *PAIN*, *44,* 263-269.

146 Johansen, O., Brox, J., & Flaten, M.A. (2003). Placebo and nocebo responses, cortisol, and circulating beta-endorphin. *Psychosomatic Medicine*, *65,* 786-790.

147 Jubb, J., & Bensing, J.M. (2013). The sweetest pill to swallow: How patient neurobiology can be harnessed to maximise placebo effects. *Neuroscience & Biobehavioral Reviews*, *37,* 2709-2720.

148 Kam-Hansen, S., Jakubowski, M., Kelley, J.M., Kirsch, I., Hoaglin, D.C., Kaptchuk, T.J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science Translational Medicine*, *6,* 218ra5.

149 Kaptchuk, T.J., Friedlander, E., Kelley, J.M., Sanchez, M.N., Kokkotou, E., Singer, J.P., Kowalczykowski, M., Miller, F.G., Kirsch, I., & Lembo, A.J. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLOS ONE*, *5,* e15591.

150 Kaptchuk, T.J., Goldman, P., Stone, D.A., & Stason, W.B. (2000). Do medical devices have enhanced placebo effects? *Journal of Clinical Epidemiology*, *53,* 786-792.

151 Kaptchuk, T.J., Kelley, J.M., Conboy, L.A., Davis, R.B., Kerr, C.E., Jacobson, E.E., Kirsch, I., Schyner, R.N., Nam, B.H., & Nguyen, L.T. (2008). Components of

placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *British Medical Journal*, *336,* 999-1003.

152 Kaptchuk, T.J., Stason, W.B., Davis, R.B., Legedza, A.T.R., Schnyer, R.N., Kerr, C.E., Stone, D.A., Nam, B.H., Kirsch, I., & Goldman, R.H. (2006). Sham device v inert pill: Randomised controlled trial of two placebo treatments. *British Medical Journal*, *332,* 391-397.

153 Karvonen, M.J., Kentala, E., & Mustala, O. (1957). The effects of training on heart rate; A longitudinal study. *Annales Medicinae Experimentalis et Biologiae Fenniae*, *35,* 307-315.

154 Kelley, J.M., Kraft-Todd, G., Schapira, L., Kossowsky, J., & Riess, H. (2014). The influence of the patient-clinician relationship on healthcare outcomes: A systematic review and meta-analysis of randomized controlled trials. *PLOS ONE*, *9,* e94207.

155 Kercher, K. (1992). Assessing subjective well-being in the old-old: The PANAS as a measure of orthogonal dimensions of positive and negative affect. *Research on Aging*, *14,* 131-168.

156 Kessner, S., Wiech, K., Forkmann, K., Ploner, M., & Bingel, U. (2013). The effect of treatment history on therapeutic outcome: An experimental approach. *JAMA Internal Medicine*, *173,* 1468-1469.

157 King, L.A. (2001). The health benefits of writing about life goals. *Personality and Social Psychology Bulletin*, *27,* 798-807.

158 Kirsch, I. (1985). Response expectancy as a determinant of experience and behavior. *American Psychologist*, *40,* 1189-1202.

159 Kirsch, I. (1997). Response expectancy theory and application: A decennial review. *Applied & Preventive Psychology*, *6,* 69-79.

160 Kirsch, I., Kong, J., Sadler, P., Spaeth, R., Cook, A., Kaptchuk, T., & Gollub, R. (2014). Expectancy and conditioning in placebo analgesia: Separate or connected processes? *Psychology of Consciousness*, *1,* 51-59.

161 Kirsch, I., Lynn, S.J., Vigorito, M., & Miller, R.R. (2004). The role of cognition in classical and operant conditioning. *Journal of Clinical Psychology*, *60,* 369-392.

162 Kirschbaum, C., & Hellhammer, D.H. (1994). Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. *Psychoneuroendocrinology*, *19,* 313-333.

163 Kirschbaum, C., & Hellhammer, D.H. (2000). Salivary cortisol. In. *Encyclopedia of stress* (pp. 379-383). *American Press*.

164 Kjøgx, H., Kasch, H., Zachariae, R., Svensson, P., Jensen, T.S., & Vase, L. (2016). Experimental manipulations of pain catastrophizing influence pain levels in patients with chronic pain and healthy volunteers. *PAIN*, *157,* 1287-1296.

165 Klinger, R. (2010). Das Potenzial des analgetischen Plazeboeffektes: S3-Leitlinien-Empfehlung zur Behandlung akuter und perioperativer Schmerzen [The potential of the analgetic placebo effect - S3-guideline recommendation on the clinical use for acute and perioperative pain management.]. *Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie*, *45,* 22-29.

166 Klinger, R., Soost, S., Flor, H., & Worm, M. (2007). Classical conditioning and expectancy in placebo hypoalgesia: A randomized controlled study in patients with atopic dermatitis and persons with healthy skin. *PAIN*, *128,* 31-39.

167 Klosterhalfen, S., Kellermann, S., Braun, S., Kowalski, A., Schrauth, M., Zipfel, S., & Enck, P. (2009). Gender and the nocebo response following conditioning and expectancy. *Journal of Psychosomatic Research*, *66,* 323-328.

168 Koban, L., Brass, M., Lynn, M.T., & Pourtois, G. (2012). Placebo analgesia affects brain correlates of error processing. *PLOS ONE*, *7,* e49784.

169 Kong, J., Spaeth, R., Cook, A., Kirsch, I., Claggett, B., Vangel, M., Gollub, R.L., Smoller, J.W., & Kaptchuk, T.J. (2013). Are all placebo effects equal? Placebo pills,

sham acupuncture, cue conditioning and their association. *PLOS ONE*, *8,* e67485.

170 Kosek, E., Rosen, A., Carville, S., Choy, E., Gracely, R.H., Marcus, H., Petzke, F., Ingvar, M., & Jensen, K.B. (2017). Lower placebo responses after long-term exposure to fibromyalgia pain. *The Journal of Pain*, *18,* 835-843.

171 Kosslyn, S.M., Ganis, G., & Thompson, W.L. (2001). Neural foundations of imagery. *Nature Reviews Neuroscience*, *2,* 635-642.

172 Kroenke, K. (2003). Patients presenting with somatic complaints: Epidemiology, psychiatric co-morbidity and management. *International Journal of Methods in Psychiatric Research*, *12,* 34-43.

173 Kroenke, K., & Price, R.K. (1993). Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. *Archives of Internal Medicine*, *153,* 2474-2480.

174 Kwekkeboom, K.L., Wanta, B., & Bumpus, M. (2008). Individual difference variables and the effects of progressive muscle relaxation and analgesic imagery interventions on cancer pain. *Journal of Pain and Symptom Management*, *36,* 604-615.

175 Kyle, B.N., & McNeil, D.W. (2014). Autonomic arousal and experimentally induced pain: A critical review of the literature. *Pain Research & Management*, *19,* 159-167.

176 Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4,* 863.

177 Lasagna, L. (1955). Placebos. *Scientific American*, *193,* 68-71.

178 Laska, E., & Sunshine, A. (1973). Anticipation of analgesia. A placebo effect. *Headache*, *13,* 1-11.

179 Lee, H.-F., Hsieh, J.-C., Lu, C.-L., Yeh, T.-C., Tu, C.-H., Cheng, C.-M., NIddam, D.M., Lin, H.-C., Lee, F.-Y., & Chang, F.-Y. (2012). Enhanced affect/cognition-related brain responses during visceral placebo analgesia in irritable bowel syndrome patients. *PAIN*, *153,* 1301-1310.

180 Levine, J.D., & Gordon, N.C. (1984). Influence of the method of drug administration on analgesic response. *Nature*, *312,* 755-756.

181 Liberman, R. (1964). An experimental study of the placebo response under three different situations of pain. *Journal of Psychiatric Research*, *2,* 233-246.

182 Lidstone, S.C., Schulzer, M., Dinelle, K., Mak, E., Sossi, V., Ruth, T.J., de la Fuente-Fernández, R., Phillips, A.G., & Stoessl, A.J. (2010). Effects of expectation on placebo-induced dopamine release in Parkinson disease. *Archives of General Psychiatry*, *67,* 857-865.

183 Linton, S.J. (2000). A review of psychological risk factors in back and neck pain. *Spine*, *25,* 1148-1156.

184 Litt, M.D. (1988). Self-efficacy and perceived control: Cognitive mediators of pain tolerance. *Journal of Personality and Social Psychology*, *54,* 149-160.

185 Ljosaa, T.M., Rustoen, T., Mork, C., Stubhaug, A., Miaskowski, C., Paul, S.M., & Wahl, A.K. (2010). Skin pain and discomfort in psoriasis: An exploratory study of symptom prevalence and characteristics. *Acta Dermato-Venereologica*, *90,* 39-45.

186 Loggia, M.L., Juneau, M., & Bushnell, M.C. (2011). Autonomic responses to heat pain: Heart rate, skin conductance, and their relation to verbal ratings and stimulus intensity. *PAIN*, *152,* 592-598.

187 Losin, E.A.R., Anderson, S.R., & Wager, T.D. (2017). Feelings of clinician-patient similarity and trust influence pain: Evidence from simulated clinical interactions. *The Journal of Pain*, *18,* 787-799.

188 Lundh, L.G. (1987). Placebo, belief, and health. A cognitive-emotional model. *Scandinavian Journal of Psychology*, *28,* 128-143.

189 Lyby, P.S., Aslaksen, P.M., & Flaten, M.A. (2010). Is fear of pain related to placebo analgesia? *Journal of Psychosomatic Research*, *68,* 369-377.

190 Lyby, P.S., Aslaksen, P.M., & Flaten, M.A. (2011). Variability in placebo analgesia and the role of fear of pain-an ERP study. *PAIN*, *152,* 2405-2412.

191 Lyby, P.S., Forsberg, J.T., Asli, O., & Flaten, M.A. (2012). Induced fear reduces the effectiveness of a placebo intervention on pain. *PAIN*, *153,* 1114-1121.

192 Macedo, A., Farre, M., & Banos, J.E. (2006). A meta-analysis of the placebo response in acute migraine and how this response may be influenced by some of the characteristics of clinical trials. *European Journal of Clinical Pharmacology*, *62,* 161-172.

193 MacLeod, A.K., Byrne, A., & Valentine, J.D. (1996). Affect, emotional disorder, and future-directed thinking. *Cognition & Emotion*, *10,* 69-85.

194 Macleod, A.K., Williams, J.M.G., & Bekerian, D.A. (1991). Worry is reasonable: The role of explanations in pessimism about future personal events. *Journal of Abnormal Psychology*, *100,* 478-486.

195 Manzoni, G.M., Pagnini, F., Castelnuovo, G., & Molinari, E. (2008). Relaxation training for anxiety: A ten-years systematic review with meta-analysis. *BMC Psychiatry*, *8,* 41.

196 Marteau, T.M., & Bekker, H. (1992). The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *The British Journal of Clinical Psychology*, *31,* 301-306.

197 Martin-Pichora, A.L., Mankovsky-Arnold, T.D., & Katz, J. (2011). Implicit versus explicit associative learning and experimentally induced placebo hypoalgesia. *Journal of Pain Research*, *4,* 67-77.

198 Matre, D., Casey, K.L., & Knardahl, S. (2006). Placebo-induced changes in spinal cord pain processing. *The Journal of Neuroscience*, *26,* 559-563.

199 Matterne, U., Apfelbacher, C.J., Loerbroks, A., Schwarzer, T., Buttner, M., Ofenloch, R., Diepgen, T.L., & Weisshaar, E. (2011). Prevalence, correlates and characteristics of chronic pruritus: A population-based cross-sectional study. *Acta Dermato-Venereologica*, *91,* 674-679.

200 McCracken, L.M. (1997). ''Attention'' to pain in persons with chronic pain: A behavioral approach. *Behavior Therapy*, *28,* 271-284.

201 McNorgan, C. (2012). A meta-analytic review of multisensory imagery identifies the neural correlates of modality-specific and modality-general imagery. *Frontiers in Human Neuroscience*, *6,* 285.

202 Meevissen, Y.M.C., Peters, M.L., & Alberts, H.J.E.M. (2011). Become more optimistic by imagining a best possible self: Effects of a two week intervention. *Journal of Behavior Therapy and Experimental Psychiatry*, *42,* 371-378.

203 Meissner, K., Fassler, M., Rucker, G., Kleijnen, J., Hroobjartsson, A., Schneider, A., Antes, G., & Linde, K. (2013). Differential effectiveness of placebo treatments: A systematic review of migraine prophylaxis. *JAMA Internal Medicine*, *173,* 1941-1951.

204 Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & Prisma Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLOS Medicine*, *6,* e1000097.

205 Mols, F., Pelle, A.J., & Kupper, N. (2009). Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Quality of Life Research*, *18,* 403-414.

206 Mondloch, M.V., Cole, D.C., & Frank, J.W. (2001). Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. *Canadian Medical Association Journal*, *165,* 174-179.

207 Montgomery, G.H., David, D., Winkel, G., Silverstein, J.H., & Bovbjerg, D.H. (2002). The effectiveness of adjunctive hypnosis with surgical patients: A meta-analysis. *Anesthesia and Analgesia*, *94,* 1639-1645.

208 Montgomery, G.H., & Kirsch, I. (1997).

Classical conditioning and the placebo effect. *PAIN*, *72,* 107-113.

209 Morton, D.L., Watson, A., El-Deredy, W., & Jones, A.K.P. (2009). Reproducibility of placebo analgesia: Effect of dispositional optimism. *PAIN*, *146,* 194-198.

210 Mun, C.J., Thummala, K., Davis, M.C., Karoly, P., Tennen, H., & Zautra, A.J. (2017). Predictors and social consequences of daily pain expectancy among adults with chronic pain. *PAIN*, *158,* 1224-1233.

211 Murray, F.S., & Weaver, M.M. (1975). Effects of ipsilateral and contralateral counterirritation on experimentally produced itch in human beings. *Journal of Comparative and Physiological Psychology*, *89,* 819-826.

212 Nakamura, Y., Donaldson, G.W., Kuhn, R., Bradshaw, D.H., Jacobson, R.C., & Chapman, C.R. (2012). Investigating dose-dependent effects of placebo analgesia: A psychophysiological approach. *PAIN*, *153,* 227-237.

213 Napadow, V., Li, A., Loggia, M.L., Kim, J., Mawla, I., Desbordes, G., Schalock, P.C., Lerner, E.A., Tran, T.N., Ring, J., Rosen, B.R., Kaptchuk, T.J., & Pfab, F. (2015). The imagined itch: Brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. *Allergy*, *70,* 1485-1492.

214 Noonan, V., & Dean, E. (2000). Submaximal exercise testing: Clinical application and interpretation. *Physical Therapy*, *80,* 782-807.

215 Ospina, M., & Harstall, C. (2002). Prevalence of chronic pain: An overview. *Alberta Heritage Foundation for Medical Research*.

216 Patel, T., Ishiuji, Y., & Yosipovitch, G. (2007). Menthol: A refreshing look at this ancient compound. *Journal of the American Academy of Dermatology*, *57,* 873-878.

217 Pavlov, I.P. (1927). Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex *Oxford University Press*.

218 Pearson, S.D., & Raeke, L.H. (2000). Patients' trust in physicians: Many theories, few measures, and little data. *Journal of General Internal Medicine*, *15,* 509-513.

219 Peerdeman, K.J., van Laarhoven, A.I.M., Bartels, D.J.P., Peters, M.L., & Evers, A.W.M. (2017). Placebo-like analgesia via response imagery. *European Journal of Pain*, *21,* 1366-1377.

220 Peerdeman, K.J., van Laarhoven, A.I.M., Donders, A.R.T., Hopman, M.T.E., Peters, M.L., & Evers, A.W.M. (2015). Inducing expectations for health: Effects of verbal suggestion and imagery on pain, itch, and fatigue as indicators of physical sensitivity. *PLOS ONE*, *10,* e0139563

221 Peerdeman, K.J., van Laarhoven, A.I.M., Keij, S.M., Vase, L., Rovers, M.M., Peters, M.L., & Evers, A.W.M. (2016). Relieving patients' pain with expectation interventions: A meta-analysis. *PAIN*, *157,* 1179-1191.

222 Peerdeman, K.J., van Laarhoven, A.I.M., Peters, M.L., & Evers, A.W.M. (2016). An integrative review of the influence of expectancies on pain. *Frontiers in Psychology*, *7,* 1270.

223 Peeters, F.P.M.L., Ponds, R.W.H.M., & Vermeeren, M.T.G. (1996). Affectiviteit en zeltbeoordeling van depressie en angst. *Tijdschrift voor Psychiatrie*, *38,* 240-250.

224 Peters, M.L., Flink, I.K., Boersma, K., & Linton, S.J. (2010). Manipulating optimism: Can imagining a best possible self be used to increase positive future expectancies? *The Journal of Positive Psychology*, *5,* 204-211.

225 Petersen, G.L., Finnerup, N.B., Colloca, L., Amanzio, M., Price, D.D., Jensen, T.S., & Vase, L. (2014). The magnitude of nocebo effects in pain: A meta-analysis. *PAIN*, *155,* 1426-1434.

226 Petersen, G.L., Finnerup, N.B., Grosen, K., Pilegaard, H.K., Tracey, I., Benedetti, F., Price, D.D., Jensen, T.S., & Vase, L. (2014). Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. *PAIN*, *155,* 2687-2698.

227 Petersen, G.L., Finnerup, N.B., Norskov, K.N., Grosen, K., Pilegaard, H.K., Benedetti, F., Price, D.D., Jensen, T.S., & Vase, L. (2012). Placebo manipulations reduce hyperalgesia in neuropathic pain. *PAIN*, *153,* 1292-1300.

228 Philips, C., & Samson, D. (2012). The rescripting of pain images. *Behavioural and Cognitive Psychotherapy*, *40,* 558-576.

229 Pollo, A., Carlino, E., & Benedetti, F. (2008). The top-down influence of ergogenic placebos on muscle work and fatigue. *European Journal of Neuroscience*, *28,* 379-388.

230 Pollo, A., Vighetti, S., Rainero, I., & Benedetti, F. (2003). Placebo analgesia and the heart. *PAIN*, *102,* 125-133.

231 Posadzki, P., & Ernst, E. (2011). Guided imagery for musculoskeletal pain: A systematic review. *Clinical Journal of Pain*, *27,* 648-653.

232 Posadzki, P., Lewandowski, W., Terry, R., Ernst, E., & Stearns, A. (2012). Guided imagery for non-musculoskeletal pain: A systematic review of randomized clinical trials. *Journal of Pain and Symptom Management*, *44,* 95-104.

233 Pozek, J.-P.J., Beausang, D., Baratta, J.L., & Viscusi, E.R. (2016). The acute to chronic pain transition. Can chronic pain be prevented? *Medical Clinics of North America*, *100,* 17-30.

234 Price, D.D., Barrell, J.J., & Gracely, R.H. (1980). A psychophysical analysis of experiential factors that selectively influence the affective dimension of pain. *PAIN*, *8,* 137-149.

235 Price, D.D., Craggs, J., Verne, G.N., Perlstein, W.M., & Robinson, M.E. (2007). Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *PAIN*, *127,* 63-72.

236 Price, D.D., Finniss, D.G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology*, *59,* 565-590.

237 Price, D.D., Milling, L.S., Kirsch, I., Duff, A., Montgomery, G.H., & Nicholls, S.S. (1999). An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *PAIN*, *83,* 147-156.

238 Quartana, P.J., Campbell, C.M., & Edwards, R.R. (2009). Pain catastrophizing: A critical review. *Expert Review of Neurotherapeutics*, *9,* 745-758.

239 Rao, J.K., Anderson, L.A., Inui, T.S., & Frankel, R.M. (2007). Communication interventions make a difference in conversations between physicians and patients: A systematic review of the evidence. *Medical Care*, *45,* 340-349.

240 Rasmussen, H.N., Scheier, M.F., & Greenhouse, J.B. (2009). Optimism and physical health: A meta-analytic review. *Annals of Behavioral Medicine*, *37,* 239-256.

241 Raune, D., MacLeod, A., & Holmes, E.A. (2005). The simulation heuristic and visual imagery in pessimism for future negative events in anxiety. *Clinical Psychology & Psychotherapy*, *12,* 313-325.

242 Rawdin, B., Evans, C., & Rabow, M.W. (2013). The relationships among hope, pain, psychological distress, and spiritual well-being in oncology outpatients. *Journal of Palliative Medicine*, *16,* 167-172.

243 Reiner, K., Tibi, L., & Lipsitz, J.D. (2013). Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Medicine*, *14,* 230-242.

244 Rescorla, R.A. (1988). Pavlovian conditioning. It's not what you think it is. *American Psychologist*, *43,* 151-160.

245 Rescorla, R.A., & Wagner, A.R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black, A.H., & Prokasy, W.F. (Eds.). *Classical Conditioning II: Current Research and Theory* (pp. 64-99). *Appleton-Century-Crofts*.

246 Roderigo, T., Benson, S., Schöls, M., Hetkamp, M., Schedlowski, M., Enck, P., &

Elsenbruch, S. (2017). Effects of acute psychological stress on placebo and nocebo responses in a clinically relevant model of visceroception. *PAIN*, *158,* 1489-1498.

247 Rodriguez-Raecke, R., Doganci, B., Breimhorst, M., Stankewitz, A., Büchel, C., Birklein, F., & May, A. (2010). Insular cortex activity is associated with effects of negative expectation on nociceptive long-term habituation. *The Journal of Neuroscience*, *30,* 11363-11368.

248 Roelofs, J., ter Riet, G., Peters, M.L., Kessels, A.G.H., Reulen, J.P.H., & Menheere, P.P.C.A. (2000). Expectations of analgesia do not affect spinal nociceptive R-III reflex activity: An experimental study into the mechanism of placebo-induced analgesia. *PAIN*, *89,* 75-80.

249 Rohleder, N., & Nater, U.M. (2009). Determinants of salivary alpha-amylase in humans and methodological considerations. *Psychoneuroendocrinology*, *34,* 469-485.

250 Rose, J.P., Geers, A.L., Rasinski, H.M., & Fowler, S.L. (2012). Choice and placebo expectation effects in the context of pain analgesia. *Journal of Behavioral Medicine*, *35,* 462-470.

251 Rotter, J.B. (1954). Social learning and clinical psychology. *Prentice-Hall*.

252 Rotter, J.B. (1967). A new scale for the measurement of interpersonal trust. *Journal of Personality*, *35,* 651-665.

253 Sanderman, R., Arrindell, W.A., Ranchor, A.V., Eysenck, H.J., & Eysenck, S.B.G. (1995). Het meten van persoonlijkheidskenmerken met de Eysenck Personality Questionnaire (EPQ): Een handleiding. *Noordelijk Centrum voor Gezondheidsvraagstukken*.

254 Sandler, A.D., & Bodfish, J.W. (2008). Open-label use of placebos in the treatment of ADHD: A pilot study. *Child Care, Health and Development*, *34,* 104-110.

255 Schaefer, M., Harke, R., & Denke, C. (2016). Open-label placebos improve symptoms in allergic rhinitis: A randomized controlled trial. *Psychotherapy and Psychosomatics*, *85,* 373-374.

256 Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. *Pharmacological Reviews*, *67,* 697-730.

257 Scheier, M.F., & Carver, C.S. (1987). Dispositional optimism and physical well-being: The influence of generalized outcome expectancies on health. *Journal of Personality*, *55,* 169-210.

258 Scheier, M.F., Carver, C.S., & Bridges, M.W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. *Journal of Personality and Social Psychology*, *67,* 1063-1078.

259 Schenk, L.A., Sprenger, C., Geuter, S., & Büchel, C. (2014). Expectation requires treatment to boost pain relief: An fMRI study. *PAIN*, *155,* 150-157.

260 Schmelz, M. (2015). Itch and pain differences and commonalities. In: Schaible, H.-G. (Ed.). *Pain Control* (pp. 285-301). *Springer Berlin Heidelberg*.

261 Schmid, J., Langhorst, J., Gass, F., Theysohn, N., Benson, S., Engler, H., Gizewski, E.R., Forsting, M., & Elsenbruch, S. (2015). Placebo analgesia in patients with functional and organic abdominal pain: A fMRI study in IBS, UC and healthy volunteers. *Gut*, *64,* 418-427.

262 Schmid, J., Theysohn, N., Gass, F., Benson, S., Gramsch, C., Forsting, M., Gizewski, E.R., & Elsenbruch, S. (2013). Neural mechanisms mediating positive and negative treatment expectations in visceral pain: A functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. *PAIN*, *154,* 2372-2380.

263 Schmidt, N.B., Lerew, D.R., & Trakowski, J.H. (1997). Body vigilance in panic disorder: Evaluating attention to bodily perturbations. *Journal of Consulting and Clinical Psychology*, *65,* 214-220.

264 Schulz, K.F., Altman, D.G., Moher, D., & Group, C. (2010). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *British Medical Journal*, *340,* c332.

265 Schwartz, N.A., Turturro, M.A., Istvan, D.J., & Larkin, G.L. (2000). Patients' perceptions of route of nonsteroidal anti-inflammatory drug administration and its effect on analgesia. *Academic Emergency Medicine*, *7,* 857-861.

266 Scott, D.J., Stohler, C.S., Egnatuk, C.M., Wang, H., Koeppe, R.A., & Zubieta, J.K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of General Psychiatry*, *65,* 220-231.

267 Severeijns, R., van den Hout, M.A., & Vlaeyen, J.W.S. (2005). The causal status of pain catastrophizing: An experimental test with healthy participants. *European Journal of Pain*, *9,* 257-265.

268 Sheehan, P.W. (1967). A shortened form of Betts Questionnaire upon Mental Imagery. *Journal of Clinical Psychology*, *23,* 386-389.

269 Sheldon, K.M., & Lyubomirsky, S. (2006). How to increase and sustain positive emotion: The effects of expressing gratitude and visualizing best possible selves. *The Journal of Positive Psychology*, *1,* 73-82.

270 Shepperd, J.A., Klein, W.M.P., Waters, E.A., & Weinstein, N.D. (2013). Taking stock of unrealistic optimism. *Perspectives on Psychological Science*, *8,* 395-411.

271 Shepperd, J.A., Waters, E.A., Weinstein, N.D., & Klein, W.M.P. (2015). A primer on unrealistic optimism. *Current Directions in Psychological Science*, *24,* 232-237.

272 Smeets, R.J., & Soest, M.V. (2009). The usability of a modified Astrand bicycle test to assess the aerobic capacity in patients with musculoskeletal pain and healthy controls. *Disability and Rehabilitation*, *31,* 1988-1995.

273 Snyder, C.R. (2002). Hope theory: Rainbows in the mind. *Psychological Inquiry*, *13,* 249-275.

274 Snyder, C.R., Berg, C., Woodward, J.T., Gum, A., Rand, K.L., Wrobleski, K.K., Brown, J., & Hackman, A. (2005). Hope against the cold: Individual differences in trait hope and acute pain tolerance on the cold pressor task. *Journal of Personality*, *73,* 287-312.

275 Snyder, C.R., Harris, C., Anderson, J.R., Holleran, S.A., Irving, L.M., Sigmon, S.T., Yoshinobu, L., Gibb, J., Langelle, C., & Harney, P. (1991). The will and the ways: Development and validation of an individual-differences measure of hope. *Journal of Personality and Social Psychology*, *60,* 570-585.

276 Sohl, S.J., Schnur, J.B., & Montgomery, G.H. (2009). A meta-analysis of the relationship between response expectancies and cancer treatment-related side effects. *Journal of Pain and Symptom Management*, *38,* 775-784.

277 Spanos, N.P., Perlini, A.H., & Robertson, L.A. (1989). Hypnosis, suggestion, and placebo in the reduction of experimental pain. *Journal of Abnormal Psychology*, *98,* 285-293.

278 Staats, P., Hekmat, H., & Staats, A. (1998). Suggestion/placebo effects on pain: Negative as well as positive. *Journal of Pain and Symptom Management*, *15,* 235-243.

279 Ständer, S., & Schmelz, M. (2006). Chronic itch and pain-similarities and differences. *European Journal of Pain 10,* 473-478.

280 Stewart-Williams, S., & Podd, J. (2004). The placebo effect: Dissolving the expectancy versus conditioning debate. *Psychological Bulletin*, *130,* 324-340.

281 Stockhorst, U., Enck, P., & Klosterhalfen, S. (2007). Role of classical conditioning in learning gastrointestinal symptoms. *World Journal of Gastroenterology*, *13,* 3430-3437.

282 Sullivan, M.J.L., Bishop, S.R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*, *7,* 524-532.

283 Terry, E.L., Thompson, K.A., & Rhudy, J.L. (2015). Experimental reduction of pain catastrophizing modulates pain report

but not spinal nociception as verified by mediation analyses. *PAIN*, *156,* 1477-1488.

284 Thompson, A.G.H., & Sunol, R. (1995). Expectations as determinants of patient satisfaction: Concepts, theory and evidence. *International Journal for Quality in Health Care*, *7,* 127-141.

285 Treister, R., Kliger, M., Zuckerman, G., Aryeh, I.G., & Eisenberg, E. (2012). Differentiating between heat pain intensities: The combined effect of multiple autonomic parameters. *PAIN*, *153,* 1807-1814.

286 Turk, D.C., Dworkin, R.H., McDermott, M.P., Bellamy, N., Burke, L.B., Chandler, J.M., Cleeland, C.S., Cowan, P., Dimitrova, R., Farrar, J.T., Hertz, S., Heyse, J.F., Iyengar, S., Jadad, A.R., Jay, G.W., Jermano, J.A., Katz, N.P., Manning, D.C., Martin, S., Max, M.B., McGrath, P., McQuay, H.J., Quessy, S., Rappaport, B.A., Revicki, D.A., Rothman, M., Stauffer, J.W., Svensson, O., White, R.E., & Witter, J. (2008). Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. *PAIN*, *139,* 485-493.

287 Tversky, A., & Kahneman, D. (1973). Availability: A heuristic for judging frequency and probability. *Cognitive Psychology*, *4,* 207-232.

288 van Beugen, S., Ferwerda, M., Hoeve, D., Rovers, M.M., Spillekom-van Koulil, S., van Middendorp, H., & Evers, A.W.M. (2014). Internet-based cognitive behavioral therapy for patients with chronic somatic conditions: A meta-analytic review. *Journal of Medical Internet Research*, *16,* e88.

289 van Breukelen, G.J.P. (2006). ANCOVA versus change from baseline had more power in randomized studies and more bias in nonrandomized studies. *Journal of Clinical Epidemiology*, *59,* 920-925.

290 van der Ploeg, H.M. (1982). De zelf-beoordelings vragenlijst (STAI-DY). *Tijdschrift voor Psychiatrie*, *24,* 576-588.

291 van Kuiken, D. (2004). A meta-analysis of the effect of guided imagery practice on outcomes. *Journal of Holistic Nursing*, *22,* 164-179.

292 van Laarhoven, A.I.M., Kraaimaat, F.W., Wilder-Smith, O.H., & Evers, A.W.M. (2010). Role of attentional focus on bodily sensations in sensitivity to itch and pain. *Acta Dermato-Venereologica*, *90,* 46-51.

293 van Laarhoven, A.I.M., Kraaimaat, F.W., Wilder-Smith, O.H., van de Kerkhof, P.C.M., & Evers, A.W.M. (2010). Heterotopic pruritic conditioning and itch - Analogous to DNIC in pain? *PAIN*, *149,* 332-337.

294 van Laarhoven, A.I.M., van der Sman-Mauriks, I.M., Donders, A.R.T., Pronk, M.C., van de Kerkhof, P.C.M., & Evers, A.W.M. (2015). Placebo effects on itch: A meta-analysis of clinical trials of patients with dermatological conditions. *Journal of Investigative Dermatology*, *135,* 1234-1243.

295 van Laarhoven, A.I.M., Vogelaar, M.L., Wilder-Smith, O.H., van Riel, P.L.C.M., van de Kerkhof, P.C.M., Kraaimaat, F.W., & Evers, A.W.M. (2011). Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *PAIN*, *152,* 1486-1494.

296 van Laarhoven, A.I.M., Walker, A.L., Wilder-Smith, O.H., Kroeze, S., van Riel, P.L.C.M., van de Kerkhof, P.C.M., Kraaimaat, F.W., & Evers, A.W.M. (2012). Role of induced negative and positive emotions in sensitivity to itch and pain in women. *British Journal of Dermatology*, *167,* 262-269.

297 Vancleef, L.M.G., & Peters, M.L. (2011). The influence of perceived control and self-efficacy on the sensory evaluation of experimentally induced pain. *Journal of Behavior Therapy and Experimental Psychiatry*, *42,* 511-517.

298 Vase, L., Petersen, G.L., Riley, J.L., 3rd, & Price, D.D. (2009). Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *PAIN*, *145,* 36-44.

299 Vase, L., Riley, J.L., & Price, D.D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo

analgesia. *PAIN*, *99,* 443-452.

300 Vase, L., Robinson, M.E., Verne, G.N., & Price, D.D. (2003). The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients: An empirical investigation. *PAIN*, *105,* 17-25.

301 Vase, L., Robinson, M.E., Verne, G.N., & Price, D.D. (2005). Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *PAIN*, *115,* 338-347.

302 Vassend, O., Roysamb, E., & Nielsen, C.S. (2013). Five-factor personality traits and pain sensitivity: A twin study. *PAIN*, *154,* 722-728.

303 Verheul, W., Sanders, A., & Bensing, J. (2010). The effects of physicians' affect-oriented communication style and raising expectations on analogue patients' anxiety, affect and expectancies. *Patient Education and Counseling*, *80,* 300-306.

304 Verhoeven, E.W.M., Kraaimaat, F.W., van de Kerkhof, P.C.M., van Weel, C., Duller, P., van der Valk, P.G.M., van den Hoogen, H.J.M., Bor, J.H.J., Schers, H.J., & Evers, A.W.M. (2007). Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. *British Journal of Dermatology*, *156,* 1346-1349.

305 Verhoeven, E.W.M., Kraaimaat, F.W., van de Kerkhof, P.C.M., van Weel, C., Duller, P., van der Valk, P.G.M., van den Hoogen, H.J.M., Bor, J.H.J., Schers, H.J., & Evers, A.W.M. (2007). Psychosocial well-being of patients with skin diseases in general practice. *Journal of the European Academy of Dermatology and Venereology*, *21,* 662-668.

306 Verkuil, B., Brosschot, J.F., Meerman, E.E., & Thayer, J.F. (2012). Effects of momentary assessed stressful events and worry episodes on somatic health complaints. *Psychology & Health*, *27,* 141-158.

307 Vögtle, E., Barke, A., & Kröner-Herwig, B. (2013). Nocebo hyperalgesia induced by social observational learning. *PAIN*, *154,* 1427-1433.

308 Waber, R.L., Shiv, B., Carmon, Z., & Ariely, D. (2008). Commercial features of placebo and therapeutic efficacy. *Jama-Journal of the American Medical Association*, *299,* 1016-1017.

309 Wager, T.D., & Atlas, L.Y. (2015). The neuroscience of placebo effects: Connecting context, learning and health. *Nature Reviews Neuroscience*, *16,* 403-418.

310 Walach, H. (2001). The efficacy paradox in randomized controlled trials of CAM and elsewhere: Beware of the placebo trap. *Journal of Alternative and Complementary Medicine*, *7,* 213-218.

311 Weimer, K., Colloca, L., & Enck, P. (2015). Age and sex as moderators of the placebo response - An evaluation of systematic reviews and meta-analyses across medicine. *Gerontology*, *61,* 97-108.

312 Weisshaar, E., & Dalgard, F. (2009). Epidemiology of itch: Adding to the burden of skin morbidity. *Acta Dermato-Venereologica*, *89,* 339-350.

313 Wells, N. (1989). Management of pain during abortion. *Journal of Advanced Nursing*, *14,* 56-62.

314 Wertli, M.M., Burgstaller, J.M., Weiser, S., Steurer, J., Kofmehl, R., & Held, U. (2014). Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain. *Spine*, *39,* 263-273.

315 Wessely, S., Chalder, T., Hirsch, S., Wallace, P., & Wright, D. (1997). The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: A prospective primary care study. *American Journal of Public Health*, *87,* 1449-1455.

316 Whaley, M.H., Brubaker, P.H., & Otto, R.M.Eds.) (2006). ACSM's guidelines for exercise testing and prescription. 7th edition. *Lippincott Williams & Wilkins*.

317 Wilner, J.G., Vranceanu, A.M., & Blashill, A.J. (2014). Neuroticism prospectively predicts pain among adolescents: Results from a nationally representative sample. *Journal of Psychosomatic Research*, *77,* 474-476.

318 Wilson, T.D., Lisle, D.J., Kraft, D., & Wetzel, C.G. (1989). Preferences as expectation-driven inferences: Effects of affective expectations on affective experience. *Journal of Personality and Social Psychology*, *56,* 519-530.

319 Yosipovitch, G., Fast, K., & Bernhard, J.D. (2005). Noxious heat and scratching decrease histamine-induced itch and skin blood flow. *Journal of Investigative Dermatology*, *125,* 1268-1272.

320 Young Casey, C., Greenberg, M.A., Nicassio, P.M., Harpin, R.E., & Hubbard, D. (2008). Transition from acute to chronic pain and disability: A model including cognitive, affective, and trauma factors. *PAIN*, *134,* 69-79.

321 Zale, E.L., Lange, K.L., Fields, S.A., & Ditre, J.W. (2013). The relation between pain-related fear and disability: A meta-analysis. *The Journal of Pain*, *14,* 1019-1030.

322 Zeidan, F., Lobanov, O.V., Kraft, R.A., & Coghill, R.C. (2015). Brain mechanisms supporting violated expectations of pain. *PAIN*, *156,* 1772-1785.

323 Zhang, W., Robertson, J., Jones, A.C., Dieppe, P.A., & Doherty, M. (2008). The placebo effect and its determinants in osteoarthritis: Meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*, *67,* 1716-1723.

324 Zigmond, A.S., & Snaith, R.P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67,* 361-370.

325 Zunhammer, M., Ploner, M., Engelbrecht, C., Bock, J., Kessner, S.S., & Bingel, U. (2017). The effects of treatment failure generalize across different routes of drug administration. *Science Translational Medicine*, *9,* eaal2999.

SAMENVATTING *(DUTCH SUMMARY)*

Placebo-effecten zijn gezondheidsverbeteringen die optreden na toediening van een inactieve behandeling (i.e., placebo). Deze effecten worden doorgaans toegeschreven aan iemands verwachtingen over de heilzame werking van een placebo. Placebo-effecten zijn veelvuldig gevonden op pijn. Pijn kan ook beïnvloed worden door placebo-achtige effecten, dat wil zeggen, effecten die veroorzaakt worden door verwachtingen over een actieve behandeling of over de ervaring van pijn zelf. Ook andere lichamelijke klachten, zoals jeuk en vermoeidheid, kunnen beïnvloed worden door placebo- en placebo-achtige effecten, hoewel dit minder vaak onderzocht is. De behandeling van lichamelijke klachten kan mogelijk verbeterd worden door het benutten van deze effecten in de klinische praktijk. Om dat op een effectieve manier te doen is een beter begrip van placebo- en placebo-achtige effecten en van de rol van verwachtingen hierin van groot belang voor zowel onderzoekers als artsen.

Het primaire doel van het huidige proefschrift was om te onderzoeken hoe placebo-effecten benut kunnen worden om pijn en andere lichamelijke klachten te verlichten. Hiervoor richtten we ons op verwachtingen. We onderzochten verschillende manieren om verwachtingen te beïnvloeden (i.e., verwachtingsinducties: verbale suggestie, conditionering en mentale verbeelding) om de effectiviteit voor het verlichten van lichamelijke klachten, met name pijn, te bepalen. Daarnaast onderzochten we de rol van behandelkenmerken (i.e., de toedieningsvorm van medicijnen) en individuele kenmerken (bijv. persoonlijkheidskenmerken) in placebo- en placebo-achtige effecten.

In **Hoofdstuk 2** vatten we de theoretische en empirische literatuur over de invloed van verwachtingen op pijn samen. In de meest invloedrijke psychologische leertheorieën spelen verwachtingen een centrale rol. Er kan onderscheid gemaakt worden tussen drie soorten verwachtingen: stimulus verwachtingen (met betrekking tot externe stimuli en gebeurtenissen, zoals het ontvangen van een recept voor medicatie), responsverwachtingen (met betrekking tot interne, onvrijwillige ervaringen, zoals pijn) en verwachtingen over zelfeffectiviteit (*self-efficacy*, met betrekking tot het vermogen om gedrag uit voeren, zoals het ondernemen van lichamelijke activiteiten ondanks pijn). Van deze drie soorten verwachtingen worden responsverwachtingen over het algemeen gezien als het kernmechanisme van placebo- en placebo-achtige effecten. Ook wordt gedacht dat zij de grootste invloed op pijn hebben, gezien ze direct betrekking hebben op de ervaring zelf. Doorgaans worden drie leerprocessen van verwachtingen omschreven: leren via instructies (bijv. verbale suggestie), leren via conditionering

(directe ervaring van de samenhang tussen stimuli en/of gebeurtenissen) en observationeel leren. Daarnaast kunnen verwachtingen mogelijk ook geleerd worden door mentale verbeelding. We beschreven ook complexere verwachtingsconcepten (bijv. optimisme) waarin de samenhang van verwachtingen met gerelateerde emoties en gedachten gevat is. Met name optimisme en het catastroferen over pijn bleken geassocieerd te zijn met pijn, maar ook vertrouwen, piekeren en neuroticisme bleken invloedrijk, hoewel het onderzoek hiernaar beperkter is. Alles bij elkaar genomen onderstreept ons literatuuronderzoek de belangrijke invloed van verwachtingen op pijn en vergroot het ons begrip van de complexiteit van verwachtingen. Het beïnvloeden van verwachtingen via de verschillende leerprocessen lijkt een veelbelovende manier om placebo- en placebo-achtige effecten te benutten.

In **Hoofdstuk 3** bestudeerden we in een meta-analyse systematisch de beschikbare empirische literatuur om de grootte van de effecten van korte verwachtingsinducties op de pijn van patiënten te bepalen. We vonden dat verbale suggestie, conditionering en mentale verbeelding de pijn van patiënten kunnen verlichten. Er was vooral sterk bewijs dat verbale suggestie over de pijnstillende eigenschappen van een (placebo of actieve) behandeling placebo- en placebo-achtige effecten op de pijn van patiënten kunnen veroorzaken; een substantieel aantal studies vond effecten die gemiddeld statistisch matig tot groot waren. Slechts enkele studies onderzochten conditioneringsprocedures, welke altijd versterkt werden door verbale suggestie. Verrassend was dat de effecten daarvan niet groter bleken dan die van enkel verbale suggestie. Korte verbeeldingsoefeningen (bijv. gebruik makend van beelden van pijnvermindering door verdoving) hadden relatief kleine, hoewel veelbelovende, effecten op de pijn van patiënten. We bekeken tevens verschillende factoren die de effecten van de verwachtingsinducties mogelijk beïnvloedden. Opmerkelijk was dat de effecten van verbale suggestie op experimenteel opgewekte pijn en met name op acute procedurele pijn (bijv. pijn na een operatie) substantieel groter waren dan de effecten op chronische pijn (bijv. voortdurende zenuwpijn). Verder vonden we indicaties dat verbale suggestie effectiever was wanneer deze naar geïnjecteerde placebo's refereerde, dan wanneer deze naar orale of lokaal op de huid toegediende placebo's refereerde. Samenvattend suggereert onze meta-analyse dat de bevindingen van experimenteel onderzoek naar klinische situaties gegeneraliseerd kunnen worden in het geval van acute procedurele pijn, hoewel in mindere mate in het geval van chronische pijn. Verwachtingsinterventies, vooral verbale suggestie, zijn hiermee veelbelovende methoden voor het optimaliseren van reguliere pijnbehandelingen in de klinische praktijk, in ieder geval in acute gevallen.

In **Hoofdstuk 4** onderzochten we de effecten van zowel verbale suggestie als mentale verbeelding op pijn, jeuk en vermoeidheid als indicatoren van lichamelijke

gevoeligheid. In deze experimentele studie vertelden we een gezonde groep deelnemers dat een (placebo) capsule de gevoeligheid voor lichamelijke sensaties (zoals pijn, jeuk en vermoeidheid) kan verminderen. We vonden dat deze suggestie de verwachtingen van de deelnemers over de effecten van de capsule sterk beïnvloedde. Ook een nieuw ontwikkelde mentale verbeeldingsoefening waarin deelnemers zich hun best mogelijke gezondheid voorstelden, beïnvloedde de positieve en negatieve toekomstverwachtingen van de deelnemers. Echter, noch de verbale suggestie, noch de verbeeldingsoefening, noch de combinatie van beide beïnvloedde de lichamelijke gevoeligheid van de deelnemers, zoals bleek uit hun zelf-gerapporteerde en fysiologische reacties op experimenteel opgewekte pijn, jeuk en vermoeidheid. We vonden evenmin bewijs dat individuele verschillen, zoals de neiging van deelnemers om meer of minder optimistisch te zijn, hun reacties beïnvloedden. Deze bevindingen suggereren dat verwachtingseffecten niet altijd optreden. Mogelijk hangen ze, onder andere, af van de mate van specificiteit van de interventies, waarbij een focus op meerdere sensaties tegelijk of gezondheid in het algemeen minder effectief is dan een focus op een specifieke ervaring.

In **Hoofdstuk 5** onderzochten we of een nieuw ontwikkelde verbeeldingsoefening die specifiek gericht is op pijn placebo-achtige effecten kan opwekken. In de eerste van twee experimentele studies verbeeldden gezonde deelnemers zich dat ze minder pijn zouden ervaren tijdens een daaropvolgende pijnlijke koudwatertaak. Dit deden ze door zich een warme, waterdichte handschoen voor te stellen. De resultaten toonden dat de verbeelding van pijnvermindering (i.e., responsverbeelding) latere pijn kan verminderen. Belangrijk is dat deze effecten verklaard konden worden door de verwachtingen van de deelnemers over de latere pijn (i.e., responsverwachtingen). De effecten op pijn gingen echter niet gepaard met corresponderende fysiologische reacties (bijv. lagere hartslag). De tweede studie repliceerde deze bevindingen. In deze studie vonden we verder dat een aanvullende verbale suggestie over de effectiviteit van de verbeeldingsoefening de pijnstillende effecten niet of nauwelijks versterkte. Bovendien zagen we dat individuele kenmerken ook in deze studies de effecten niet voorspelden. Beide studies tonen dat placebo-achtige effecten op pijn opgewekt kunnen worden met responsverbeelding. Responsverbeelding lijkt daarmee een veelbelovende methode voor de behandeling van pijn, zelfs nog voordat de pijn daadwerkelijk optreedt.

In **Hoofdstuk 6** bekeken we verschillen in placebo-effecten van diverse toedieningsvormen van medicijnen (wat we ook in Hoofdstuk 3 zagen) door in een online vragenlijstonderzoek de onderliggende verwachtingen te meten. Een grote steekproef, representatief voor de Nederlandse bevolking, scoorde de verwachte

effectiviteit van zowel pijn- als jeuk-verlichtende medicijnen in verschillende toedieningsvormen: oraal, via injectie of lokaal op de huid. Overeenkomstig met onze eerdere bevindingen verwachtten respondenten dat injecties het meest effectief zouden zijn voor het verlichten van pijn. Voor het verlichten van jeuk daarentegen verwachtten respondenten dat lokaal toegediende medicijnen het meest effectief zouden zijn. Deze bevindingen geven aan dat de verwachte effectiviteit van medicijnen, en daarmee placebo- en placebo-achtige effecten, afhangen van zowel de toedieningsvorm als van de behandelde klacht. Aanvullende analyses toonden dat een hogere verwachte effectiviteit samenhing met verwachtingen dat de medicijnen langer aanhoudende effecten, een snellere werking, een grotere veiligheid en groter gebruiksgemak hebben. De verwachte effectiviteit was niet of slechts zwak geassocieerd met verwachte bijwerkingen, prijs en mate waarin de toedieningsvorm als beangstigend werd gezien. Ook individuele verschillen in demografische kenmerken, gezondheid, frequentie van medicijngebruik en persoonlijkheidskenmerken hingen niet of slechts zwak samen met de verwachte effectiviteit. Alles bij elkaar genomen suggereren deze bevindingen dat invasieve behandelingen niet per se krachtiger zijn dan minder invasieve behandelingen. In plaats daarvan spelen ook andere factoren een rol, zoals het soort klacht dat behandeld wordt en mogelijk ook de locatie van de klacht en de gangbaarheid van een specifieke toedieningsvorm voor de klacht.

Tot besluit onderstrepen de bevindingen van het onderzoek in dit proefschrift de invloed van verwachtingen op pijn en het potentieel van verwachtingsinterventies voor het verbeteren van de behandeling van pijn en andere lichamelijke klachten. We vonden dat placebo- en placebo-achtige effecten opgewekt kunnen worden via verbale suggestie, conditionering en mentale verbeelding. Vooral verbale suggestie lijkt de korte-termijneffecten van pijnbehandelingen te verbeteren bij patiënten. We vonden bovendien, voor het eerst, dat mentale verbeelding van verminderde pijn (i.e., responsverbeelding) pijnvermindering kan veroorzaken via de effecten op responsverwachtingen. Daarnaast zagen we dat verwachtingen over de effectiviteit van medicijnen ook afhangen van de toedieningsvorm en de behandelde klacht. Concluderend kunnen we stellen dat het benutten van placebo-effecten door ons te richten op verwachtingen veelbelovend is voor het verbeteren van de reguliere behandeling van lichamelijke klachten zoals pijn.

PUBLICATIONS

Articles in international peer reviewed journals

Peerdeman, K.J.*, Tekampe, J.*, van Laarhoven, A.I.M., van Middendorp, H., Rippe, R.C.A., Peters, M.L., & Evers, A.W.M. (in press). Expectations about the effectiveness of pain- and itch-relieving medication administered via different routes*. European Journal of Pain.* doi: 10.1002/ejp.1163*. *joint first authorship.* OPEN ACCESS

Bartels, D.J.P., van Laarhoven, A.I.M., Stroo, M., Hijne, K., **Peerdeman, K.J.**, Donders, A.R.T., van de Kerkhof, P.C.M., & Evers, A.W.M (2017). Minimizing nocebo effects by conditioning with verbal suggestion: A randomized clinical trial in healthy humans. *PLOS ONE*, *12*, e0182959*.* doi*:* 10.1371/journal.pone.0182959. OPEN ACCESS

Peerdeman, K.J., van Laarhoven, A.I.M., Bartels, D.J.P., Peters, M.L., & Evers, A.W.M. (2017). Placebo-like analgesia via response imagery. *European Journal of Pain, 21*, 1366–1377*.* doi: 10.1002/ejp.1035. OPEN ACCESS

Peerdeman, K.J., van Laarhoven, A.I.M., Peters, M.L., & Evers, A.W.M. (2016). An integrative review of the influence of expectancies on pain. *Frontiers in Psychology, 7*, 1270. doi: 10.3389/fpsyg.2016.01270. OPEN ACCESS

Peerdeman, K.J., van Laarhoven, A.I.M., Keij, S.M., Vase, L., Rovers, M.M., Peters, M.L., & Evers, A.W.M. (2016). Relieving patients' pain with expectation interventions: A meta-analysis. *PAIN, 157*, 1179-1191. doi: 10.1097/j.pain.0000000000000540.

Peerdeman, K.J., van Laarhoven, A.I.M., Donders, A.R.T., Hopman, M.T.E., Peters, M.L., & Evers, A.W.M. (2015). Inducing expectations for health: Effects of verbal suggestion and imagery on pain, itch, and fatigue as indicators of physical sensitivity. *PLOS ONE, 10,* e0139563. doi: 10.1371/journal.pone.0139563. OPEN ACCESS

Book chapter

Evers, A.W.M., **Peerdeman, K.J.**, Bartels, D.J.P., & van Laarhoven, A.I.M. (2016). Placebo and nocebo effects on itch: Methodological and clinical implications. In L. Misery & S. Ständer (Eds.). *Pruritus. 2nd edition* (pp. 103-110). *Springer International Publishing*.

National (non refereed) article

Evers, A.W.M., & **Peerdeman, K.J.** (2016). Hoe het placebo-effect kan bijdragen aan een betere gezondheidszorg. *MFM Praktijkgerichte nascholing over farmacotherapie, 6*, 46.

CURRICULUM VITAE

Kaya Peerdeman was born on September 26, 1986 in Hoorn, the Netherlands. After obtaining her Gymnasium diploma at the OSG West-Friesland (with merit) in 2004, she completed her bachelor in Clinical Psychology at the University of Amsterdam (UvA) (with merit). In 2011, she completed the Research Master's programme in Psychology (major Clinical Psychology, minor Cognitive Neuropsychology; cum laude) and the master in Clinical Psychology at the UvA. Her main research project focused on the modes of thinking that determine the dysfunctionality of rumination. She obtained practical experience in psychodiagnostics and psychotherapy at the Universitair Psychiatrisch Centrum KU Leuven, campus Kortenberg, in Belgium. During her studies, she worked as a research assistant on various projects in Developmental Psychology and Religion Studies and organized lectures and an international conference on the Psychology of Religion for the psychology study association (VSPA).

She started her PhD research in 2011 at the Medical Psychology department of the Radboud university medical center in Nijmegen. In 2014, she moved with the whole research group to continue her work at the newly formed Health, Medical and Neuropsychology unit of Leiden University. Her research was funded by a NWO Vidi grant and later also an ERC consolidator grant awarded to prof. dr. Andrea Evers. During her PhD, in early 2015, she was a visiting scholar at Aarhus University in Denmark with prof. dr. Lene Vase. For her paper on the placebo-like analgesic effects of response imagery (Chapter 5), she received the EPP article award 2015/2016. During her PhD and as a lecturer at the department, she supervised a multitude of bachelor projects and master theses, taught workgroups, and gave several lectures. She was a member of the local and international organizing committee of the 1st official SIPS conference on Placebo Studies.

Currently, she is working as a post-doctoral researcher on prof. dr. Andrea Evers' Vici project to study the role of nocebo effects in the sensitization of somatic symptoms. In parallel, she continues her work as a lecturer.

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