SUMMARY
In clinical settings, a patient's previous positive and negative experiences of symptoms and treatment can carry across symptoms and across treatments [1,2]. This transferability from prior experience to a new situation is called generalization, and is a form of adaptive learning [3] . Two types of generalization can be distinguished: stimulus generalization (where a generalization stimulus that resembles the previous stimulus evokes the same response), and response generalization (where a generalization response to a stimulus is similar to the previous response) [4,5]. These generalization effects in clinical practice have been experimentally studied in placebo and nocebo effects, which are beneficial and adverse effects that do not arise from active treatment components, respectively [e.g.,6–8]. Some studies, related to stimulus generalization, suggest that placebo/nocebo effects generalize over various placebo treatments or contextual factors. Less attention has been paid to response generalization, and the few existing studies indicate that placebo/nocebo effects on one symptom could influence other symptoms. Understanding the generalization of placebo and nocebo effects would help modulate carryover effects in clinical practice. In particular, investigations of response generalization could be of value in understanding treatment outcomes for similar symptoms or for symptoms that co-occur in some diseases. For example, pain and itch could be considerably experienced by patients recovering from burn injury. The main aim of the current dissertation was to: (1) summarize and discuss the existing studies to offer an overarching picture of generalization effects in the placebo field; provide future recommendations (Chapter 2); (2) investigate response generalization of placebo effects on one type of pain to another type of pain and to another bodily sensation (Chapter 3); and (3) investigate response generalization of nocebo effects on one type of pain or itch to another bodily sensation (Chapters 3 and 4). Additionally, this thesis aimed to contribute to the limited studies exploring predictors for the generalization of placebo and nocebo effects (Chapter 5). Note that the current studies only included healthy participants.

Generalization effects for placebo and nocebo effects of various somatic symptoms
Chapter 2 summarized all the studies available on the generalization of placebo and nocebo effects – at both the response and stimulus levels – on prevalent somatic symptoms (i.e., pain, itch, dyspnea, nausea, and fatigue). Most studies investigated pain; fewer studies investigated itch, dyspnea, nausea and fatigue. Furthermore, the studies reviewed showed that the generalization of placebo and nocebo effects is likely stronger when generalization stimuli and responses closely resemble the initial stimulus and response. However, more studies are needed to draw firm conclusions. The neurobiological mechanism behind these generalization effects has barely been studied. Also, few studies in this field have examined the role of individual characteristics as predictors of these generalization effects. Future studies are warranted to better understand generalization processes with respect to somatic symptoms and accordingly improve treatments.

Placebo effects generalized within pain modality, but did not generalize across modality
Chapter 3 investigated response generalization of placebo effects from one pain sensation to another pain sensation and to an itch sensation. First, placebo effects on heat pain were evoked by a combination of verbal suggestion (by telling that pain is reduced when the placebo device is turned on) and classical conditioning (by actually offering a lower level of pain stimulus when the placebo device is on). We then tested whether the evoked placebo effects on heat pain generalized to

pressure pain and to cowhage-evoked itch (cowhage spicules are derived from the tropical bean mucuna pruriens). It is important to note that the combination of verbal suggestion and classical conditioning was only applied to influence expectations toward heat pain (initial response), but not toward pressure pain and cowhage-evoked itch (generalization responses). The results showed that placebo effects can generalize from heat pain to pressure pain. However, placebo effects did not generalize from heat pain to cowhage-evoked itch. The main finding was that these sensation reducing effects generalized to another type of pain, but not to itch.

Nocebo effects generalized within pain and itch modality, but may not generalize across pain and itch modality

Chapter 3 investigated response generalization of nocebo effects within two types of pain sensations and from pain to itch. Similarly to the results on placebo effects as mentioned above, nocebo effects were found to generalize from heat pain to pressure pain, but did not generalize to cowhage-evoked itch. Also, Chapter 4 found similar results on the generalization of nocebo effects from one itch sensation to another itch sensation and to a touch sensation. Nocebo effects on cowhage-evoked itch induced by verbal suggestion alone could aggravate another type of itch: mechanical itch (evoked by thin nylon hairs), but not unambiguously to mechanical touch-evoked itch (evoked by thin nylon hairs). Therefore, nocebo effects can generalize from one type of itch or pain sensation to another type, but not or barely from pain to itch or from itch to touch.

Predictors for generalization of placebo and nocebo effects within and across somatosensory sensations

In Chapters 3, 4, and 5, no clear individual characteristics could predict either the induction or generalization of placebo and nocebo effects within and across somatosensory sensations. Specifically, these generalization effects were not associated with expectancies (Chapters 3 and 4). The magnitude of the initial evoked placebo and nocebo effects was also not associated with the magnitude of the generalization effects found (Chapters 3 and 4). Furthermore, in Chapter 5, affect (i.e., anxiety and stress symptoms) or cognition (i.e., attention to pain and pain catastrophizing) did not predict the extent to which placebo and nocebo effects were evoked and generalized from one sensation to another. This is largely in line with previous research, but may also be due to the small sample sizes and target population of healthy subjects in the current studies.

Conclusion

The current dissertation has demonstrated that previously learned placebo and nocebo effects can generalize to another bodily sensation similar to the original sensation (e.g., from one type of pain to another type of pain), but may not or less likely generalize from one bodily sensation to another (e.g., from pain to itch). This underlines the importance of taking prior treatment outcomes for similar symptoms into account in the clinical decision-making process. Further investigation into the mechanisms underlying the generalization of placebo and nocebo effects (including approaches to counteract such processes) could contribute to amplifying the carryover effects of therapeutic success and blunting the carryover effects of therapeutic failure in clinical practice.

Reference

1. Müller M, Kamping S, Benrath J, et al. Treatment history and placebo responses to experimental and clinical pain in chronic pain patients. *Eur J Pain (United Kingdom)*. 2016;20(9):1530–1541. doi:10.1002/ejp.877
2. Yalcin I, Bump RC. The effect of previous treatment experience and incontinence severity on the placebo response of stress urinary incontinence. *Am J Obstet Gynecol*. 2004;191(1):194–197. doi:10.1016/j.ajog.2004.03.089
3. Ghirlanda S, Enquist M. A century of generalization. *Anim Behav*. 2003;66(1):15–36. doi:10.1006/anbe.2003.2174
4. Shepard RN. Stimulus and response generalization: A stochastic model relating generalization to distance in psychological space. *Psychometrika*. 1957;22(4):325–345. doi:10.1007/BF02288967
5. Shepard RN. Stimulus and response generalization: Deduction of the generalization gradient from a trace model. *Psychol Rev*. 1958;65(4):242–256. doi:10.1037/h0043083
6. Wolters F, Peerdeman KJ, Evers AWM. Placebo and Nocebo Effects Across Symptoms: From Pain to Fatigue, Dyspnea, Nausea, and Itch. *Front Psychiatry*. 2019;10:1–13. doi:10.3389/fpsyt.2019.00470
7. Evers AWM, Blease C, Atlas LY. Implications of Placebo and Nocebo Effects for Clinical Practice : Expert Consensus. *Psychother Psychosom*. 2018;(87):204–210. doi:10.1159/000490354
8. Zunhammer M, Ploner M, Engelbrecht C, et al. The effects of treatment failure generalize across different routes of drug administration. *Sci Transl Med*. 2017;9(393):1–8. doi:10.1126/scitranslmed. aal2999