# Optimizing placebo effects in medical contexts: utilizing learning theories and exploring communication strategies

Smits, R.M.

# 1. General introduction



Several anecdotes exist about the first encounters with the phenomenon of the *placebo effect* (1, 2). In terms of its terminology, it is argued that the word ‘placebo’ stems from a mistranslation by St Jerome of Psalm 116 in which he wrote “I will please the Lord in the land of the living” (“*Placebo Domino in regione vivorum*”) instead of “I will walk before the Lord in the land of the living”(3). In terms of placebo use, the first form of application was described by the Catholic church in the 16th century, where individuals who were assumed to have occult beliefs were given fake relics. If these relics (placebos) evoked erratic behaviors, it was then concluded that their behaviors were merely a product of their imagination, and possession was ruled out(4). Later in the 18th century, first reports of an innovative research paradigm were described that incorporated placebos, which were called randomized controlled trials (RCTs). In RCTs, both patients and doctors were unaware of the patients’ allocation to the treatment group or the placebo group (‘double blind’). The total effect of the treatment itself was then compared to a placebo group. In case of superiority of the experimental drug over the placebo group, the treatment would be considered as effective(2). The placebo effect itself gained more attention during World War II, when anesthesiologist Henry Knowles Beecher reviewed results from studies that compared placebos to analgesics (e.g. compared to acetylsalicylic acid, codeine, and morphine) in his paper ‘The powerful placebo’ in 1955(5, 6). After this publication, Beecher was known as the first clinician to elaborate on the therapeutic effects of placebos(1). Since then, decades of placebo research have elucidated important biological, psychological and social mechanisms involved in steering placebo effects and have demonstrated the importance of placebo effects in therapeutic contexts(2, 7). In the past decades, the therapeutic benefits of placebo effects have increasingly gained attention. Methods that optimize these effects in medical contexts are researched more frequently and many physicians recognize the importance of placebo effects in daily practice(1).

Placebo effects can be viewed from different perspectives. On one hand, placebos often serve as an important tool in RCTs to elucidate the efficacy of a newly developed experimental drug therapy(8). From this perspective, placebo effects are unwanted and efforts are often made to minimize these effects, because it hinders the effects of the experimental drug. On the other hand, placebo effects can be viewed from a perspective to induce therapeutic benefits that can be exploited to

maximize treatment outcomes, save costs and potentially reduce side effects by focusing on their underlying mechanisms as described above(9). This dissertation will mainly focus on the latter perspective of placebo effects.

To clearly understand what placebo effects entail and how this can inflict therapeutic beneficial effects, it is also important to address the paradox that is often described in placebo research. Placebos itself are frequently described as inert substances that inherently lack properties to induce any effect. However, the effects that placebos evoke through their demonstrated neurobiological and psychological underlying mechanism are substantial, as reflected in psychological and physiological outcomes, and reported in a broad range of conditions and in different medical contexts(1, 2, 7, 10). Moreover, it is important to address the distinction in terminology between placebo responses and placebo effects. In 2018, the terminology in placebo research has been specified by a large consortium of placebo experts(11). Consequently, placebo responses have been defined to include all positive health changes that result after administration of an inert treatment by comparing before and after treatment effects. In line with this terminology, placebo responses also include regression to the mean and natural history which are often misinterpreted for placebo effects(12). Placebo effects have been defined as beneficial effects in clinical or laboratory medical context that can be specifically traced back to their underlying psychosocial or neurobiological mechanisms, such as positive expectations or associative learning principles (i.e. classical conditioning)(11).

**Placebo responses**
All positive health changes that result after administration of an inactive treatment.

**Placebo effects**
Psychosocial or neurobiological mechanisms that induce beneficial effects in a clinical or laboratory medical context.

**Placebos**
Inert substances that inherently lack properties to induce any effect.

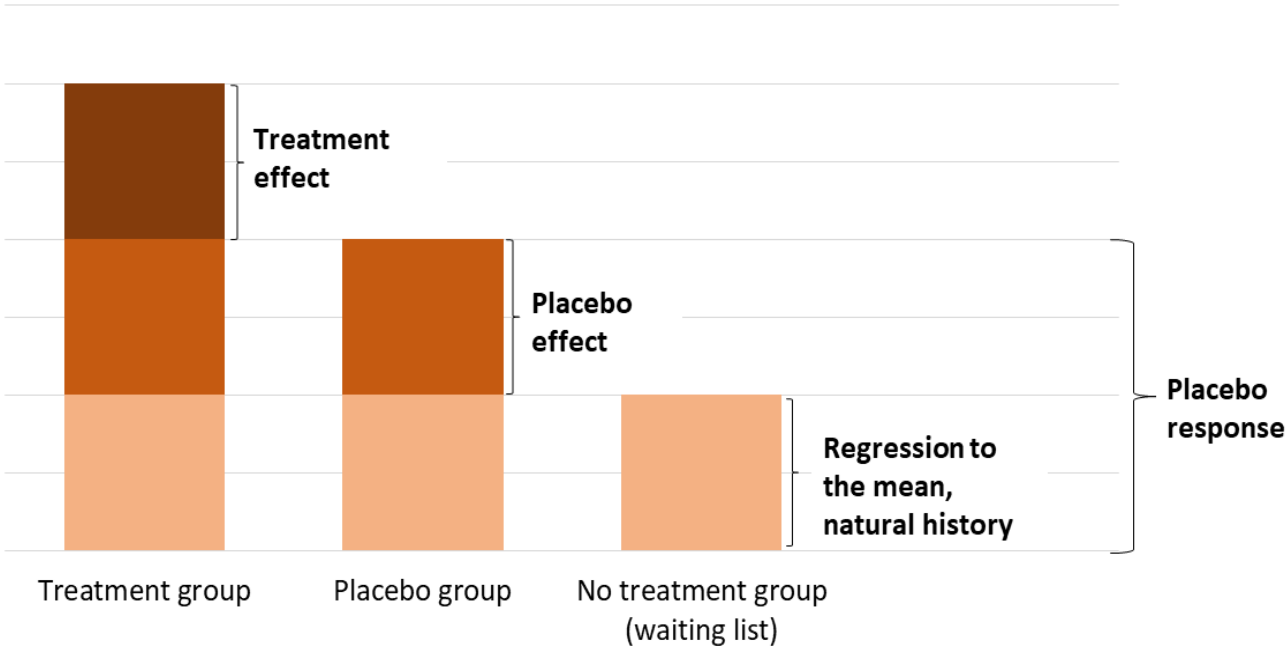



**Fig 1.** Conceptual framework of placebo responses, placebo effects and treatment effects in RCTs or clinical practice. *Note: All three aspects are separately depicted here, but are not mutually exclusive in reality. Factors can interact, for example placebo effects can be intertwined within treatment effects. Adapted from Howick and colleagues(13).*

## Mechanisms that steer placebo effects

Overall, placebo effects are driven by expectancies about treatment outcomes, which may in turn inflict therapeutic benefit(2). At least three main mechanisms have been identified that induce expectancies through learning, and encompass instructional learning, classical conditioning, and social observational learning.

To shape expectancies, verbal suggestions are often used, which is also referred to as instructional learning(10). The effects of verbal suggestions have become evident in experimental settings, and also in clinical contexts where the importance of message framing and emphasis on positive outcomes is underlined(14-17). For example, previous studies have underlined the role of positive expectancies induced by verbal suggestions in pain research, and found that these can induce pain relief, which is termed placebo analgesia (i.e., pain relief after placebo administration)(7, 18-21). One of the many interesting findings from the field of pain research is that

verbal suggestions about treatment benefit (i.e. positively induced expectations) could be blocked by the opiate antagonist naloxone. This was later supported by the finding that verbally induced expectations of placebo analgesia activate μ-opioid receptors that in turn cause pain relief(22, 23). Moreover, placebo analgesia has demonstrated to activate brain regions that are also involved in pain modulation(24). For example, previous studies demonstrated activation of μ-opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens(19, 23, 25). These findings elucidate that positive expectations use the same pathway as endogenous opioids when inducing pain relief and could be used for therapeutic benefit. The power of shaping expectancies by verbal suggestions and its significant effects on neurobiological processes and clinical outcomes are however not only restricted to pain research. Since the last decades, a large body of research has supported the involvement of instructional learning in other fields than pain analgesia, for example in Parkinson's disease or in heart surgery patients, where positive expectancies activated dopaminergic systems (i.e. nigrostriatal and mesoaccumbens projections), or increased pro-inflammatory cytokine concentrations (i.e. interleukin-6 and interleukin-8)(17, 26). Alternatively, negative expectations (i.e. induced by negative verbal suggestions) can in turn have detrimental effects on treatment outcomes and are referred to as nocebo effects(11). Therefore, it is very important to manage expectations and harness their effects on treatment outcomes.

Besides instructional learning, another important learning mechanism has been elucidated to play a role in placebo effects, namely classical conditioning(12, 21, 27). In classical conditioning, a neutral stimulus is combined with another stimulus that induces a bodily response to create a learned association. This learned association in turn elicits a bodily response, without the presence of the initial stimulus that evokes this response. In Pavlov's famous salivation experiment with dogs, this neutral stimulus was a metronome (often referred to as a bell, serving as the conditioned stimulus; CS) which was paired with food (serving as the unconditioned stimulus; UCS) to create a learned association. Ultimately, the presentation of the metronome alone induced a salivatory response (conditioned response; CR) which previously was only caused by the UCS(28). The importance of conditioning in

placebo effects finds its support in many research fields, but in particular in the field of immunology, where it was found that immune functions are prone to conditioning principles and are also referred to as *learned immune responses*(19, 29-32). Conditioning with immune parameters has become evident in animal models that used a similar paradigm as Pavlov, consisting of an acquisition phase (or learning phase) and an evocation phase (or testing phase)(15, 33, 34). During the acquisition phase, an initial neutral stimulus (conditioned stimulus, CS) is coupled with a pharmacological agent (unconditioned stimulus, UCS). To accommodate the effects of conditioning, the CS that is used usually contains distinct potent gustatory or visual properties, such as a saccharine solution or a green novel tasting drink(15, 33, 34). After a strong association is formed with repeated pairings of the CS and the UCS during the learning phase, conditioned responses are evoked by presentations of the CS alone and are reflected on the subjective level by conditioned taste aversion, and objective levels by modulations in immune parameters, which is termed the conditioned response (CR). Making use of conditioning principles in medication regimens is termed pharmacotherapeutic or pharmacological conditioning, in which conditioned immunologic responses are evoked by placebos because of the learned association with the color, shape, and context of an identical looking treatment(29, 30, 35-41).

A third learning mechanism involved in shaping expectancies and thereby inducing placebo effects, is social observational learning. In social observational learning, the observation of therapeutic benefit in others induces placebo effects, and is another learning mechanism that is frequently studied in the placebo literature(42). One of the first studies that recognized this mechanism discovered this by using a widely used experimental design where colors are associated with painful and non-painful stimuli. In such experimental paradigms, verbal suggestions and classical conditioning principles are used to induce placebo effects. Additionally, participants in this study watched another person rate painful and non-painful stimuli (behavioral modeling) which resulted in placebo analgesic responses after the observation of non-painful stimuli. Moreover, the results of this study demonstrated that placebo effects induced by observation were of equal magnitude as placebo effects induced by classical conditioning, and exceeded placebo effects induced by verbal suggestion(43, 44).

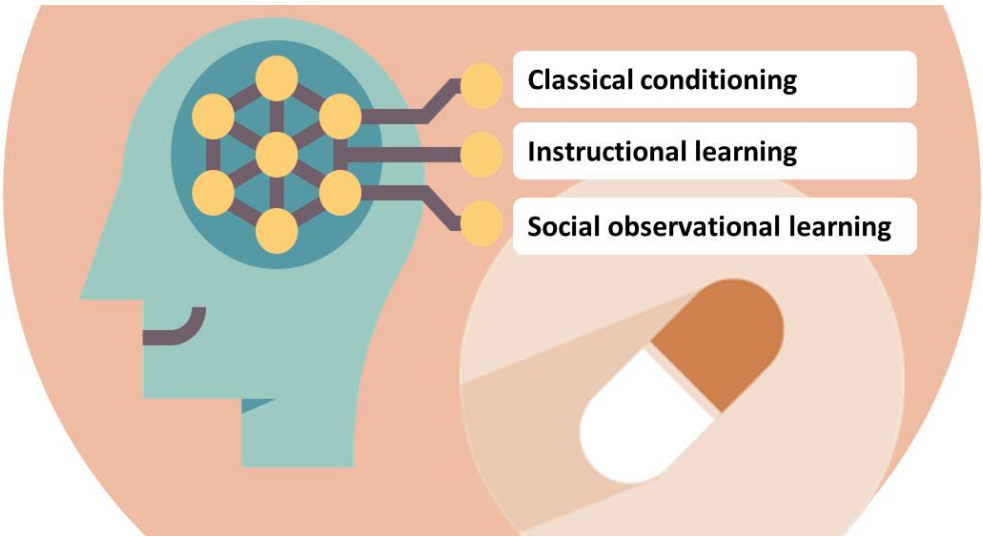



**Fig 2.** Learning mechanisms that steer placebo effects.

Next to the three abovementioned learning mechanisms that shape placebo effects, other contextual or environmental factors can influence treatment outcomes, such as the relationship between physicians and patients. The influence of warm and empathic communication is a prominent factor in treatment and has been studied in many different patient samples. For example, Di Blasi and colleagues (2001) examined the therapeutic effects of the doctor-patient relationship in a meta-analysis and found consistently that when physicians adopted a warm and reassuring communication style, the therapeutic outcomes exceeded the outcomes from physicians who kept consultations formal and did not offer reassurance(45). In line with these findings, a RCT with irritable bowel syndrome patients was carried out by Kaptchuk and colleagues (2008) in which different communication styles of physicians were manipulated to investigate their effects on treatment outcomes. In one experimental group, a warm and empathic communication style (the 'augmented' group) was employed, and compared with another experimental group that employed a more formal communication style (the 'limited' group). Results of this study showed significant higher rates of adequate relief in the 'augmented' group than the 'limited' group, thereby underlining the importance of doctor-patient communication, and the role of the doctor-patient relationship(14). Despite the proven effectiveness of empathic communication styles, the exact content of communication is not clear yet and research that investigates these placebo information strategies remain scarce. Moreover, other contextual factors in treatment can play a role in the placebo

response. For example, high price, brand label, placebo invasiveness, and high placebo dose are found to be associated with higher placebo effects(46, 47). Besides the abovementioned learning mechanisms, or contextual and environmental factors that influence placebo effects, the field of placebo research encompasses many aspects involved in placebo effects. For example refined underlying neurological circuitries that play a part in placebo effects(10, 12, 19, 20). Altogether, different facets involved in placebo effects could be used to induce benefit on different types of outcomes, for example on a subjective level (i.e. self-reported outcomes) or on an objective level (i.e. brain activity) (see Figure 2).

The main aim of this dissertation is to **optimize placebo effects in medical contexts** and will be approached from two different modes of action**,** namely utilizing **learning theories** and exploring **communication strategies.** Both of these modes can separately or interactively inflict treatment benefit. First, we will examine the role of placebo effects in physiological outcomes, in particular in immune-related disorders, and review different research designs that have integrated placebo effects, mainly through **pharmacological conditioning** to induce treatment benefit. Secondly, we will give an example of how these findings can be translated into medication regimens, by proposing an innovative research design that makes use of pharmacological conditioning, specifically designed by an interdisciplinary group of health professionals and researchers for patients with juvenile idiopathic arthritis. Next, this dissertation brings forward strategies that focus on **communication** about placebo effects. Despite the large body of evidence that emphasizes on the therapeutic benefits of placebo effects, little is known about the communication strategies that can be used to make use of placebo effects. The communication strategies investigated in this dissertation do not only focus on verbal suggestions to induce positive treatment outcomes, but also explain how placebo effects can have beneficial effects by taking into account the patient and health care provider perspective. Finally, an experimental research design was developed by the **integration** of our findings in which we combined learning mechanisms (**classical conditioning** and **instructional learning**) with communication strategies via a RCT to induce a non-deceptive form of placebo effects to study open-label placebo (OLP) effects in healthy volunteers as a proof of concept study.

## Learning theories & Immune responses

- **Exploration of placebo effects in immune-related conditions**

To investigate placebo effects, the conceptualization of an experimental design of the RCT plays an essential role. Besides the integration of a treatment group and a placebo group (mostly referred to as a control group)(2), some RCTs also include a natural history group, or a waiting list group. In these groups no treatments or placebos are administered, and therefore patients could not have developed any expectations about the efficacy of a treatment. In other words, a waiting list group or natural history group may serve as a group that reflects the absence of treatment expectations(48). In the first part of **Chapter 2**, we will review the outcomes of RCTs found in placebo groups and waiting list groups that reported on immune-related diseases such as allergies, asthma, gastro-intestinal diseases, arthritis, multiple sclerosis and patients suffering from heart disease, but also in patient groups where immunological changes were measured (e.g. modulations in cytokine proliferation). In the second part of Chapter 2, we built upon these findings and demonstrate how immune-related outcomes are susceptible to the underlying learning mechanisms of placebo effects, such as classical conditioning. We thereby report on experimental research designs based around the concept of the learned immune response, where conditioned responses are established and reflected on an immunological level (i.e. in lymphocyte proliferation or inflammation markers). Furthermore, we provide an introduction in how these placebo mechanisms could be translated to clinical advantages and review preliminary results of clinical trials that use pharmacological conditioning based on partial reinforcement. In a partial reinforcement schedule, regular doses of a pharmacological agent are intermittently administered with lower subtherapeutic dosages. During the administration of the subtherapeutic dosages, therapeutic effects are assumed to be maintained, because of the effects of conditioning. One of the leading examples of this paradigm was proposed by Ader and colleagues, published as a pilot study in 2010. In this research design, conditioning effects were evoked in a partial reinforcement schedule for psoriasis in which dosages of corticosteroid cream were intermittently administered with a placebo cream(49). This study brought forth promising clinical outcomes from the partial reinforcement group, and demonstrated a novel intervention based on the combination of classical conditioning pharmacological effects. Altogether, Chapter 2

provides an introduction of how immune parameters can be susceptible to the effects of conditioning and propose promising research designs which we will elaborate more on in **Chapter 3**(49).

**Learning theories & Immune responses**

- **Translation of placebo effects into a pharmacological conditioning design**

In **Chapter 3,** we focus on the clinical application of the learned immune response by conceptualizing an optimal trial design. We considered all previous studies that made use of pharmacological conditioning and reviewed how learning mechanisms could be integrated in medication regimens, building upon the partial reinforcement of Ader and colleagues(46). Moreover, we reviewed other ways of integrating placebos in medication regimens to evoke learning effects, namely by using placebos as 'dose extenders'. For example, Kirchhof and colleagues successfully enhanced therapeutic effects of cyclosporin A in renal transplant patients by adding placebos to medication regimens to 'boost' therapeutic effects and demonstrated an increase in effectiveness of the medication without an increase in dosing, which was also reflected on an immunological level, namely by a significant learned inhibition of T cell proliferative capacity(50). Based on these findings we propose an innovative research design for a patient group that may particularly benefit from this approach, namely children with juvenile idiopathic arthritis (JIA). This patient group is dependent on long-term medication treatment of the drug methotrexate (MTX), which is unfortunately hampered by high intolerance rates, reflected by severe side effects such as anticipatory nausea and stomachache in approximately half of the patients(51). With the possibilities that arise from pharmacological conditioning therapies, such as lowered dosing and reduced side effects, this patient group seems especially suited for this research paradigm. Moreover, previous attempts to reduce methotrexate intolerance (i.e. by cognitive behavioral therapy or anti-emetics) have been proven unsuccessful so far(52). Given these complications in treatment, a research design that makes uses of pharmacological conditioning in order to optimize treatment outcomes for patients with JIA was developed by an interdisciplinary group of clinicians, pharmacologists, psychologists, and patient representatives. Based on this collaboration, we provide recommendations for an optimal and innovative research

design, for example in medication schedules, the integration in patient care and relevant clinical and research outcome measures.

**Communication strategies**

- **Explaining placebo effects for medical practice**

Besides the facilitation of placebo mechanisms through learning principles in medication schedules, placebo effects can also be induced by informing participants or patients about the potential benefits of placebo effects. Even though many years of placebo research has elucidated a potential role of placebo effects for medical contexts, information strategies that explicitly employ these mechanisms remain scarce. Moreover, transparency and shared decision-making have become recurrent topics in patient samples, which underlines the need for patient involvement in therapeutic regimens when making use of placebo mechanisms(53). As abovementioned, many different aspects are involved that steer placebo effects, such as positive expectations, classical conditioning, social observational learning, and the the doctor-patient relationship. These aspects could all serve as explanations to educate individuals about the impact of placebo effects on treatment outcomes, and can ultimately be used to induce therapeutic benefit. However, the exact content of what placebo information should consist of remains unclear. In **Chapter 4**, we aimed to address this current knowledge gap and examined information strategies in the general population to get a broad understanding of what individuals would like to hear about the benefits of placebo effects. Eight different explanations about placebo effects that were built around well-known placebo effects were formulated, and compared to explore preferences for each explanation. Moreover, we assessed in what ways participants were willing to receive placebos as a (component of their) treatment to gain more insights in the applicability of placebos in practice. In addition, in **Chapter 5** we built upon these findings by assessing similar themes in health care professionals (i.e. nurses, physicians and medical psychologists), namely by investigating current knowledge of placebo effects, frequency of placebo use, interests in learning more about placebo and acceptability towards placebo use in treatment. By integrating the findings from Chapter 4 and 5 we are able to provide an

inclusive overview from different perspectives of health care givers and recipients, and demonstrate how placebo effects could be used and explained for daily practice.

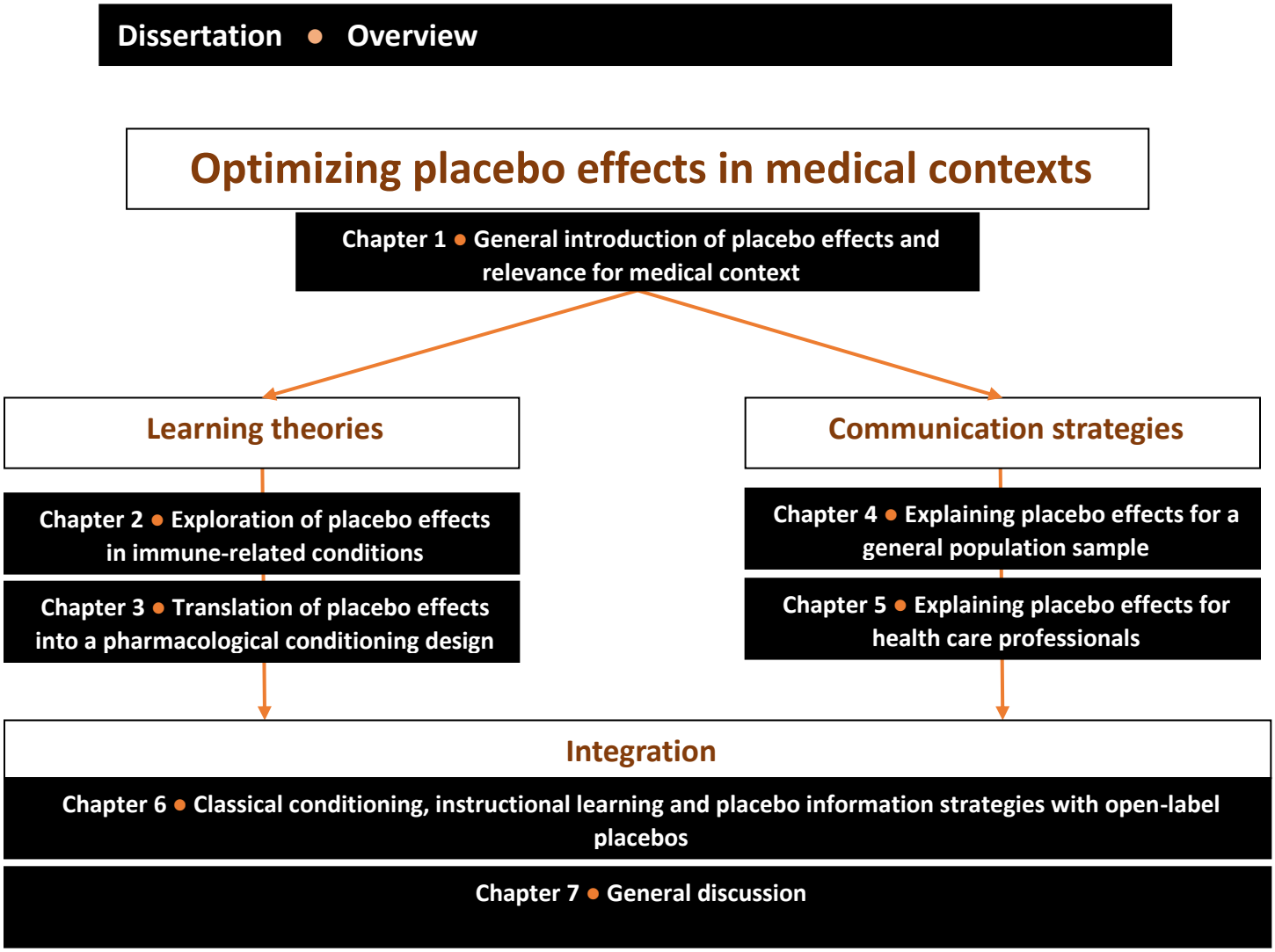
**Integration**

- **Learning theories and information strategies with open-label placebos**

Despite the large body of work that supports the potential of placebo effects in clinical implementation, the deceptive nature of placebo administration is often criticized as this poses ethical concerns(54). However, new developments in placebo research have taken place that surpass these ethical constraints. Findings from several clinical studies found that placebo administration can also take place in a transparent manner while still resulting in relevant therapeutic effects, called open-label placebos (OLP)(55-59). With OLPs, the nature of placebo administration is disclosed and has proven its therapeutic benefit by exceeding efficacy of no treatment groups, and showing comparable results to traditional (deceptive) placebos(54). Evidence for OLPs stem from various RCT findings, for example in patients with chronic low back pain(55), cancer-related fatigue(60), irritable bowel syndrome(57), major depressive disorder(58), attention deficit hyperactivity disorder(61), and allergic rhinitis(62), thereby demonstrating the potential for clinical implementation. Based on the clinical potential of OLP, in **Chapter 6,** we will employ an innovative OLP research design to integrate of our findings from the previous chapters. First, we used a well-validated experimental paradigm(63) in which we combined both the mechanisms of classical conditioning and instructional learning induced by verbal suggestions, of which the modes of action has been discussed in **Chapters 2 and 3.** Moreover, we integrated our newly developed placebo information strategies from **Chapters 4 and 5** to educate participants about the potential of (honest) placebo effects in the OLP group to further explore what underlying mechanisms steer OLP effects in healthy volunteers and investigate the potential for clinical application.

In sum, this dissertation covers several relevant aspects of placebo research by an **exploration** of the role of placebo effects (i.e. learning theories) in both psychological and physiological outcome measures for immune-related conditions, by proposing a research design based on the **translation** of placebo effects into medication

regimens and propose a potential solution for MTX intolerance. Moreover, we explained how placebo **communication** strategies can be developed based on general population and clinical samples. Finally, all insights were combined for the **integration** in our final study design, thereby contributing to the main objective of this body of work: *optimizing placebo effects in medical contexts.*



## REFERENCES


1. Meissner K, Kohls N, Colloca L. Introduction to placebo effects in medicine: mechanisms and clinical implications. The Royal Society; 2011.
2. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol. 2008;59:565-90.
3. Aronson J. Please, please me. Bmj. 1999;318(7185):716.
4. Kaptchuk TJ. Intentional ignorance: a history of blind assessment and placebo controls in medicine. Bulletin of the History of Medicine. 1998;72(3):389-433.
5. Beecher HK. The powerful placebo. Journal of the American Medical Association. 1955;159(17):1602-6.
6. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? Journal of clinical epidemiology. 1997;50(12):1311-8.
7. Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? Nature reviews Drug discovery. 2013;12(3):191.
8. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: gold standard or golden calf? Journal of clinical epidemiology. 2001;54(6):541-9.
9. Doering BK, Rief W. Utilizing placebo mechanisms for dose reduction in pharmacotherapy. Trends in pharmacological sciences. 2012;33(3):165-72.
10. Schedlowski M, Enck P, Rief W, Bingel U. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. Pharmacological reviews. 2015;67(3):697-730.
11. Evers AW. Using the placebo effect: how expectations and learned immune function can optimize dermatological treatments. Experimental dermatology. 2017;26(1):18-21.
12. Klosterhalfen S, Enck P. Psychobiology of the placebo response. Autonomic Neuroscience. 2006;125(1-2):94-9.
13. Howick J, Friedemann C, Tsakok M, Watson R, Tsakok T, Thomas J, et al. Are treatments more effective than placebos? A systematic review and meta-analysis. PloS one. 2013;8(5):e62599.
14. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. Bmj. 2008;336(7651):999-1003.
15. Pacheco-López G, Engler H, Niemi M-B, Schedlowski M. Expectations and associations that heal: immunomodulatory placebo effects and its neurobiology. Brain, behavior, and immunity. 2006;20(5):430-46.
16. Peerdeman KJ, van Laarhoven AI, Keij SM, Vase L, Rovers MM, Peters ML, et al. Relieving patients' pain with expectation interventions: a meta-analysis. Pain. 2016;157(6):1179-91.
17. Rief W, Shedden-Mora MC, Laferton JA, Auer C, Petrie KJ, Salzmann S, et al. Preoperative optimization of patient expectations improves long-term outcome in heart surgery patients: results of the randomized controlled PSY-HEART trial. BMC medicine. 2017;15(1):4.
18. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Annu Rev Pharmacol Toxicol. 2008;48:33-60.
19. Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. Neuron. 2014;84(3):623-37.
20. Colloca L, Barsky AJ. Placebo and Nocebo Effects. New England Journal of Medicine. 2020;382(6):554-61.
21. Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. Philosophical Transactions of the Royal Society B: Biological Sciences. 2011;366(1572):1922-30.
22. Levine J, Gordon N, Fields H. The mechanism of placebo analgesia. The Lancet. 1978;312(8091):654-7.
23. Zubieta J-K, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, et al. Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. Journal of Neuroscience. 2005;25(34):7754-62.

24. Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, et al. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron. 2009;63(4):533-43.
25. Wager TD, Scott DJ, Zubieta J-K. Placebo effects on human μ-opioid activity during pain. Proceedings of the National academy of sciences. 2007;104(26):11056-61.
26. Lidstone SC, Schulzer M, Dinelle K, Mak E, Sossi V, Ruth TJ, et al. Effects of expectation on placebo-induced dopamine release in Parkinson disease. Archives of general psychiatry. 2010;67(8):857-65.
27. Ader R. The role of conditioning in pharmacotherapy. The placebo effect: An interdisciplinary exploration. 1997:138-65.
28. Schedlowski M, Pacheco-López G. The learned immune response: Pavlov and beyond. Brain, behavior, and immunity. 2010;24(2):176-85.
29. Ader R, Cohen N. Behaviorally conditioned immunosuppression. Psychosomatic medicine. 1975;37(4):333-40.
30. Albring A, Wendt L, Benson S, Nissen S, Yavuz Z, Engler H, et al. Preserving learned immunosuppressive placebo response: perspectives for clinical application. Clinical Pharmacology & Therapeutics. 2014;96(2):247-55.
31. Albring A, Wendt L, Benson S, Witzke O, Kribben A, Engler H, et al. Placebo effects on the immune response in humans: the role of learning and expectation. PloS one. 2012;7(11):e49477.
32. Exton MS, von Hörsten S, Strubel T, Donath S, Schedlowski M, Westermann J. Conditioned alterations of specific blood leukocyte subsets are reconditionable. Neuroimmunomodulation. 2000;7(2):106-14.
33. Tekampe J, Peerdeman K, van Middendorp H, van Laarhoven AI, Rippe RC, Peters ML, et al. Development and Validation of the General Attitude Towards Medication Questionnaire (GAMQ)-Preprint. 2019.
34. Tekampe J, van Middendorp H, Meeuwis SH, van Leusden JW, Pacheco-López G, Hermus AR, et al. Conditioning immune and endocrine parameters in humans: A systematic review. Psychotherapy and psychosomatics. 2017;86(2):99-107.
35. Ader R. The placebo effect as a conditioned response. Experimental foundations of behavioral medicine: Conditioning approaches. 1988:47-66.
36. Exton MS, Gierse C, Meier B, Mosen M, Xie Y, Frede S, et al. Behaviorally conditioned immunosuppression in the rat is regulated via noradrenaline and β-adrenoceptors. Journal of neuroimmunology. 2002;131(1):21-30.
37. Goebel MU, Hübell D, Kou W, Janssen OE, Katsarava Z, Limmroth V, et al. Behavioral conditioning with interferon beta-1a in humans. Physiology & behavior. 2005;84(5):807-14.
38. Hadamitzky M, Bösche K, Engler A, Schedlowski M, Engler H. Extinction of conditioned taste aversion is related to the aversion strength and associated with c-fos expression in the insular cortex. Neuroscience. 2015;303:34-41.
39. Hadamitzky M, Bösche K, Wirth T, Buck B, Beetz O, Christians U, et al. Memory-updating abrogates extinction of learned immunosuppression. Brain, behavior, and immunity. 2016;52:40-8.
40. Kirchhof J, Petrakova L, Brinkhoff A, Benson S, Schmidt J, Unteroberdörster M, et al. Learned immunosuppressive placebo responses in renal transplant patients. Proceedings of the National Academy of Sciences. 2018:201720548.
41. Lückemann L, Unteroberdörster M, Kirchhof J, Schedlowski M, Hadamitzky M. Applications and limitations of behaviorally conditioned immunopharmacological responses. Neurobiology of Learning and Memory. 2017.
42. Klinger R, Colloca L. Approaches to a complex phenomenon: The basic mechanisms and clinical applications of placebo effects. 2014.
43. Bajcar EA, Bąbel P. How does observational learning produce placebo effects? A model integrating research findings. Frontiers in psychology. 2018;9:2041.
44. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136(1-2):211-8.

45. Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. The Lancet. 2001;357(9258):757-62.
46. Meissner K, Linde K. Are blue pills better than green? How treatment features modulate placebo effects. International review of neurobiology. 139: Elsevier; 2018. p. 357-78.
47. Narkus A, Lehnigk U, Haefner D, Klinger R, Pfaar O, Worm M. The placebo effect in allergen-specific immunotherapy trials. Clinical and translational allergy. 2013;3(1):42.
48. Benedetti F. Placebo effects: Oxford University Press, USA; 2014.
49. Ader R, Mercurio MG, Walton J, James D, Davis M, Ojha V, et al. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosomatic Medicine. 2010;72(2):192.
50. Kirchhof J, Petrakova L, Brinkhoff A, Benson S, Schmidt J, Unteroberdörster M, et al. Learned immunosuppressive placebo responses in renal transplant patients. Proceedings of the National Academy of Sciences. 2018;115(16):4223-7.
51. Bulatović M, Heijstek MW, Verkaaik M, Van Dijkhuizen E, Armbrust W, Hoppenreijs E, et al. High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. Arthritis & Rheumatology. 2011;63(7):2007-13.
52. Scheuern A, Tyrrell PN, Haas J-P, Hügle B. Countermeasures against methotrexate intolerance in juvenile idiopathic arthritis instituted by parents show no effect. Rheumatology. 2017;56(6):901-6.
53. Bishop FL, Aizlewood L, Adams AE. When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views. PLoS One. 2014;9(7):e101822.
54. Colloca L, Howick J. Placebos without deception: outcomes, mechanisms, and ethics. International review of neurobiology. 138: Elsevier; 2018. p. 219-40.
55. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain. 2016;157(12):2766.
56. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Scientific reports. 2018;8(1):2784.
57. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PloS one. 2010;5(12):e15591.
58. Kelley JM, Kaptchuk TJ, Cusin C, Lipkin S, Fava M. Open-label placebo for major depressive disorder: a pilot randomized controlled trial. Psychotherapy and psychosomatics. 2012;81(5).
59. Sandler AD, Bodfish JW. Open-label use of placebos in the treatment of ADHD: A pilot study. Child: care, health and development. 2008;34(1):104-10.
60. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Scientific reports. 2018;8(1):1-8.
61. Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in ADHD? Journal of developmental and behavioral pediatrics: JDBP. 2010;31(5):369.
62. Schaefer M, Sahin T, Berstecher B. Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. PloS one. 2018;13(3):e0192758.
63. Yeung STA, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. PAIN®. 2014;155(6):1110-7.