Generalization of placebo and nocebo effects on somatosensory sensations

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CHAPTER 6

Summary and General Discussion

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.

GENERAL DISCUSSION

The aim of this thesis was to answer the question of whether previously learned placebo and nocebo effects can generalize within and across somatosensory sensations. Specifically, the thesis investigated whether placebo and nocebo effects can generalize within and beyond pain and itch modality. The mechanisms of generalization of placebo and nocebo effects were discussed and proposed. Additionally, the thesis also explored the role of individual characteristics as predictors (e.g., anxiety, stress, attention, catastrophizing) for the generalization of placebo and nocebo effects. In the following sections, the dissertation addresses the limitations of the work and directions for future research, as well as giving implications for clinic practice.

Generalization of placebo and nocebo effects within and across modalities

Generalization of placebo and nocebo effects within modality

Chapter 3 showed that placebo and nocebo effects on heat pain induced by the combination of verbal suggestion and conditioning can generalize to pressure pain. That is, pressure pain intensities were decreased in the placebo group and increased in the nocebo group. Similarly, Chapter 4 found that nocebo effects on cowhage-evoked itch induced by verbal suggestion can generalize to mechanical itch. The findings in Chapters 3 and 4 are in line with previous studies illustrating response generalization of placebo and/or nocebo effects within pain and itch modality [9,10]. It could be that participants perceive these sensations as being in either a 'pain' or an 'itch' category, respectively, since these stimuli induce sensations of pain or itch. The process of categorizing sensations may have been facilitated by rating their pain/itch intensities on the same pain/itch scale. Generalization of placebo and nocebo effects thus likely occurs within similar responses. This finding mirrors the results in Chapter 2 (the review) summarized from the studies of both stimulus and response generalization [e.g., 8,11–16]. The review suggests that, notwithstanding a few inconsistencies [17], generalization of placebo and nocebo effects is more likely to occur when generalization (future) stimuli and responses closely resemble the initial conditioned ones. For instance, Kampermann and colleagues used a facial image (an initial conditioned stimulus) associated with decreased pain intensity. They found the strongest pain alleviation with the conditioned facial image, and a graded effect of pain relief with the other facial images (generalization stimuli) on the perceptual continuum [14]. Selective attention may contribute to these generalization effects. The more similar stimuli/responses could attract selective attention involuntarily, which may be caused by memory representations of previous stimuli/responses, and individuals may therefore respond to these more similar ones [18–20]. Furthermore, the findings are in line with the response expectancy theory proposed by Kirsch [21,22], and with predictive coding [23,24], suggesting that expectancies within individuals' responses could help the changes of sensations, and that the magnitude of expectancies probably modulates the distance

between perceived sensations and sensory input. For instance, in the context of placebo analgesia, future cues that more closely resemble the initial one may induce stronger and more specific expectancies of pain alleviation. Consequently, these expectancies lead to perceived pain sensations paired with future cues that are lower than the sensory input (generalization of placebo effects). It is recommended to test theoretical models such as a predictive coding framework regarding generalization of placebo and nocebo effects on somatosensory sensations.

Generalization of placebo and nocebo effects across modalities

Chapter 3 found that both placebo and nocebo effects on pain did not generalize to cowhage-evoked itch. This contrasts with previous studies that found that placebo effects did generalize beyond modalities, such as from pain to fatigue, and from pain to negative emotion [11,12]. It is important to note that those previous studies used verbal suggestion on both initial sensation and generalization sensations (i.e., fatigue and negative emotion), which may have induced placebo effects on fatigue or negative emotion rather than generalization effects. This could complicate the finding of the generalization of placebo effects beyond modalities. In addition, the occurrence of generalization effects may also differ across various sensations. The absence of generalization effects from pain to itch may be due to the psychophysical differences between these two sensations [5,25]. Notwithstanding a large neurobiological overlap between pain and itch [e.g.,26,27], the two were perceived by participants as dissimilar sensations. Participants thus probably did not expect similar responses between heat stimulation (pain) and cowhage spicules (itch), which would be consistent with the response expectancy theory and predictive coding. As heat stimuli and cowhage spicules are dissimilar, expectancies on the alleviation or increase of itch evoked by cowhage may not be specific or generated, and thus the perceived itch sensations could be close to the itch sensory stimuli (no placebo/nocebo effects). On the other hand, in Chapter 4, the result remains inconclusive regarding the generalization of nocebo effects from cowhage-evoked itch to mechanical touch. Although our planned analysis found generalization across modalities, the sensitivity check (run for individualized filaments that induced relatively pure either touch or itch at baseline) did not confirm it. It should be noted that in the sensitivity check, 39 out of 44 participants (who rated at least 1 filament as itchy at baseline) were analyzed for individualized mechanical itch, and 29 out of 44 participants (who rated at least 1 filament as touchy at baseline) were analyzed for individualized mechanical touch. Therefore, the finding of generalization to mechanical touch needs to be interpreted with caution. Future studies should conduct a calibration procedure where perceptions at baseline are as intended. Despite further confirmation being required, the findings seem to be consistent with a pattern found in Chapter 2 that placebo and nocebo effects probably do not generalize to generalization stimuli/responses that are dissimilar to the initial one.

Mechanisms of generalization of placebo and nocebo effects

When it comes to the mechanisms underlying the generalization of placebo and nocebo effects, expectancies can be considered one such mechanism, on the basis of the few existing imaging studies illustrating that novel placebo treatments can activate brain areas related to expectancy [28,29]. However, the results of the associations between self-report expectancies and generalization effects are inconsistent. Chapters 3 and 4 did not find a relationship [e.g.,30,31], and one study reported modulation effects of expectancy on generalization effects: only participants who learned placebo/nocebo effects during the conditioning phase showed generalization effects [17]. It needs to be taken into consideration that expectancies can also be induced unconsciously; therefore, reliance on self-report expectancies may underestimate the importance of expectancies in generalization effects [32]. Although further confirmation is necessary, an assumption could be proposed that the prior learned experience could help predict (the likelihood of) future experiences via expectancies. More research is required to study the role of expectancies in these generalization effects. For instance, studies might explore whether and how expectancies, in the predictive coding framework, may be generated and modified between prior experience and incoming sensory data dynamically.

Similarity between initial and future stimuli/responses may drive generalization effects in the placebo field. The review (Chapter 2) illustrates that generalization of placebo and nocebo effects is more likely when there is greater similarity between initial and future stimuli/responses, either at the perceptual or at the categorical level [e.g.,16,17]. This finding appears to be in line with the experimental work in Chapters 3 and 4. Nevertheless, in placebo and nocebo effects, the question of how to perceive the similarity between stimuli/responses remains to be investigated. It is worth noting that stimuli/responses can be perceived as similar or dissimilar in various aspects, and that the weight of these aspects may vary across individuals [19,33]. For instance, some participants may perceive heat and pressure pain as in the same pain category due to painful sensations, but a few may categorize them as different due to the different equipment used and the differences in the sensations.

Emotions such as anxiety and fear may play a role in the process of these generalization effects. The few imaging studies conducted suggest that, during the generalization of placebo effects from pain to negative emotion, activities in brain areas related to emotional processes were decreased [34,35]. However, in this case, it is hard to say whether the altered activities in these areas were associated with the initial placebo pain relief or caused by generalization responses of negative emotion. On the other hand, the results from self-reported state anxiety- and stress symptoms, which were measured prior to the testing of generalization effects, do not seem to predict the generalization of placebo and nocebo effects (Chapters 5) [14,36]. This result needs to be interpreted with caution due to the low

levels of anxiety symptoms in the healthy participants included in the study. Indirect evidence from fear generalization research suggests that higher anxiety can increase generalization effects to novel stimuli that are dissimilar to the initial one [37,38]. A potential assumption is that emotions such as anxiety and fear acquired from prior experience may likely be elicited by similar stimuli/responses and may modify the magnitude of generalization effects to novel stimuli/responses via cognitive processes. Further research is required, for instance by manipulating factors such as pain-/itch-related fear and investigating its role in the generalization of nocebo effects within pain or itch modalities.

Memory may also contribute to the generalization of placebo and nocebo effects, based on the fact that generalization could depend on the comparison between incoming information and prior experience extracted from memory [20,39]. In addition, evidence in the generalization field suggests that individuals with poor memory tend to have flattened generalization gradients, as they likely forget stimuli attributes over time and may respond to previously dissimilar stimuli [20]. The role of memory on generalization effects may be affected by sleep, since sleep may enrich the extraction of features and generalization effects by facilitating the active re-processing of new information into existing memory networks [40,41]. It would be worthwhile to investigate the role of memory and sleep in the generalization of placebo and nocebo effects over time, for instance by testing multiple generalization trials across successive days.

Incorporating the factors mentioned above, an assumption is that generalization may be activated if future stimuli/responses resemble the initial stimulus/response. Prior experiences with the initial stimulus/response, such as reactions and emotions, could be recalled from memory, which would allow future ones to be compared and analyzed. These analyses could help develop the relevant expectancy for these future stimuli/responses, which could drive the outcome changes of generalization stimuli/responses. Nevertheless, these assumptions need to be investigated, and it remains to be seen whether this assumption can be applied to both stimulus and response generalization. These investigations may be helpful to obtain a comprehensive picture of the mechanisms underlying stimulus and response generalization of placebo and nocebo effects.

Predictors for generalization of placebo and nocebo effects

Chapters 2, 3, and 4 suggest that neither the magnitude of initial placebo and nocebo effects, nor psychological characteristics predict generalization of placebo and nocebo effects within and across modalities [e.g.,42,43]. Specifically, despite a few findings illustrating positive associations between initial nocebo effects on cowhage-induced itch and generalization to mechanical itch on peak itch, Chapters 3 and 4 did not find that the magnitude of initial placebo and nocebo effects was associated with their generalization effects. Likewise, cognitive-affective factors related to the fear-avoidance model – such

as anxiety and stress symptoms, attention to pain/itch, and pain/itch catastrophizing – do not seem to play a role in generalization of placebo and nocebo effect within and across modalities [36]. This is in line with inconsistent results in the literature regarding the role of cognitive-affective factors in placebo and nocebo effects [e.g., 44,45]. Nevertheless, in light of the low number of studies and their small sample sizes, the impact of initial effects and cognitive-affective factors investigated on these generalization effects cannot be excluded. It could be fruitful for future studies to investigate other factors, such as pain-/itch-related fear [46], for predicting the magnitude of the generalization of placebo and nocebo effects.

Limitations

Several limitations related to the experiments in this thesis need to be discussed. One limitation is that the samples studied, i.e., young healthy participants, are not fully representative of the general population and clinical samples. However, given that the research on generalization effects is in its infancy, investigations of healthy samples can provide putative findings and could provide some insight into understanding the onset of generalization effects in daily life. Notably, the participants in the experiments were mostly female students. Although participants were stratified for sex, it cannot be ruled out that the findings may have been affected by the fact that most data were from females. Nevertheless, there are no firm conclusions on the role of sex in the induction of placebo and nocebo effects [47,48]. Recruiting relatively equal sample sizes of males and females would help to resolve this limitation.

Second, the current sample sizes are small, which may lead to restrictions on the results of the predictors for generalization of placebo and nocebo effects in Chapter 5. Although the sample size met a minimum requirement (i.e., N = 25 for multiple regressions) [49], false negative findings may have occurred, because only large effects can be detected with the current sample sizes. Additionally, young healthy samples in the presented study reported low levels of negative affect, including anxiety and stress, which may limit the generalization of the current findings to various levels of negative affect. Future studies could investigate multiple factors (including cognitive-affective factors at various levels) in a large cohort to replicate the current findings and explore the predictors for generalization of placebo and nocebo effects.

Third, blinding is a possible limitation in the current experimental research (Chapters 3 and 4). On the one hand, experimenters needed to know whether an intervention involved either placebo or nocebo effects, as they had to apply different verbal suggestion and conditioning procedures for each effect. On the other hand, participants may also have been aware of these intervention types or the research aims, and by definition they were aware of the self-reported ratings of their responses. In this way, experimenter bias

and performance bias may have occurred unintentionally [50,51]. To limit these biases, the thesis maximized blinding within manipulations of the experiments. For example, the conditioning and test phases were presented directly after each other to minimize the biases not only for the participants but also for the experimenters. To rule out experimenter and performance biases, future studies should consider an optimal double-blind procedure in the placebo and nocebo research.

Another limitation that can be considered is the potential impact of the color of the cues on placebo and nocebo effects as well as their generalization, as cues to indicate the control and placebo/nocebo treatment were not counterbalanced. Chapter 3 always used the control cue in a yellow circle (indicating that the placebo treatment was off), and the experimental cue in a purple circle (indicating that the placebo treatment was on) for all participants; these two cues were displayed on the screen in the conditioning phase. Chapter 4 always used a bottle with a yellow label as the control cue (indicating the control treatment), and a bottle with a red label as the experimental cue (indicating the nocebo treatment). Previous research suggested that pills in both red and yellow were associated with a stimulant effect [52]. Purple was perceived as one of the most pleasant hues [53], but one study showed that patients mostly disliked purple pills [52]. It cannot be excluded that the color affected placebo and nocebo effects as well as their generalization in the studies reported in Chapters 3 and 4. This can be easily addressed in future studies by counterbalancing the color of the control and experimental cues.

Experimental models need to be highly controlled. However, this may bring up a further limitation in relation to the discrepancy between highly controlled experimental models and clinical phenomena. The current experimental studies carefully attempted to mimic the clinical situations with regard to carryover effects of treatment success and failure. Despite that, the experimental settings (e.g., the characteristics of certain stimuli or conditioning manipulations) may still lack clinical ecological validity. For instance, the current studies induced acute pain and itch, which likely limits the representational powers of their findings to chronic pain or itch. In addition, outside of the laboratory classical conditioning as used in Chapter 3 is unlikely to occur in clinical practice, as a patient may not experience the effectiveness of one treatment every time. Nevertheless, the current findings could still offer indications that placebo and nocebo effects on somatosensory sensations can carry over to similar symptoms and treatments in daily life and clinical practice. Future studies would be valuable to improve the ecological validity of laboratory experiments to test generalization effects, such as using partial reinforcement, where a placebo is paired with the outcome of decreased or increased sensations in some, but not all trials [54,55].

Future research directions

Several additional future directions can be discussed, related to the current experimental models. First, the studies used verbal suggestion and/or classical conditioning to induce placebo and nocebo effects. In addition, Chapter 2 suggests that the combination of verbal suggestion and classical conditioning is an effective method to investigate these generalization effects. It remains to be seen whether other learning methods – such as observational learning and operant (or instrumental) conditioning – can induce generalization within or across stimuli/responses. For instance, individuals may observe that a placebo treatment can alleviate pain, and may subsequently be tested with the initial as well as other types of pain or other sensations. Second, the current studies mostly investigated pain [e.g.,8,14]; only a few studies investigated other somatic sensations such as itch, fatigue, and nausea [11,31,56]. It would be fruitful to extend further research toward other somatic sensations. For instance, as both nausea and fatigue can be observed in patients with diabetes [57], further studies may investigate generalization effects between these two symptoms.

An important next step could be to explore strategies to modulate generalization of placebo and nocebo effects. Although it may seem obvious, generalization effects cannot occur in the absence of initially induced placebo or nocebo effects. Due to the essential role of learning in these effects, research on learning strategies used to manipulate the conditioned effects may hint at inhibiting the development of generalization of placebo and nocebo effects. Therefore, to enhance generalization of placebo hypoalgesia, a potent avenue would be to repeat the learned conditioning effects before evoking generalization effects [30]. It remains to be investigated what the effects in this regard are of the magnitudes of diverse timing and quantity of the repetition. To inhibit generalization of nocebo effects, several learning strategies can be considered, including counterconditioning, overshadowing, and latent inhibition. One study thus far suggested that counterconditioning of nocebo effects on an initial itch sensation successfully generalized to a novel itch sensation [10]. During counterconditioning, a conditioned stimulus was originally paired with an unconditioned stimulus, but now the unconditioned stimulus is replaced by the unconditioned stimulus of opposite valence. For example, if a sham device (conditioned stimulus) previously was paired with high-intensity pain stimuli (unconditioned stimulus), the pain stimuli could be replaced by no-pain stimuli or monetary reward (the unconditioned stimulus of opposite valence) [58]. Another promising method to reduce the generalization of nocebo effects is overshadowing, where a combination of two stimuli as potential conditioned stimuli is paired with an unconditioned stimulus, with one of the conditioned stimuli being less salient than the other conditioned stimulus. Later, the presence of this less salient conditioned stimulus would induce a weaker conditioned response than if this conditioned stimulus had been paired with the unconditioned stimulus alone [59,60]. For instance, the combination of a

sham device and a strong-tasting food is associated with high-level pain stimuli during a learning phase, but the strong-tasting food is not present at test. Latent inhibition refers to preexposure to a to-be-conditioned stimulus [61,62]. For instance, participants could be preexposed to the test room in the absence of noxious stimuli, prior to a nocebo conditioning and generalization paradigm of nocebo effects. Also, generalization of placebo and nocebo effects may be modulated by verbal suggestion. One study showed that providing an explanation of nocebo effects served as an intervention to reduce the nocebo effects on symptoms [63]. Nevertheless, evidence shows that placebo and nocebo effects could be induced by explicitly explaining placebo or nocebo effects with the administration of inert treatments (called open-label placebo/nocebo effects) [64,65]. Therefore, future research could examine to what extent explaining the phenomenon of these so-called open-label generalization effects to participants may modulate generalization of placebo and nocebo effects. Moreover, it would be of interest to study whether the effectiveness of these strategies on modulating the generalization of placebo/nocebo effects varies between stimulus and response generalization.

Additional research could advance knowledge about the neurobiological mechanisms underlying the generalization of placebo and nocebo effects [12,29]. The review (Chapter 2) shows that research on neuroimaging and other related approaches such as electroencephalography is rare in this regard, and no firm conclusions can be drawn about neurobiological outcomes. More studies are warranted, and replication of the existing experimental models is also necessary to confirm the findings. Additionally, the few existing neuroimaging studies generally focus on a single part regarding generalization effects [66], which likely neglects to examine a dynamic process of how initial placebo/nocebo effects generalize to diverse stimuli and responses. Future studies could, for instance, apply electroencephalography to participants continuously during both the induction and generalization phases of placebo effects, to record the dynamic electrical signals of the processing of generalization effects. Furthermore, it is worth mentioning that neuroimaging studies may offer some insight into modulating the generalization of placebo and nocebo effects by changing the neural activity of specific brain regions using neuromodulational approaches including repetitive transcranial magnetic stimulation (rTMS). Future studies would be necessary to design reproducible and rigorous neuroimaging experiments to enrich the understanding of these generalization effects.

Lastly, more research is needed to examine the predictors for the generalization of placebo and nocebo effects. Chapter 2 showed that, within the limited studies thus far, no consistent individual characteristics (i.e., self-report expectancies and cognitive-affective factors) have been observed to predict the generalization of placebo and nocebo effects, usually with sample sizes only being able to detect moderate to large effect sizes. Studying these generalization effects in a large cohort could be a potent solution, as mentioned

above. However, two studies exploring individual characteristics (e.g., anxiety and catastrophizing) on placebo and nocebo effects also yield mixed results despite a large sample size [67,68]. This may imply that the intricate interplay between diverse factors such as psychoneurobiologial and treatment context factors plays a role in generalization effects. Notably, predictors may vary between healthy and patient samples, especially in patients with an extensive treatment history that may influence the process of generalizing placebo and nocebo effects over treatments and symptoms. It goes without saying that investigating predictors for these generalization effects would aid in precluding their onset in clinical settings. Future studies could advance these investigations, for example, by combining the measures of multiple individual psychological characteristics with other factors such as treatment history [e.g.,1] and treatment contexts [e.g.,69].

Clinical implications

Most research is of an experimental nature, and caution is called for in extrapolating from the findings. However, based on current knowledge, several promising avenues may be explored to improve clinical ecological validity. Verbal suggestion stands out from other learning methods in that it is closer to the instructions given by healthcare providers [70]. It would thus be worth improving the clinical value of verbal suggestion, for instance by discussing verbal instructions with healthcare providers and then framing the suggestion in such a way as to modulate placebo and nocebo effects and their generalization. Furthermore, Chapters 3 and 4 have illustrated that nocebo effects can generalize within symptoms. Prior negative outcomes of treatment on symptoms could result in negative outcomes with regard to other similar symptoms, which could provide potential explanations for repeated treatment failure. Research into nocebo effects and their generalization is needed to improve medical treatment outcomes in clinical practice and thereby reduce clinical costs [71].

Evidence suggests that placebo and nocebo effects seem to generalize across similar treatments/symptoms (e.g., from a placebo patch to a placebo tablet, or from heat pain to pressure pain) [8,15], while generalization of placebo and nocebo effects does not occur between dissimilar treatments/symptoms [29,30]. Further research could highlight the dissimilarity between initial and future treatments/symptoms (e.g., verbally describe the differences) after initial treatment failure, which may offer some insight into how to blunt the generalization of nocebo effects. By contrast, emphasizing the similarity between initial and future treatments/symptoms may help boost generalization of placebo effects. Additionally, given that generalization effects can occur with regard to treatment outcomes, it may be fruitful to take the order of treatments into account when setting up treatment schemes, e.g., first providing the treatment which can be expected to provide the highest beneficial effects.

Treatment-contextual factors such as the patient-therapist relationship have also been known to alter patients' perception of symptoms as well as their treatment outcomes in many ways [72,73]. Moreover, two studies thus far (reported in Chapter 2) have found that generalization of placebo and nocebo effects seems to occur across treatments contexts, i.e., generalization of nocebo effects on nausea across two similar testing rooms [56], and placebo pain relief across physician's faces that gradually vary across a perceptual continuum [14]. Future studies are called for the investigations of how placebo and nocebo effects generalize across diverse contextual factors. Also, it remains to be investigated whether underlining the similarities between initial and subsequent contextual factors can maximize generalization of placebo effects. In addition, it is of value to study whether stressing the dissimilarity can minimize generalization of nocebo effects. Future studies are called for to investigate how placebo and nocebo effects generalize across diverse contextual factors. Another potential method might be to break negative associations that pair contextual factors (e.g., a healthcare provider) with symptoms, to reduce the carryover effects of contextual factors. This could possibly be investigated in experimental studies by establishing a new association between novel contextual factors (e.g., a new experimenter) and a sensation (e.g., pain) to replace the previous negative association with that sensation, such as after the onset of nocebo effects or multiple nocebo effects on consecutive days [74].

Finally, it is necessary to study stimulus and response generalization of placebo and nocebo effects in clinical samples, as this would help to understand the clinical validity and value of experimental studies as well as the carryover effects in patients. For instance, it remains to be seen whether the magnitude of the generalization of placebo and nocebo effects may vary between healthy and patient samples. In some clinical conditions, patients can suffer from more than one symptom. For example, patients recovering from a burn injury usually suffer from pain and itch simultaneously [75]. These patients may be more prone to perceive pain and itch as similar symptoms than healthy participants who lack this experience with burn wounds. Future studies could compare whether the process of categorizing or discriminating sensations (or symptoms) varies between healthy and patient samples. Moreover, investigating these generalization effects in patient samples with multiple relevant symptoms would be valuable to explore the function of response generalization of placebo and nocebo effects on diverse symptoms in clinical practice, although such investigations remain challenging. This could also aid in establishing individualized treatment schemes by exploring whether and how prior treatment outcomes influence future treatment outcomes across symptoms.

Conclusion

In the current dissertation, we investigated the generalization of placebo and nocebo effects over stimuli and responses. A narrative review was conducted of the literature on

both response and stimulus generalization of placebo and nocebo effects on somatic sensations (e.g., pain), to comprehensively understand these generalization effects. Experimental studies investigated response generalization of placebo and nocebo effects within and beyond pain and itch modalities. Taken together, the findings show that placebo and nocebo effects may generalize within pain and itch modalities, but seem not – or only to a limited extent – to generalize either from pain to itch or from itch to touch-evoked itch. Evidence, including the current experiments indicates that placebo and nocebo effects can generalize to similar stimuli and responses. The generalization effects likely are stronger when future stimuli/responses closely resemble the initial one. These findings could imply that previous positive or negative experiences of the course of symptoms and treatment outcomes predict the outcomes for similar symptoms or treatments. Future experimental and clinical studies are called for to explore these generalization effects with regard to various stimuli and responses. Making use of multiple methods, including psychophysical and neuroimaging techniques, in ecologically valid studies would benefit the understanding of both stimulus and response generalization of placebo and nocebo effects. This would provide the potential to harness the carryover effects of treatment history to future treatments as well as symptoms and thus advance treatments in clinical practice.

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