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

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And in the end
the love you take
is equal
to the love you make.

- Lennon J., & McCartney P. (1969). The End. On *Abbey Road*. Sony/ATV Music Publishing LLC.

Be so full that even if
they take & take
& take & take
You can still be overflowing.

- Malee, A.A.

7. Summary and General discussion

The main aim of this dissertation was to **optimize placebo effects in medical contexts,** which we addressed from two different approaches. Our first approach focused on **learning theories** involved in placebo effects**,** such as classical conditioning and instructional learning. In the first chapter we reviewed the susceptibility to, and prevalence of placebo effects in immune-related conditions. Subsequently, we developed an innovative research paradigm in which placebo effects were integrated in a medication regimen through pharmacological conditioning, to optimize treatment effects for juvenile idiopathic arthritis. Our second approach focused on **communication strategies** to facilitate the clinical application of placebo effects, which explored how placebo effects can be explained. To develop these communication strategies, we first explored different placebo information strategies in a general population sample and subsequently explored these strategies and frequency of placebo use in a sample with health care professionals. Finally, we combined both approaches by an integration of the **learning theories** (conditioning and instructional learning) and **communication strategies** in a research design to induce a non-deceptive form of placebo effects to study open-label placebo (OLP) analgesic effects in healthy controls as a proof of concept study. Altogether, this dissertation covered several relevant aspects of placebo research by providing insights in learning mechanisms involved in placebo effects, recommendations for placebo information strategies, and a research design in which these insights were implemented.

Utilizing learning theories

In **Chapter 2,** the role of placebo effects in immune-related conditions was reviewed. A large variety of literature that reported on placebo effects in immune-related diseases (e.g. arthritis), but also in patient groups where immunological changes (e.g. modulations in cytokine proliferation), was discussed. We found that immunologic processes were susceptible to the learning mechanisms from placebo effects across different types of complaints and conditions, such as allergies, asthma, gastro-intestinal diseases, arthritis, multiple sclerosis and patients suffering from heart disease. However, it is worthy to note that due to the heterogeneous immunologic outcome measures presented, only cautious conclusions on comparing placebo rates between conditions could be drawn. Moreover, this literature review

elucidated several factors that played a role in inducing placebo effects such as the doctor-patient relationship and treatment invasiveness.

In addition, Chapter 2 introduced the *learned immune response*(10, 28, 49), in which insights were provided by demonstrating how conditioned responses of immunologic parameters can be established. We reviewed this from a mechanistical viewpoint in demonstrating how classical conditioning principles can be integrated in different research designs, for example through conditioned taste aversion and conditioned immunosuppression in animal models, but also in humans studies. These studies demonstrated that different immune parameters could be affected by conditioning principles such as interleukin-2 and interferon-γ, with the (intermittent) use of Cyclosporin A interspersed with placebos. Subsequently, we reviewed pioneer studies that integrated the principles of pharmacological conditioning in medication regimens in clinical samples, for example in patient groups with psoriasis, irritable bowel syndrome and attention deficit disorder, which demonstrated promising results for clinical implementations. From a more fundamental approach, we addressed the neurobiological mechanisms involved in the learned immune response which proposes an important role of noradrenaline to regulate the conditioned immune response, and on the brain level, described the involvement of the insular cortex, amygdala and ventromedial nucleus of the hypothalamus (VMH)(32, 38, 125). Conversely, not all modes of action in the CNS involved in placebo effects are understood yet. For example, the role of conditioning in immune outcomes are evident in the literature, but through which afferent pathways these changes are detected in the peripheral immune system remains unclear and needs to be addressed in future research.

In sum, Chapter 2 sheds light on the role of placebo effects in immune-related conditions and the possible utilization of these underlying learning mechanisms into medical contexts. In addition, we advocated for future directions of pharmacological conditioning therapies, which could be utilized in medication regimens for chronic diseases to maximize treatment outcomes, save costs and potentially reduce side effects, which we built upon in Chapter 3.

In **Chapter 3**, we developed an innovative research design in which pharmacological conditioning principles could be applied to optimize treatment for juvenile idiopathic

arthritis (JIA). To develop this research design an integrative collaboration between medical psychologists, pediatric rheumatologists, pharmacologists and patient groups was set up. To conceptualize an optimal design that could also be used for patient care, a research design was developed based on an urgent concern in the treatment for the JIA patient group, namely to reduce methotrexate (MTX) side effects. MTX therapy is the first choice of treatment for JIA due to its high remission rates, but unfortunately this treatment is also hampered by burdensome side effects, such as nausea and vomiting in nearly half of the patients(126). In contrast, the adult patient group (Rheumatoid Arthritis; RA) which receives similar MTX treatment is much less affected by these side effects. Moreover, MTX side effects in children also seem to have a high psychological (nocebo) component, as many patients report to experience intolerance before MTX intake and when thinking of MTX, known as anticipatory and associative complaints. So far, strategies that have aimed to reduce MTX intolerance, consisting of anti-emetic therapy, changing the route of administration, and dose reduction, have been unsuccessful. In our research design, we specifically tailored the intervention based on this patient group, i.e., the chronic nature of this condition, the long term medication treatments, and the psychological burden of side effects. For example, we based the period of the acquisition phase on the point where remission was achieved, allowing the formation of a positive association between the drug and its therapeutic effects during this first period of MTX intake. After remission would be achieved, patients could be randomized to the intervention or control group. In the intervention group, conditioned responses would then be utilized by integrating pharmacological conditioning principles through a variable reinforcement schedule. In this schedule, intermittent standard MTX doses and lower MTX doses supplemented with placebos are provided to evoke a conditioned response in the low dose weeks. Similar to previous conditioning trials, we propose that this reduced drug dosing may ultimately lead to lower MTX intolerance, while maintaining therapeutic efficacy. In the control group, patients would receive MTX treatment as usual. Throughout the study, we recommend that patients will be closely monitored during standard clinical visitations for flare-ups and side effects. Finally, study participation would be concluded with an end-of-study one year after the intervention period. The outcome measures that were established for this research design were MTX side effects as a primary outcome measure (based on patient request) and immune parameters as a secondary outcome. For the

primary outcome measure, the Methotrexate Intolerance Severity Scale would be assessed throughout the study. For the secondary outcome, the effects of conditioning on an immunological level would be explored, for example in clinical measures (e.g. erythrocyte sedimentation rate and C-reactive protein level), and cytokines (IL-1β, IL-6, IL-8, Interferon-γ (IFN-γ), and Tumor Necrosis Factor-α (TNF-α), and more, which have been established by our integrative research team of immunologists and pediatricians.

To conclude, in **Chapter 3** we have proposed a state-of-the-art research design to optimize JIA treatment, which was specifically designed for clinical implementation. Our research team is highly motivated to execute this trial design in the future. Due to several constraints, we were not able to execute this design in the current dissertation. Since promising findings have recently been found in the field of placebo effects with respect to immunological conditions, we are optimistic about the potential of this proposed trial design and its future application.

Exploring communication strategies

In **Chapter 4** and **5** we aimed to facilitate clinical application of placebo effects for medical contexts from another perspective, namely by exploring how participants could be educated about the potential benefits of placebo effects in treatments.
In **Chapter 4,** we developed and investigated placebo information strategies in a general population sample to optimize their potential use for clinical practice by assessing three themes: current placebo knowledge, preferences for different placebo explanations (built around well-known mechanisms involved in placebo effects), and attitudes and acceptability towards the use of placebo effects in treatment. To assess current placebo knowledge, we developed a PlaceboQuiz that contained statements such as “Positive expectations can have a positive effect on health” or “Placebos can induce a physical reaction”. Our results showed that the participants in our sample (N=377) were quite knowledgeable about what placebo effects entail, which was reflected in a mean score of total correct answers of 81%. Moreover, we found that participants were less aware of the notion that placebo effects can also be induced without deception, and that placebos can induce side effects. These are insightful indications to focus future placebo education strategies on. Secondly, we developed 8 different placebo information strategies that were

partly based on instructions used in previous open-label studies, and partly based on underlying placebo mechanisms that were not used in placebo explanations in previous studies. The placebo information strategies entailed explanations about classical conditioning, expectations, brain mechanisms, mind and body healing processes, social learning, trust, transparency, and finally a neutral explanation (which stated that placebo effects work for some people, not all, and that it is not entirely clear why). Our results indicated that participants preferred the explanations based on positive expectations and brain mechanisms significantly over the other explanations, and that the neutral explanations were significantly preferred the least. These findings are useful for clinical application, because providing a comprehensive placebo rationale is essential for open-label placebo designs as this boosts (or induces) treatment effects when combined with placebos. Lastly, we explored attitudes and acceptability about placebo use, and were the first to find the nuances in acceptability for different complaints and conditions, for example in psychological complaints or chronic diseases. Overall, our results showed that participants were amenable towards placebo use in treatment, thereby encouraging clinical implementation.

In **Chapter 5,** we further explored placebo use and beliefs, but this time in a sample with health care professionals. To investigate the use for placebo effects in clinical practice, we assessed thee themes: knowledge about placebo effects, frequency of placebo use, and attitudes towards acceptability and transparency of placebo use in treatment.

In the current knowledge theme, we also assessed the different placebo information strategies, but this time we asked participants about the influence of the proposed placebo mechanisms (positive expectations, patient-physician relationship, mind-body interaction, social learning, personal experience, brain mechanisms, classical conditioning) in treatment outcomes. Results from this study were in line with the results from Chapter 4. Knowledge gaps in placebo use and placebo effects were related to the effectiveness of non-deceptive use of placebo and nocebo effects. Additionally, we found that health care professionals rated processes that involve mind and body interaction, brain activation and positive expectations in placebo effects as the most influential factors in treatment effects, similar to the most preferred placebo information strategies from the general population sample.

Moreover, it was found that health care professionals were more acceptant towards the use of placebos and placebo effects in treatment than the general population sample, with higher acceptability percentages on most scenarios and types of complaints and conditions.

Integration of learning theories and communication strategies

In **Chapter 6**, we integrated the insights gathered from learning theories and communication strategies to construct an experimental design in which conditioning principles and positive verbal suggestions were applied to induce placebo analgesic effects. To facilitate clinical implementation, we opted to include open-label placebos (OLP), which has an important ethical advantage over placebo use in its traditional way, which is often used in a deceptive context. With the use of OLPs, placebo administration is fully disclosed and previous research demonstrates that placebo induced analgesia can still occur, even though a person is aware of placebo administration. Moreover, with the integration of OLP, we also made use of our newly developed placebo information strategies. In our experimental design, we used a well-validated heat pain conditioning paradigm in which participants were conditioned to low and high intensities of thermal heat pain, coupled with a placebo sham device (TENS) that was indicated activation and deactivation to induce placebo effects. Participants were randomized to one of three groups: an OLP group, a deceptive placebo group, and a control group. Both placebo groups underwent a conditioning procedure, and the control group underwent a sham conditioning procedure. In the OLP group, participants were made aware that the device served as a placebo device, but may still induce pain relief because of placebo effects which were explained by the most preferred placebo information strategies as evident from the previous studies, namely the explanation of placebo effects as the ‘power of positive expectations’ and ‘brain activation involved in placebo effects’. Our results showed a significantly larger placebo analgesic effect in the OLP group than the control group (significant larger difference in pain scores between placebo activation and placebo deactivation). Moreover, we found no significant difference between pain analgesic effects for deceptive and open-label placebos. These findings underline the potential for a transparent and ethical form of placebo use for clinical implementation.

Strengths and limitations

The overall strength of the current dissertation is the potential for clinical application of placebo effects that was taken into consideration in all aspects during the development of the research designs. In **Chapter 2** and **3** we specifically aimed to apply conditioning principles in patient groups that may particularly benefit from pharmacological conditioning therapies and proposed specific practical indications in how these principles could be applied for clinical practice. In **Chapter 4** and **5**, we focused on a more practical concern for the implementation of placebo effects in practice, namely how placebo effects could be explained so that patients could be involved in possible placebo treatments. Our main aim of this study was to create some consensus in placebo information strategies, since the previous studies that implemented open-label placebos have shown clinically relevant outcomes, but have all employed different explanations about placebo effects. Our findings may therefore contribute to future OLP studies. Finally, in **Chapter 6** we made use of open-label placebos since this form of placebo use would be ethical to use in future clinical practice. In this chapter, we were the first to demonstrate placebo analgesic effects of OLPs over a control group in healthy controls by integrating OLPs in a well-validated conditioning paradigm. Moreover, we used the developed communication strategies from the previous chapters that could be implemented in future clinical and research applications. In sum, this dissertation represented the potential of placebo effects in medical context in various outcome measures (i.e., immunological outcome measures, self-report outcome measures), by integrating different methodologies (i.e., survey studies, experimental research designs), by involving experts from disciplines outside of the placebo research field (i.e., immunologists, pediatricians, pharmacologists), and from perspectives of different samples (i.e., general population sample, health care providers).

Aside from the strengths from this dissertations, several limitations need to be addressed. An important limitation pertains to the samples that were used in our research. Even though the current dissertation focuses on the clinical implementation of placebo effects, none of the samples consisted of patients (aside from the patient representatives that were involved in the conceptualization of the trial design in Chapter 3). However, we did aim to include a heterogeneous representation of

samples in this dissertation by including participants from a general population sample (Chapter 4), health care professionals (Chapter 5) and healthy controls (Chapter 6). Moreover, since the experimental design described in Chapter 6 was a proof-of-concept study to study placebo information strategies within an OLP paradigm, it was decided to firstly investigate these with healthy volunteers before implementing this in more vulnerable patient groups. Since our findings did bring forth placebo information strategies that were significantly more preferred than other explanations, and indicated significant open-label placebo analgesic effects, it would be insightful to address these topics in clinical samples in future research.
Moreover, based on the reviewed literature of conditioning principles in immune-related conditions in Chapter 2, we proposed a research design that was described in Chapter 3. Because most experimental conditioning paradigms with immune outcomes focused on the immune suppressant effects of Cyclosporin A, it could be argued that implementing pharmacological conditioning principles for MTX may yield different results. However, there are indications that MTX is prone to conditioning effects in animal models. Furthermore, based on the reviewed literature, conditioning effects have not only been demonstrated with Cyclosporin A, but have also shown to be effective in heterogeneous patient samples with various medication regimens (i.e., for allergies, psoriasis, organ transplant patients, irritable bowel syndrome, Attention Deficit Hyperactivity Disorder).

Future research directions

As a growing body of literature supports the beneficial impact of placebo effects on both self-reported measures and physiological measures, this dissertation strongly advocates for two focal points in future research direction. First, it is necessary to further understand the underlying learning mechanisms that steer placebo effects, for example by examining immunological processes and pathways that are activated by conditioning principles. Moreover, it would be insightful to investigate a wider variety of pharmacological agents in experimental conditioning paradigms to explore their potential for application in pharmacological conditioning medication regimens.

Another important direction for future research would be to stimulate effective communication strategies with specific attention to the use of open-label placebos and to gain more understanding in how this ethical permissible method of placebo

treatment can be applied. With the insights we brought forth with regard to placebo information strategies, we encourage future researchers to use uniform placebo information strategies since these specific verbal suggestions harness the expectations that induce OLP effects, for example by using placebo rationales that were most preferred (Chapter 4) or rationales that were rated as most influential (Chapter 5). Furthermore, it would be insightful to explore these information strategies in clinical samples to assess the generalizability of our findings. Moreover, since our experimental design demonstrated that OLP analgesic effects were found to be effective when combined with conditioning principles, future research with OLP should further explore the possibilities of combining conditioning paradigms with OLP. Given these recommendations, recent publications show promising designs of trials that are currently being conducted that elaborate on the use of pharmacological conditioning and OLPs. For example, two studies are currently investigating open-label placebos as dose-extenders for opioid use disorder and several other OLP studies are currently being conducted with different patient groups, for example for the treatment of women with premenstrual syndrome, and a novel study design where OLP and double-blind placebos are compared in patients with irritable bowel syndrome(127-130).

Implications for clinical practice

The results of the present dissertation demonstrate the potential to utilize placebo effects in medical context, and practical insights how to apply these effects. In Chapter 2, we demonstrated how learning mechanisms affect immune responses and contribute to innovative interventions that demonstrate clinically relevant outcomes in a variety of diseases and immune parameters. In Chapter 3, we integrated these findings to develop an innovative research design in collaboration with clinicians, immunologists, psychologists and patient representatives. Chapter 3 specifically addressed the clinical implications of placebo effects in medication regimens, and translated the reviewed literature from chapter 2 into a specific research design. In this research design, we tackled practical considerations (i.e. reducing the burden of study participation by aligning a research design with standard clinical care), medication schedules (i.e. per units of body surface area for children proportionally intermittent with placebos), and logistics (i.e. laboratory and

pharmacy arrangements for the analysis of clinical parameters and fabrication of MTX and MTX-looking placebo pills). Ideally, we aimed to inspire future RCTs that implement pharmacological conditioning therapies and contribute to future study designs by our proposed trial design.

Another important clinical implication from this dissertation was the focus on placebo information strategies. Since the use of OLPs increases in popularity, the variety in placebo information strategies that are being used in OLP studies also grows. With the studies from Chapter 4 and 5 we have aimed to create some consensus and provide future guidelines in how health care professionals can explain the benefits of placebo use to patients, thereby stimulating patient involvement and transparency. In Chapter 4, we demonstrated that participants from a general population sample were mostly interested in placebo explanations that focused on positive expectations and brain mechanisms, and the findings from Chapter 5 supported these findings in a sample with health care professionals. The placebo information strategies that came from these studies can be directly applied for research of clinical purposes.
Other important findings for clinical implementation from Chapters 4 and 5 were that participants from both samples were quite knowledgeable about placebo effects, with the exception of open-label placebos and nocebo effects, these knowledge gaps can be addressed in educational tracts, for example in curricula for medical students or in psychology courses. In addition, both samples were amenable towards the use of placebo effects in treatments, which encourages the use of placebo effects in clinical implementation.

Conclusion

This dissertation covered several relevant cycles of placebo research with the main aim to **optimize placebo effects in medical contexts.** To address this aim, previous literature about **learning theories involved in placebo effects** were reviewed and findings were translated to an optimal research design to benefit a specific patient group. In addition, this dissertation brought forth new **placebo communication strategies** that could be used in clinical practice and for the general population. Finally, these insights were combined in an integrative experimental research design that investigated an ethical and clinical applicable form of placebo, namely by

demonstrating that open-label placebos can induce pain analgesia when combined with learning theories and placebo information strategies. Altogether, this dissertation provided insights in learning mechanisms, communication strategies, and research paradigms that involve the optimization of placebo effects in medical context.

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