Harnessing placebo effects by targeting expectancies

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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.