Nocebo hyperalgesia and pain progression: prediction, acquisition, and recovery

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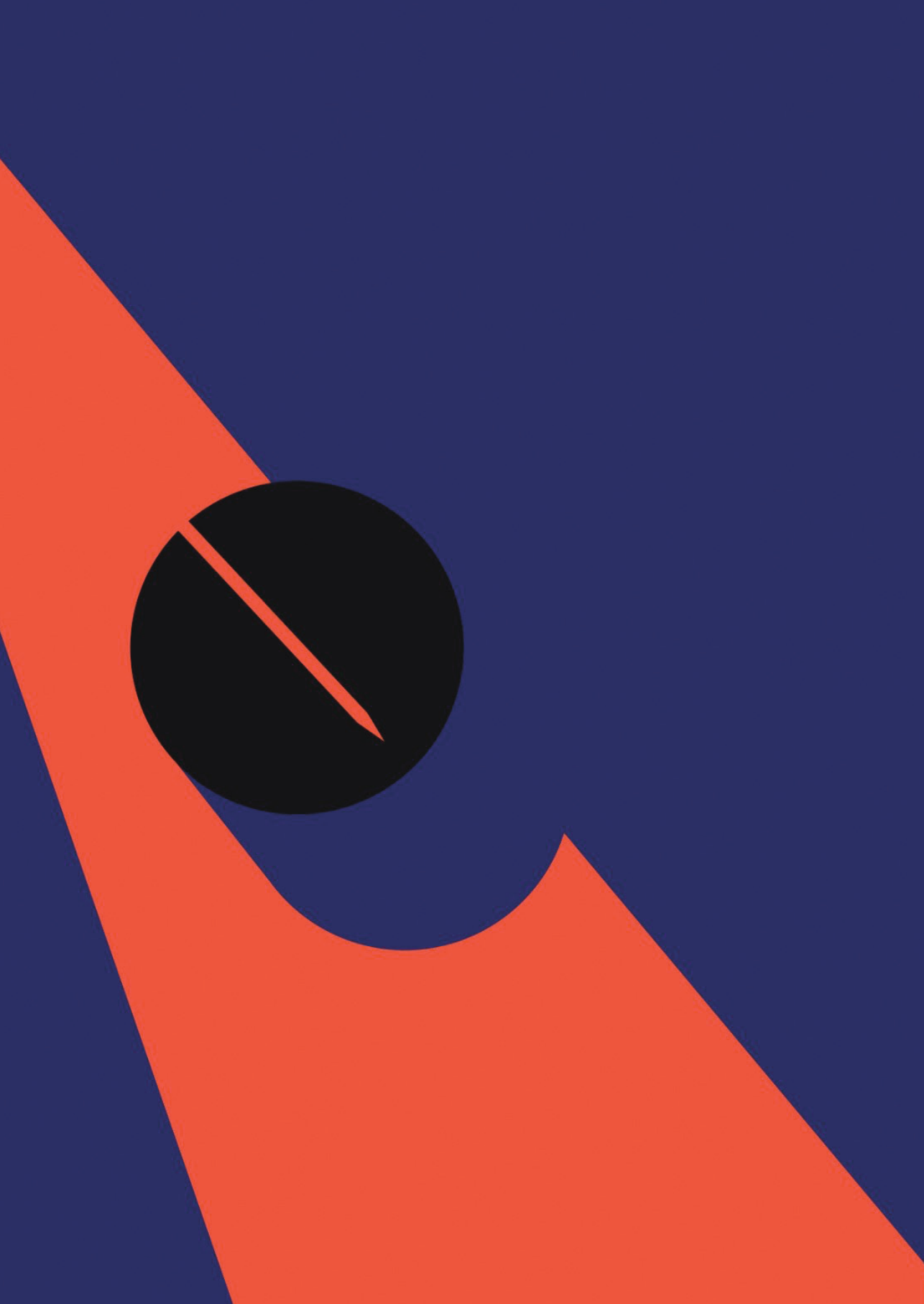

CHAPTER 7

General Discussion

Pain is a complex phenomenon that can be shaped by top-down factors such as expectancies and learning. Only in the past few decades, expectancies of adverse treatment outcomes, as key factor in nocebo effects, have been considered for their role in aggravating pain-related symptoms. While research on nocebo hyperalgesia is prevalent in healthy individuals, more investigation is needed in ecologically-valid chronic pain modalities and chronic pain conditions, such as fibromyalgia, using different learning strategies (e.g., open- and closed-label verbal suggestions, classical conditioning, counterconditioning, extinction), to identify their potential role in pain progression. In addition, investigation into individual differences in acquiring and recovering from nocebo hyperalgesia could result in useful markers of susceptibility to nocebo-related modulation of pain. To address these topics, the current dissertation first investigated ways to experimentally manipulate nocebo hyperalgesia by administering pressure stimuli to evoke pain (i.e., an ecologically-valid pain modality for musculoskeletal disorders such as fibromyalgia), and by utilizing open-label counterconditioning as novel strategy for manipulating nocebo hyperalgesia in healthy female participants. Moreover, we investigated the predictors of (experimentally-induced) nocebo hyperalgesia and the recovery therefrom in the same healthy female sample. Next, we compared the magnitude of (closed-label) experimental induction and reduction of nocebo effects on pressure pain in female patients with fibromyalgia versus matched healthy controls, while repeating the same experimental procedures at one-month follow-up to assess stability of nocebo effects. Lastly, we employed an ecological momentary assessment (EMA) method in the form of an electronic diary study in the same fibromyalgia sample to investigate whether (experimentally-induced) nocebo hyperalgesia predicts diary-assessed pain.

In this closing chapter, the main findings of this dissertation are summarized in relation to the current literature, while discussing limitations and the implications for research and clinical practice. Moreover, recommendations are provided for future research directions.

Identifying ways to experimentally induce and reduce nocebo effects on pain

In **chapter 2**, our main aim was to study novel ways to induce and reduce nocebo hyperalgesia in a healthy female sample. We aimed to 1) determine whether experimentally inducing pain using pressure stimuli, i.e., an ecologically-valid pain modality for musculoskeletal disorders like fibromyalgia, can be used in the induction and reduction of nocebo hyperalgesia as observed in previous studies using heat and electrical pain modalities[1–4]; 2) test whether providing open-label suggestions, i.e., informing participants on the inert treatment properties and the underlying mechanisms behind nocebo effects, during conditioning is an effective strategy for inducing nocebo hyperalgesia; 3) test the efficacy of open-label counterconditioning as a novel intervention

strategy for attenuating nocebo hyperalgesia. In line with this, we conducted an RCT to investigate the open-label induction and reduction of nocebo effects on pressure pain in a healthy female sample. The pressure pain evocation method tested in the current study was intended to be later used in studies involving patients with fibromyalgia (see **chapter 4** and **chapter 5**).

Our results showed that open-label conditioning combined with suggestions on the pain-increasing function of a sham TENS device was effective in inducing nocebo effects on pressure pain, as compared to sham conditioning. This study was the first to show that open-label induction of nocebo effects on pressure pain is possible, confirming the earlier findings on the efficacy of open-label nocebo conditioning on itch[5]. Important to note here is that in daily life, conditioning more closely resembles the closed-label paradigms, since participants are not deliberately aware of the associations between pain and certain stimuli. Nonetheless, it is relevant to know that open-label instructions on nocebo effects impact hyperalgesia, as this may increase awareness on how to communicate specific treatment information to people. In line with previous (closed-label) counterconditioning studies on other pain modalities[2] and itch[6], open-label counterconditioning of pressure pain was found to be a more effective nocebo-reduction strategy compared to an open-label extinction and control condition in which nocebo conditioning was continued. In particular, counterconditioning did not only reduce nocebo hyperalgesia, but also induced a similar level of conditioned placebo analgesia as placebo conditioning. This indicates that deceptive methods may not be necessary for treating nocebo effects. Open-label counterconditioning of nocebo effects is thus promising for the future design of ethical (non-deceptive) learning-based interventions for chronic pain conditions.

Predicting nocebo-hyperalgesia acquisition and recovery

The aim of **chapter 3** was to identify the predictors of nocebo hyperalgesia acquisition and recovery. More specifically, we conducted additional exploratory analyses on the same experimental study (in **chapter 2**) to identify the psychological predictors of nocebo hyperalgesia. Moreover, we studied whether the reduction of nocebo hyperalgesia can be predicted by susceptibility to (experimentally-induced) nocebo hyperalgesia and psychological characteristics. For this, factors that have been previously shown to be possibly related to nocebo effects (dispositional optimism, trait and state anxiety, pain catastrophizing, fear of pain, and body vigilance) were assessed via validated questionnaires at baseline, prior to the experimental nocebo manipulations. The results showed that stronger nocebo hyperalgesia was predicted by lower optimism and higher trait anxiety. Moreover, larger nocebo hyperalgesia magnitude and higher trait anxiety predicted a larger nocebo reduction across all interventions (i.e., counterconditioning, extinction, and control). In addition, larger nocebo-hyperalgesia magnitude and lower

optimism predicted the largest nocebo reduction after counterconditioning. Our findings indicate that susceptibility to nocebo hyperalgesia, dispositional optimism, and trait anxiety may shape the degree to which nocebo effects on pain are reduced. Individuals high in trait anxiety are likely to benefit from either nocebo-reduction strategy (counterconditioning or extinction) whereas those with larger nocebo hyperalgesia or lower optimism are likely to benefit the most from counterconditioning. Identifying individual differences in the acquisition and recovery from nocebo hyperalgesia can help design more personally-tailored nocebo interventions.

Nocebo hyperalgesia in patients with fibromyalgia versus healthy controls

In **chapter 4**, we aimed to identify potential differences in acquiring and recovering from nocebo hyperalgesia for people with or without chronic pain. Here, we investigated group differences for the magnitude of induced and reduced nocebo hyperalgesia in female patients with fibromyalgia versus female healthy controls that were matched on age and education level. In the lab, nocebo effects on pressure pain were induced via (closed-label) conditioning combined with verbal suggestions on the pain-increasing function of a sham TENS device, which was later decreased via extinction. One month later, the same experimental procedures were repeated in both groups to measure the stability of these effects to identify the role time plays in potential fluctuations (e.g., progression) in nocebo-hyperalgesia levels. In line with previous studies in healthy participants, nocebo hyperalgesia was successfully induced in this group both at baseline and follow-up. However, in the patient group, nocebo hyperalgesia was not significantly induced during the baseline session. During follow-up, nocebo hyperalgesia was observed also in the patient group, while there were no differences in hyperalgesia magnitude compared to healthy controls. Extinction was effective in decreasing nocebo hyperalgesia only in the baseline session of healthy individuals. Post-hoc investigations showed that extinction did take place in those individuals where nocebo effects were induced in either group, in both sessions. Moreover, across all participants the magnitude of nocebo-hyperalgesia induction and decrease was stable after one month. Contrary to our expectations, we did not observe a stronger magnitude of nocebo hyperalgesia, or resistance to extinction, in patients with fibromyalgia compared to healthy individuals. In fact, patients could be either equally or less responsive to the experimental nocebo manipulations compared to healthy controls. As this study was, to the best of our knowledge, the first in comparing differences in nocebo hyperalgesia in people with versus without chronic pain, replication of our current findings is warranted.

Predicting pain progression based on nocebo hyperalgesia

In **chapter 5**, we aimed to predict fibromyalgia pain based on individual differences in nocebo hyperalgesia magnitude. Here, we combined our experimental findings from

chapter 4 with ecological momentary assessment (EMA). Using EMA, we investigated whether experimentally-induced nocebo hyperalgesia magnitude and diary-assessed expectancy-related factors (pain expectancy, anxiety, pain catastrophizing, optimism) predicted changes in daily-pain intensity in the same fibromyalgia sample. Also, the relations between nocebo hyperalgesia and other expectancy-related factors were explored. Following the baseline experimental session (**chapter 4**), the same patient group filled out an electronic diary for 3 times a day for 3 weeks. Our findings showed that particularly higher pain expectancy and higher pain catastrophizing were related to moment-to-moment pain increase. Experimentally-induced nocebo hyperalgesia did not predict pain and was unrelated to diary-assessed expectancy-related factors. Although we did not find evidence for (experimentally-induced) nocebo hyperalgesia being a predictor of fibromyalgia pain progression, pain expectancy and pain catastrophizing (factors related to susceptibility to nocebo hyperalgesia) in particular seem promising for future consideration. This finding could be useful for, for example, future treatment strategies to also target overprediction of upcoming pain (i.e., pain expectancy) and catastrophizing thoughts for reducing fibromyalgia pain.

Differences in nocebo hyperalgesia between people with and without chronic pain

The current dissertation investigated the learning mechanisms behind nocebo hyperalgesia in healthy individuals and in patients with fibromyalgia. Although group differences have not yet been researched before in the nocebo context, previous research exists on how chronic pain populations respond to nocebo hyperalgesia as well as on the group differences inside placebo- and fear-conditioning fields.

Experimental research demonstrates that patients with irritable bowel syndrome (IBS)[7] and with postoperative pain[8] have shown nocebo effects on clinical pain after verbal suggestions of pain increase. One experimental study in patients with chronic low back pain has combined both conditioning and verbal suggestions to induce nocebo effects on clinical pain; however, this study has found placebo effects, potentially due to verbally suggesting both the positive and negative effects of a sham opioid treatment where the placebo suggestions possibly prevailed over the nocebo ones[9]. To the best of our knowledge, our experimental study (**chapter 4**) was the first in combining conditioning with verbal suggestions of (mere) pain increase regarding the activation of a sham TENS device, where we observed no group differences in nocebo hyperalgesia magnitude between patients with fibromyalgia and healthy controls. Also, in the placebo context, a recent brain-imaging study has found no differences between patients with fibromyalgia and healthy controls in their neural response to placebo analgesia[10]. Placebo analgesia induced via conditioning and verbal suggestions led to comparable decreases in both

groups for pain intensity and unpleasantness ratings as well as for the activity in areas related to the neurological pain signature[10]. Similar findings were observed in placebo studies comparing healthy individuals versus patients with the chronic pain conditions temporomandibular disorder[11], episodic migraine[12], and IBS[13].

Research to date suggests that patients with chronic pain respond in a similar manner as healthy controls to placebo and nocebo manipulations. This would suggest that research in healthy populations offers a good proxy for research in patients, as research in healthy individuals may be generalizable to patients. However, although insights into placebo analgesia are useful indicators of expectancies in chronic pain conditions, the psychological and neurobiological mechanisms behind placebo effects do not fully overlap with those of nocebo effects [14–16]. Therefore, further experimental nocebo research is needed in chronic pain conditions to determine whether the lack of group differences observed for placebo effects generalizes to nocebo effects, with our study being the first to provide indications in that direction.

Further informative group comparisons between patients with fibromyalgia and healthy controls come from fear conditioning literature in the context of learning[17–19]. In (pain-related) fear-conditioning paradigms, patients with fibromyalgia were found to have impaired contingency learning (i.e., impairment in learning that one event predicts the presence or absence of another event) and excessive stimulus generalization (i.e., learning of a specific US-CS association is more easily broadened to other stimuli) compared to healthy controls[17-19]. Future research is recommended to examine whether these learning deficits in fibromyalgia play a role in nocebo-learning paradigms. Learning deficits may be also a potential explanation for the inconsistencies we observed across baseline and follow-up sessions for the nocebo hyperalgesia magnitude of patients. For example, not being able to identify the safety cue (i.e., control cue) compared to the experimental cue predicting higher pain could potentially impact the measurement of nocebo hyperalgesia magnitude. Therefore, future studies are recommended to employ additional measurements of contingency awareness between experimental and control cues during the testing phase of nocebo conditioning to gain further insights into group comparisons in nocebo hyperalgesia.

Altogether, our findings demonstrate that patients with fibromyalgia and healthy controls do not show clear group differences in their acquisition of (experimentally-induced) nocebo hyperalgesia and its extinction. However, further replication studies and research considering the previously observed contingency-learning deficits in fibromyalgia are warranted.

Individual differences in nocebo hyperalgesia acquisition and recovery

Accurately identifying individuals at risk of acquiring nocebo effects is vital for the future of clinical treatment, since nocebo effects are detrimental to patients' well-being and quality of life, as well as costly to the healthcare system. Also, identifying individuals who are likely to recover from nocebo effects is important for the design of learning-based interventions for reducing nocebo effects. In terms of predictors, we identified lower dispositional optimism and higher trait anxiety (**chapter 2**) to be related to stronger nocebo-hyperalgesia acquisition in healthy participants. This is in line with previous findings from a systematic review that identified higher optimism to be related to placebo analgesia and higher anxiety with nocebo hyperalgesia[15]. Nevertheless, we were not able to replicate our findings on dispositional optimism and (trait and state) anxiety in our second experimental study (**chapter 4**) in neither a healthy nor patient group. Similarly, the diary-assessed optimism and anxiety levels of patients were found unrelated to (experimentally-induced) nocebo hyperalgesia (**chapter 5**). However, findings should be generally interpreted with some caution given the limited sample sizes and the differences in study methodologies.

Our mixed findings on these predictors could be potentially (partly) explained by our choice of measurement method. A recent meta-analysis points out that trait anxiety, for instance measured via baseline questionnaire, may be limited in predicting the magnitude of nocebo effects, whereas state (or situationally-induced) anxiety appears more critical for the induction of nocebo effects[20]. Therefore, additional to our questionnaire assessments, a trial-by-trial assessment of these psychological factors could have provided additional insights into their situational changes and relevance for the subsequent induction of nocebo hyperalgesia in both participant groups. Moreover, experimentally-induced nocebo hyperalgesia was unrelated to the situational changes (in optimism, anxiety, pain catastrophizing, and pain expectancy) that were assessed via electronic diary in patients. The heterogeneity between these measurement methods could be a potential explanation of our findings. For future studies, it is important to explore additional ecologically-valid ways of measuring potential predictors of nocebo hyperalgesia, such as via electronic diary.

In terms of predictors of nocebo recovery, we found preliminary evidence for susceptibility to (experimentally-induced) nocebo hyperalgesia, dispositional optimism, and trait anxiety being related to nocebo hyperalgesia reduction (**chapter 2**). This finding could be possibly explained by a stronger desire for pain relief when perceived pain is higher during greater nocebo hyperalgesia and lower dispositional optimism, which could in turn increase the efficacy of upcoming interventions[21]. Another possible explanation could be related to the fact that participants who are more susceptible to nocebo hyperalgesia might be

also susceptible to learning strategies in general. This could be potentially facilitated by showing more selective attention towards conditioned stimuli in the environment, and thereby responding equally strongly to upcoming nocebo-reduction interventions[22].

Altogether, we found preliminary evidence for individuals with lower dispositional optimism and higher trait anxiety to be more susceptible to (experimentally-induced) nocebo hyperalgesia. Moreover, individuals with larger baseline nocebo hyperalgesia, lower dispositional optimism, and higher trait anxiety seemed to benefit the most from nocebo-reduction interventions. Our findings provide promising insights into how individual susceptibility to nocebo hyperalgesia, dispositional optimism, and trait anxiety might be modulating pain in either direction. Future replication studies could consider selecting these predictors while investigating the acquisition and recovery of nocebo hyperalgesia in healthy and clinical populations.

Limitations

There are several limitations related to the research questions in the current dissertation. One important limitation in all studies was the inclusion of only female participants. The main argument behind this selection was that fibromyalgia is reportedly more common in women than in men with a proportion up to 9:1 based on epidemiological and population studies[23]. Although research shows that female sex is a risk factor in fibromyalgia[24], some studies argue that this could be a result of women likely consulting their physician more frequently than men[23]. A recent study also highlights the fact that fibromyalgia is not exclusively observed in women, since widely varying estimates of female ratio might be due to participant selection bias in clinical studies, lowering the actual female predominance from 90% to less than 60%[25]. In our studies, we chose female participants to increase the comparability of current findings with existing literature. Also, we aimed to avoid introducing potential bias into our data collection, such as sex differences in pain sensitivity[26]. Moreover, a systematic review has found sex differences in nocebo effects, with females responding stronger than men, potentially due to a larger increase in stress and anxiety after nocebo induction in females[27]. Given that the current patient studies (**chapters 4** and **5**) were the first in the nocebo field, we chose not to introduce sex-related bias. However, the generalizability of our findings to males is limited and requires further investigation. Similarly for our findings with healthy participants (**chapters 2** and **3**), who were university-educated young females, further investigation in males, older populations, and vocation-educated individuals are warranted.

Moreover, small participant samples require a point of attention in placebo and nocebo studies, especially for the statistical analyses involving predictors. Since power calculations were conducted in the current studies to estimate sample sizes required for testing our

primary research questions, our effect sizes especially for secondary research questions involving predictors had wide confidence intervals and/or small effect sizes were not detected. A potential solution other than running large-scale studies, could be a meta-analysis of different studies in the field to assess predictors from a cumulatively larger sample.

Furthermore, the external validity of experimental nocebo hyperalgesia paradigms is a common issue in the field. Although we tried to select an ecologically-valid pain modality for inducing nocebo hyperalgesia, the extent in which pressure pain relates to daily pain experiences in fibromyalgia is debatable. We speculate that experimentally-evoked pressure pain may not have been sufficiently fear- or anxiety-inducing to generate strong nocebo effects in the lab, considering that daily pain experiences of patients might be in comparison more harmful, less predictable, and longer in duration than a safe and controlled experimentally-evoked pain experience. To gain a better insight into this, our experimental procedure could have benefited from additional trial-by-trial measures of fear[28] or anxiety[29]. In our lab studies, we only measured self-reported pain intensity after sham TENS-cue presentation in each trial. Important to note here is that the self-reported evaluation of multiple measures before and after cue presentation could become confusing for participants as this requires a rapid cognitive abstraction of different somatic changes. Moreover, also the external validity of the nocebo conditioning paradigm may have been limited in reproducing learning experiences as they appear in daily life. For example, when exposed to daily pain, pain-related associations might generalize to other cues than only sham treatment (i.e., the conditioned stimulus). Our reasoning for preferring closed-label over open-label instructions in our patient study (**chapter 4**) was to decrease the predictability of pain outcomes to better mimic nocebo effects and extinction as they occur in daily life. To strengthen our research, we have consulted patient partners during the design process of our study, for example to more extensively test the nocebo procedures in the lab. Future studies could consider involving them in other ecologically valid paradigms, such as diary studies.

Another limitation was that for safety purposes the experimenter was present in the lab at all times, which could have influenced the reporting of pain ratings in **chapter 2,** given that the experimenter logged these values into the computer after participants verbally indicated their pain intensity. In **chapter 4**, the experimenter was also present at all times, but the participants themselves logged their pain-intensity ratings into the computer. Moreover, double blinding was not possible for the study with the open-label paradigm due to its non-deceptive nature, which made sure participants and the experimenter were consciously aware of the experimental learning manipulations. Participants were only blinded to the surreptitious change in pressure intensity during the testing phase of

conditioning. For the study with the closed-label paradigm, both healthy participants and patients underwent the same experimental procedures, thereby eliminating the need for blinding of the experimenter. Participants were blinded to the real study aims, along with the surreptitious change in pressure intensity during the testing phase of conditioning. However, participants could not be blinded to the experimental manipulations during the learning phase of conditioning since the pressure intensity administered in this part was aligned with the verbal suggestions provided about the sham TENS function.

Lastly, the COVID-19 pandemic overlapped with studies in the current dissertation. For studies in **chapters 2** and **3**, experimental data collection ended prematurely since data possibly collected during the pandemic was considered incomparable to previously collected data, due to additional safety measures. For studies in **chapters 4** and **5**, additional safety measures were introduced in the lab (e.g., participant and researcher wore mouth masks, a lab set-up was created to ensure sufficient distance between the researcher and the participant). We do not expect this to influence our experimental manipulations; however, the potential impact of the pandemic on participants' expectations and psychological well-being, and its subsequent effects on the outcomes relevant for our study, remains unknown.

Implications and future research directions

There are several implications of our findings for future research and clinical practice regarding group differences in nocebo hyperalgesia, methodological recommendations surrounding experimental procedures, predictors of nocebo hyperalgesia acquisition and recovery, and the potential role of nocebo hyperalgesia in pain progression.

First, we found that it was possible to experimentally induce nocebo hyperalgesia through pressure pain, an ecologically-valid pain modality for musculoskeletal disorders, in both healthy participants and patients with fibromyalgia. The current findings indicate no clear group differences in nocebo hyperalgesia magnitude. The fact that we did not find evidence for group differences could be interpreted as a positive finding. Potentially, patients with fibromyalgia might be under less risk of nocebo hyperalgesia than previously anticipated[30–33]. However, future studies are recommended to also take into account the Bayesian framework for statistical analysis compared to the traditional statistical framework applied in the current studies[34], to better disentangle any latent group differences in experimental settings.

Second, certain methodological issues regarding the nocebo conditioning paradigm are recommended to be revisited by future studies. For example, it would be worthwhile to additionally account for contingency-learning deficits and stimulus overgeneralization

previously observed in patients with fibromyalgia, which could impact learning processes, such as nocebo conditioning[17–19]. Moreover, the selection of conditioned stimuli (CS), which was a sham TENS device in our studies, could be customized by selecting a more personalized CS that represents patients' treatment expectations on pain outcomes. To tackle this, first, a consultation could take place to understand which aspects of the treatment are experienced as harmful, e.g., including contextual factors such as the treatment procedure or aspects of the patient-doctor alliance. Then those aspects could be targeted via positively/negatively framed verbal suggestions to manipulate placebo and nocebo effects, respectively. Although the use of personalized measures is characterized by additional statistical challenges, such as in terms of standardization of outcome measures, this could provide a more ecologically-valid translation of a CS in the lab.

Third, the studies in this dissertation have provided indications to decrease the occurrence of nocebo effects or reduce them and for potential individual tailoring of healthcare. Our research has shown that as a predictor of recovery, nocebo hyperalgesia could be harnessed to increase the efficacy of nocebo-reduction interventions. Counterconditioning, in particular may most benefit patients with higher nocebo hyperalgesia, higher trait anxiety, and lower optimism. Moreover, open-label induction and reduction of nocebo hyperalgesia provided additional insights that deception is not required for their experimental manipulation. This has implications for clinical practice, such that physicians can be honest while employing nocebo-reduction strategies in their patients. Future studies are recommended to further investigate the generalization of our findings to more heterogeneous samples, including males and older individuals of different education levels.

Fourth, we did not find evidence for (experimentally-induced) nocebo hyperalgesia to predict pain progression in fibromyalgia in the diary study. Considering existing methodological limitations surrounding the nocebo conditioning paradigm, this research question could be revisited after employing more externally-valid methods of measuring nocebo hyperalgesia. Also, the role of nocebo hyperalgesia magnitude in pain progression is recommended to be investigated at different fibromyalgia stages, for example at onset as well as at later stages, since this could provide insights into the longitudinal effects of nocebo hyperalgesia on disease progression. Further investigation into the association between central sensitization (i.e., pain-processing abnormalities in the central nervous system[36]), and nocebo hyperalgesia is warranted, given that central sensitization is a characteristic of fibromyalgia and is a framework commonly used for explaining the mismatch in perceived pain intensity during minimal physical impairment or in the absence of clear pathophysiology or injury[36]. This mismatch in pain processing leads to exaggerated processing of bottom-up sensory signals and has

implications for correctly predicting upcoming pain[31]. According to the predictive coding[34] and Bayesian brain[31] frameworks, the brain constantly generates top-down predictions about incoming bottom-up sensory data, where this incoming data serves as a corrective feedback mechanism on top-down predictions. During this process, the brain corrects for possible prediction errors arising between the top-down predictions and bottom-up signals by updating the top-down prediction model, for example by modulating the sensory input to match the prediction model[31,34]. In the context of nocebo hyperalgesia, negative expectancies are thought to directly modulate top-down predictions[31]. This mechanism mimics the bias observed in chronic pain during central sensitization, which unproportionally shifts sensory bottom-up data into top-down painful predictions[31]. Therefore, it could be hypothesized that nocebo effects can further strengthen the top-down prediction bias observed during amplified pain experiences in fibromyalgia. Future prospective research is recommended to examine the long-term impact of nocebo hyperalgesia on pain progression.

Conclusion

The field of nocebo research is rapidly growing, with an increasing number of studies focusing on chronic pain. The current dissertation aimed to find answers to the questions of whether the magnitude of nocebo hyperalgesia is comparable in patients with fibromyalgia and healthy controls, what the predictors are of nocebo hyperalgesia acquisition and recovery through extinction and counterconditioning, and whether nocebo hyperalgesia predicts fibromyalgia pain progression in daily life. Our findings have shown that both open- and closed-label strategies were promising for the experimental manipulation of nocebo effects on pressure pain. Patients with fibromyalgia and healthy individuals did not differ with regard to nocebo hyperalgesia. We identified dispositional optimism and trait anxiety as possible predictors of nocebo hyperalgesia; where these and also susceptibility to nocebo hyperalgesia were identified as predictors of nocebo-reduction interventions, such as counterconditioning. Lastly, diary assessments of nocebo-related pain expectancy and pain catastrophizing, but not experimentally-induced nocebo hyperalgesia, predicted moment-to-moment increases in fibromyalgia pain. These insights are useful for the future design of personalized learning-based interventions for targeting chronic pain. Targeting nocebo hyperalgesia and related factors, such as pain expectancies, pain catastrophizing, anxiety, and lack of optimism, might be promising for attenuating nocebo-induced pain during clinical treatments.

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