Learning to perceive: psychological and neural processes underlying placebo and nocebo effects on cutaneous sensations

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CHAPTER 9

General Discussion

The past decades of research into placebo and nocebo effects has demonstrated the potential these effects hold to change treatment outcomes for better or worse. Still, much remains unknown about psychological processes and neural makers associated with these effects. This dissertation aimed to advance our understanding on both fronts, by investigating the contributions of different learning processes and methodological factors in shaping placebo and nocebo effects, as well as the neural markers of these effects with measures and manipulations focused on discerning patterns of neural activity and connectivity across the brain. In this final section, we discuss the results of the previous chapters and how they relate to one another and the wider literature. The limitations of this dissertation, as well as its implications for future research and potential applications are also considered.

Psychological mechanisms of placebo and nocebo effects

In **chapters 2, 3, and 4,** we investigated how psychological learning processes and methodological factors manifest placebo and nocebo effects on pain and itch. From these chapters, we can see that the formation of placebo and nocebo effects is the result of a complex interaction between numerous psychological factors. Similar to the broader literature, we found that the number and type of learning processes used to induce an expectancy effect remains the most consistent determinant of the resulting effect size [26, 33, 103]. We also demonstrated the robustness of placebo and nocebo effects. With verbal suggestion, classical conditioning, and observational learning, these effects can arise for numerous different kinds of pain and itch stimuli **(chapters 2, 3),** following brief or extended learning paradigms **(chapters 2, 4),** and the effects of these learning processes are clearly not dependent on lab- or study-specific methodological factors **(chapter 2)**.

Of the three learning processes we focused on in this dissertation, observational learning has received the least attention in the broader literature for its role in placebo and nocebo effects [35], especially for itch. While our meta-analysis of placebo effects in pain and itch (**Chapter 2**) included 68 pain studies that used classical conditioning with verbal suggestion and 39 pain studies that used verbal suggestion alone, only five studies employing observational learning paradigms were identified and included for pain, and none for itch. The placebo effect magnitudes of these five included studies were highly heterogeneous, and while the average effect size for observational learning was about the same as seen for classical conditioning, more experiments are needed for a precise estimate. In our own experimental work into nocebo effects on itch (**Chapter 4**), observational learning appeared to be less effective than learning directly through classical conditioning, a finding consistent with a placebo pain experiment that compared the two learning processes head to head [21]. Given this conflicting evidence, and the small number of studies to begin with, more research is needed. Additionally, future experiments testing whether observational learning and classical conditioning may have an additive effect when used in combination, for outcomes like reduction of

pain intensity or resistance to extinction, would be important to better understand the interplay of these two learning processes.

Beyond learning processes, our meta-analysis (**Chapter 2**) and narrative review (**Chapter 3**) explored other facets of learning paradigms and experimental design as they relate to magnitudes of placebo and nocebo effects. While factors like the number of acquisition trials used in a classical conditioning paradigm, and the difference in calibrated intensity of placebo and control pain stimuli have been found to impact placebo effect magnitudes within individual studies [85, 371, 372], these factors did not seem to moderate effects when compared across all studies in the meta-analysis. This was an unexpected finding, and seemingly at odds with a conclusion from the narrative review that a major challenge studying expectancy effects in itch is a lack of itch induction methods that can reliably induce distinctly high and low itch intensities over repeated trials with some precision, a necessary element of classical conditioning paradigms. From a theoretical perspective, a predictive coding account of placebo hypoalgesia also places emphasis on the importance of precision in producing the top-down expectancies thought to underlie placebo effects [3]. More precise expectancies regarding the magnitude of sensation relief or exacerbation, induced by manipulating the intensity of sensory stimuli with precision, should yield larger effects than imprecise expectancies brought about by imprecise stimuli. When considering the lack of relation between number of acquisition trials and magnitude of placebo effect observed in the meta-analysis, we may suggest that after a certain, currently unknown point, additional acquisition trials are not increasing the precision of the placebo expectancy. Habituation or sensitization processes, known to alter the perception of pain and itch stimuli over repeated exposure [373-375], could potentially reduce precision as a pain stimulus that once felt moderately painful becomes more or less so, respectively. Additionally, the relative lack of precision in experimental itch stimuli may account for the somewhat smaller effect sizes observed in placebo effects on itch compared to those on pain documented in the meta-analysis.

When considering these chapters together, we can see that placebo and nocebo effects arise from a constellation of numerous and likely interacting psychological factors. How these factors relate to one another, whether their effects are additive, cancel one another out, or interact in another way is largely still unknown. This hypothetical network of factors may be understood or studied in the future through a predictive coding framework [376], in which factors and their interactions are weighted according to their impact on the expected magnitude and precision of placebo and nocebo expectancies.

Neural markers of nocebo effects

In **chapters 5, 6,** and **7,** we investigated the neural makers of nocebo effects with electroencephalography (EEG) and pharmacological functional magnetic resonance imaging (fMRI). Across the imaging studies, we observed neural activity indicative of top-down processing that differentiated between nocebo-augmented- and control or baseline pain stimuli. From **chapter 5,** increased alpha-band power was measured

during nocebo augmented pain relative to baseline pain stimuli, and stronger long range temporal correlations measured prior to classical conditioning predicted larger nocebo effects. In **chapter 7,** there was a stronger BOLD in the ACC during nocebo acquisition trials relative to control trials, a region thought to be involved in numerous cognitive processes including learning [377-379], and a stronger BOLD response in the right operculum during nocebo pain stimuli relative to baseline pain stimuli. During states of heightened alertness, the operculum, in concert with the cingulate gyrus, appears to be a source of alpha-band oscillations [380, 381]. Potentially, expectations for worse pain in the presence of nocebo stimuli led to states of increased alertness, explaining these findings. Similarly, in **chapter 6,** anticipatory processing, measured with SPN at electrode Cz, was greater prior to nocebo pain stimuli relative to control. Greater anticipation of nocebo-augmented pain relative to control may again be tied to a state of increased alertness or arousal. Taken together, these results support a role for top-down processing in nocebo effects, and suggest that the expectations purportedly driving nocebo effects may be characterized by neural activity indicative of states of heightened alertness or anticipation.

Another goal of this dissertation was to better understand the unique contributions of different brain regions known to be engaged during nocebo effects, and their interaction. In **chapter 6**, testing an a priori model, we measured functional connectivity (i.e. information transfer) from frontal to temporoparietal regions one second before to one second after the onset of both nocebo and control pain stimuli. The results indicated that functional connectivity from frontal to temporoparietal regions occurred for both nocebo and control trials in the two second window, and in one of the four pairs of nodes, frontal right to temporoparietal right, there appeared to be larger GC estimates for nocebo trials over control trials. This pattern of activity may represent the process of top-down expectancies shaping the experience of both nocebo and control pain stimuli, with only subtle differences between the two. In **chapter 7,** we attempted to manipulate neuroplasticity with DCS during fMRI to test the potential role of NMDA dependent learning in nocebo effects and observe what regions of the brain underlie this process. As no effect of DCS was found in neural activity or magnitude of the nocebo effect, and we do not know to what extent DCS actually influenced NMDA-receptor activity, we can neither rule in nor rule out a potential role of NMDA dependent learning and neuroplasticity. In addition to its role in neuroplasticity [382], NMDA may also play a specific role in feedback loops in the descending pain modulatory system, and top-down expectancies more broadly [3, 66]. Evidence suggests that activity by neurons in the periaqueductal gray and rostral ventromedial medulla, which can be modulated by NMDA receptors, represents a feedback signaling process predicted by the Bayesian brain hypothesis [38]. Blockade of NMDA receptors with pharmacological antagonists is thought to limit the influence of top-down predictions, and we speculate that NMDA activity enhanced with pharmacological agonists like DCS would increase the influence of prior expectancies in sensory perception. Given these dual processes by which NMDA agonists may theoretically impact the formation of nocebo effects, either

through increased neuroplasticity enhancing the effects of classical conditioning, or increased weighting of top-down predictions in the descending pain modulatory system, our null finding should not dissuade further study on this topic.

In summary, the findings from these chapters adds to our understanding of the neural mechanisms by which top-down prior expectations can meld bottom-up sensory inputs to produce nocebo effects on pain. Increases in alpha band power, SPN, GC, ACC and operculum activity are all potentially markers for higher order cognitive processes that are differentially when a nocebo effect is present, substantiating a role for expectancies in shaping sensory experience. These results also demonstrate the importance of applying a theoretical framework such as predictive coding to both the psychology and neuroscience of placebo and nocebo effects, without which we would not be able to infer what specific processes are taking place when we observe differential activity in a given brain region between nocebo and control trials.

Limitations

The current dissertation presents new data on both the psychological mechanisms and neural markers of placebo and nocebo effects. These findings are not without their limitations, which we consider here.

The diversity of methods used in this dissertation, and in the field of placebo an nocebo effects in general, can be thought of as both a strength and a limitation. This field of research is still in its infancy, with many unanswered questions prompting diverging lines of research and methodology. In the present dissertation we studied placebo and nocebo effects on pain and itch, and sought to address both behavioral and neuroscientific research questions. While we advanced on each front, we were also unable to replicate and build on our own previous work as much as if we had taken a narrower focus. Even though four chapters **(chapters 4-7)** from this dissertation used classical conditioning methods, in each chapter the methods were different (e.g. different types of sensation, types of sham treatment, or amount and duration of stimuli). Different methods are needed to address different research questions, and although it is encouraging that placebo and nocebo effects can be induced with a wide variety of methods, it also stymies replications and the comparison of results across studies.

A second limitation of this dissertation is the potentially limited applicability of these results outside of fundamental science. The laboratory studies on healthy participants with models of acute pain and itch presented here are not ideal models for clinical applications. This research is valuable in understanding the psychological and neural mechanisms that underlie these effects, but the methods and results may not be not clinically applicable. While it should not be the goal of all fundamental science to be applied outside of the lab, it may also be considered a limitation of this dissertation that our work did not do more to advance our fundamental understanding of placebo and nocebo effects towards such applicability. For example, while in **chapter 4** we used cowhage to model nocebo effects on itch with a pruritic stimulus that acts on the pathways engaged in chronic atopic dermatitis, we still only used a brief, single day

study design. A longer design would have been feasible, and would have yielded more clinically relevant results. A similar consideration applies to the neuroimaging studies **(chapters 5-7)**, where we only have a picture of the neural markers of nocebo effects on *acute* pain, when it is for *chronic* pain that these effects are most relevant. Looking beyond experimental methods, the use of young, healthy, and well-educated participant samples may also limit external validity of this work to patients and the general public. Studies that have compared experimental placebo manipulations and results between healthy and patient samples have produced mixed findings, sometimes showing the same pattern of results [383, 384], and others indicating diverging results [13, 105, 385]. While this does not diminish the importance of fundamental research, it is a limitation of this dissertation and the field as a whole to be mindful of.

A third limitation which also impacts the generalizability of this dissertation's results is the gender and age distribution of the participants included in the experimental studies **(Chapters 4-7)**. The included samples, which drew largely from undergraduate psychology students at Leiden University, were disproportionately young and female relative to the general population. As observed in the meta-analysis of placebo effect studies **(Chapter 2),** this demographic pattern occurs commonly across the field. Although the processes underlying placebo and nocebo effects are generally thought to operate in the same manor across gender and age, there is some evidence that men may tend to report larger placebo effects than women, especially when the effect is induced by verbal suggestion [88]. Therefore, a bias towards women in the participant samples of this dissertation and the field as a whole may lead to a slight underestimation of placebo effect sizes. While the age of the participants in the studies making up this dissertation was generally capped at 35 to promote homogeneity of the sample, the mean age in each study was much younger, in the early 20s. It may be considered a limitation that this dissertation cannot offer insights into how placebo and nocebo effects may vary across even the age range that was accepted in each study, 18-35 years. Although not a goal of the present dissertation, more research into how placebo and nocebo effects vary across the adult lifespan and in elderly samples would be of great value, given the elderly's increased use of healthcare.

The exploration of new methods over replicative science, the disconnect between fundamental and applied research, and the demographic distribution of the experimental studies can be considered limitations present in this dissertation, and the young field of placebo and nocebo studies generally. At the same time, these limitations are to be expected of a new field that is exploring what methods work best and how they might eventually be applied outside of a lab environment. As the field matures, we would expect to see a shift in focus towards confirmatory studies over exploratory ones, increased attention paid to the utility of key findings and methods when applied to clinical settings, and more research done with samples that better represent the demographics of the general population.

Future Research

The findings from this dissertation prompt new questions and lines of inquiry for further study. Beyond the previously mentioned importance of replication studies, we have suggestions for future lines of research into the psychological and neural mechanisms of placebo and nocebo effects.

Psychological mechanisms. As highlighted in **chapter 2,** research into placebo and nocebo effects on pain receives considerably more investment and attention than research into these effects on itch. This is understandable, given that pain is already frequently studied in other fields of psychology such as fear conditioning, and established methods allow researchers to manipulate pain intensity and duration in ways that are less straightforward for itch. Although it is likely the case that many findings from research on placebo and nocebo effects on pain can be applied to our understanding of how these effects work for itch, there are important differences between the two as well. So far, experimental placebo and nocebo effects on pain appear to be larger than those seen for itch. Whether this is due to methodological constraints limiting the precision with which acute itch can be induced, greater experience in working with pain, or some other as of yet unknown factor warrants further inquiry. How expectancy effects differ between pain and itch on metrics other than size of the effect, such as resistance to extinction could also be investigated. Despite the disproportionate attention paid to pain, acute and chronic itch symptoms are incredibly common, at times difficult to treat, and would benefit from well-tailored psychological treatments on top of other medical interventions.

The results in the present dissertation highlight the additive effect of using multiple learning processes when inducing placebo and nocebo effects. However, it remains to be seen how combining verbal suggestion, classical conditioning, and observational learning in one paradigm would affect the resulting magnitude of these effects. In experimental research, observational learning for placebo and nocebo effects typically involves observing a classical conditioning paradigm [21, 31, 32, 82, 100], so its added effect on top of experiencing classical conditioning firsthand may be negligible. On the other hand, knowing that others respond to a treatment the same way as you do may provide a social component that strengthens the effects of classical conditioning, potentially yielding effects that are more resistant to extinction, if not larger in magnitude. Studying the interaction of observational learning with the more commonly used instructional and associative learning processes would both add to our understanding of the mechanisms which influence the magnitude and durability of expectancy effects, and help us see how these processes operate in everyday life where observational learning frequently occurs.

Future research on factors germane to classical conditioning paradigms is also warranted. As noted in **chapter 2**, while manipulating variables like the number of learning trials or calibrated difference between placebo and control pain intensities influences placebo magnitudes within studies, the lack of any effect of these factors across studies likely indicates that other variables are at play as well. A predictive coding theory of placebo effects posits that while increasing the calibrated difference between

placebo and control trials should generate expectancies for greater pain relief and in turn yield larger placebo effects, within limits [386, 387], the precision of these expectancies is also theorized to play a role. Though this concept is often overlooked, an initial study in placebo effects on pain [388], and other recent studies on expectations for pain [237, 389] have demonstrated that more precise expectations yield stronger effects of the expectation on pain perception. However, precision is not easily manipulated. Myriad factors like habituation [390], sensitization [374], attention [391, 392], or emotion [393] may all contribute to fluctuations in experienced pain or itch intensity, generating variably precise predictions from one participant to the next. This may also explain why longer classical conditioning paradigms do not inherently yield larger placebo and nocebo effects. While a longer acquisition phase gives more opportunity to reinforce expectancies, it also gives more opportunity for imprecision to be introduced through habituation to the pain stimuli, attention to waiver from boredom, etc. This imprecision may blunt the other benefits of a longer acquisition phase. To add to the studies that have already implemented manipulations of precision on pain expectations, future research could measure the imprecision of perceived stimulus intensity relative to the calibrated intensity to test if individuals with more precise pain ratings relative to the calibrated intensity of the pain stimuli reported larger ensuing placebo and nocebo effects. This could even be measured in existing datasets if individual trial data were preserved. Demonstrating whether and to what extent precision impacts placebo and nocebo effects would advance both our understanding of the factors that influence these effects and better integrate them in a predictive coding framework.

Neural markers of nocebo effects. From the findings in **chapters 5, 6, and 7**, we can also suggest future directions for research into the neural markers of nocebo effects. As seen more commonly in behavioral research, it would be useful to include clinical samples in future imaging studies. Just as differences arise between healthy and clinical samples in behavioral studies, we would expect to see differences in imaging findings as well. While we do not expect imaging will one day be used to detect nocebo effects in clinical populations, understanding the potential differences in the underlying mechanisms of expectancy effects between healthy and clinical populations will better inform our understanding of nocebo hyperalgesia. Identifying these differences could potentially shed light on the mechanisms by which psychological factors exacerbate chronic disease in some individuals.

Future research into the neural markers of nocebo effects would also do well to apply a predictive coding framework. Similar to what has been theorized for placebo effects, we would expect to see two interacting networks of neural activity, one generated by top-down expectancies, and another driven by bottom-up sensory inputs. To that end, we would suggest that future imaging studies place more emphasis on measures of functional connectivity and information transfer across over identifying singular regions of interest. When specific ROIs are still investigated, manipulations of the psychological learning processes (e.g. comparing classical conditioning with high and low precision cues, or between lesser and greater calibrated differences in nocebo and control stimuli)

could be used to explore the distinct roles that different regions play in the theorized feedforward and feedback loops underlying predictive coding.

Pharmacological manipulations offer another potential means of exploring the neural circuitry of nocebo effects. While our manipulation of neuroplasticity with DCS was unsuccessful, there are reasons to believe that a higher dose, different experimental design, or other NMDAergic compound would yield an effect. Given the strong theoretical and neuroanatomical case for a role of NMDA receptor activity in expectancy effects and learning more broadly [3, 61, 63, 382], future research with a higher dose of DCS or use of an NMDA receptor antagonist such as low, non-psychotomimetic dose of ketamine administered before any classical conditioning had taken place should be considered. It has been speculated that NMDA receptor activity plays a role in modulating prior expectations and pain processing at the periaqueductal gray (PAG; [3, 394, 395], and an effect on self-reported pain and corresponding changes in activity at the PAG would support this theory, and a predictive coding account of nocebo effects generally.

Brain stimulation with technologies like transcranial magnetic stimulation [396] or transcranial direct current stimulation [397] could also be employed in future research to modulate the function of specific cortical regions during the acquisition and evocation of placebo and nocebo effects. By increasing or decreasing activity in a discrete cortical site, its potential causal role in placebo- or nocebo-augmented sensation could be tested experimentally, and with more specificity than pharmacological manipulations allow. Loci such as the anterior cingulate cortex and sensory cortex are easily accessible for such noninvasive brain stimulation techniques given , and would be logical targets for investigation given that previous neuroimaging work has already shown that these regions are active during placebo and nocebo effects on sensory perception [398, 399]. While passive imaging studies may suggest corollary relations between activity in these regions and the experience of placebo or nocebo effects, neuromodulation with noninvasive brain stimulation would allow for testing causal relationships between activity in shallow brain regions and these effects.

Conclusion

In the present dissertation, we set out to advance our understanding of the psychological mechanisms and neural markers of placebo and nocebo effects on pain and itch. On both fronts, our findings demonstrate the complex interplay of numerous factors, be they facets of various learning processes or loci in the brain. We have systematically replicated previous findings showing that a combination of learning processes is more effective at inducing expectancy effects on pain than any one process used alone, and extended this research to itch, finding a similar pattern of results with smaller effects than those seen in pain. We added to the field's understanding of the neural markers of nocebo effects on pain, confirming previous findings for the involvement of cognitive control regions like the ACC, and provided novel insight into the increased anticipatory processing and frontal-to-temporoparietal functional connectivity that occurs during nocebo-augmented pain. The complex web of psychological factors and neural markers

that characterize placebo and nocebo effects on pain and itch can be understood through a predictive coding framework, a theory which we argue should guide future research into these effects. With a whole and holistic understanding of how prior expectations and sensory inputs integrate to shape our conscious experience, we can most effectively apply this field of research towards better management of pain, itch, and any experience that may be influenced by our expectations.

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