SUMMARY

Nocebo effects are adverse treatment outcomes that are not caused by active treatment components. They can compromise patients' well-being and quality of life, and introduce additional costs on the healthcare system. Previous research shows that nocebo effects are guided by negative outcome expectancies, which can be induced and reduced via learning. Compared to the field of placebo effects, the field of nocebo effects is more recent, with most research conducted with healthy participants. Nocebo research in patients with chronic pain has been scarce, but remains important, given that patients' relationship with pain treatment and the surrounding treatment context might be more complex due to the long-term persistence of pain and lack of effective treatments. This could possibly lead to a stronger acquisition of nocebo effects as compared to healthy individuals and also less recovery in patients with chronic pain. Therefore, further investigation is needed for the learning mechanisms behind nocebo hyperalgesia in both healthy individuals and chronic pain patients. Moreover, identifying not only patients but also healthy individuals who are at risk for acquiring nocebo hyperalgesia is crucial for clinical treatment. Equally important is identifying individuals who are likely to recover from nocebo hyperalgesia for developing learning-based interventions targeting nocebo reduction. Pain is a complex phenomenon that can be shaped by top-down processes, such as expectancies. Consequently, investigation into nocebo hyperalgesia in chronic pain conditions, for instance fibromyalgia, could provide additional insights into nocebo-related pain progression in daily-life. Insights into the prediction, acquisition, and recovery of nocebo hyperalgesia and pain progression could be useful for researchers and clinicians, as targeting expectancy-related factors such as nocebo effects is promising for treating pain in chronic pain conditions.

In the current dissertation, we aimed to investigate the experimental learning mechanisms behind the induction (for example, conditioning, open- and closed-label verbal suggestions) and reduction (for example, extinction, counterconditioning), or in other words the recovery, of nocebo hyperalgesia in healthy individuals and patients with fibromyalgia, and to determine potential differences between groups in the acquisition and recovery of nocebo hyperalgesia. Additionally, we investigated the predictors of nocebo hyperalgesia acquisition and recovery to identify individuals susceptible to these effects. Lastly, in an electronic diary study we aimed to determine whether (experimentally-induced) nocebo hyperalgesia plays a role in daily pain progression in fibromyalgia.

In **Chapter 2**, we aimed to determine novel ways to experimentally induce and reduce nocebo effects on pain. As such, we applied pressure pain, an ecologically-valid pain modality for musculoskeletal disorders such as fibromyalgia, to induce nocebo effects in healthy participants. We also employed open-label, instead of closed-label, verbal suggestions to investigate more ethical ways to manipulate nocebo effects. Participants were informed about the inert treatment properties of a sham Transcutaneous Electrical Nerve Stimulation (TENS) device and were explained how this could still affect pain through the expectancy mechanisms behind nocebo effects. Moreover, we tested counterconditioning as a novel intervention strategy to reduce nocebo effects. Accordingly, a 2-part RCT was conducted in healthy female participants. After we induced nocebo effects on pressure pain using conditioning combined with (open-label) verbal suggestions, we compared open-label extinction, counterconditioning, and continued nocebo conditioning (control) for reducing

nocebo effects on pressure pain. Our results showed that open-label conditioning combined with verbal suggestions was effective in inducing nocebo effects. Moreover, we found that (open-label) counterconditioning was more effective in reducing nocebo effects compared to (open-label) extinction and repeated nocebo inductions. These findings are promising for the future development of more ethical (non-deceptive) learning-based interventions for reducing nocebo effects.

In **chapter 3**, we aimed to identify the predictors of nocebo hyperalgesia acquisition and recovery. Building on the findings in **Chapter 2**, we conducted additional exploratory analyses to determine whether experimentally-induced nocebo hyperalgesia can be predicted by psychological characteristics assessed through questionnaires, such as dispositional optimism, trait and state anxiety, pain catastrophizing, fear of pain, and body vigilance. We also investigated whether the reduction of nocebo hyperalgesia can be predicted by susceptibility to nocebo hyperalgesia and the same psychological characteristics. Our results showed that lower optimism and higher trait anxiety were related to stronger nocebo hyperalgesia induction. Moreover, stronger nocebo hyperalgesia and higher trait anxiety predicted the overall efficacy of nocebo reduction interventions (i.e., counterconditioning and extinction). We also found that participants with stronger nocebo hyperalgesia and lower dispositional optimism had a larger nocebo reduction during counterconditioning than participants with lower nocebo hyperalgesia and higher dispositional optimism. Interestingly, lower dispositional optimism and higher trait anxiety were involved in both stronger acquisition and recovery of nocebo hyperalgesia. Our findings indicate that susceptibility to nocebo hyperalgesia, dispositional optimism, and trait anxiety may shape pain experiences in either direction. Individuals high in trait anxiety are likely to benefit from either nocebo reduction strategy (counterconditioning or extinction) whereas those with stronger nocebo hyperalgesia or lower optimism are likely to benefit the most from counterconditioning.

In **chapter 4**, we aimed to detect the potential group differences in the magnitude of nocebo hyperalgesia induction and reduction in patients with fibromyalgia versus healthy controls. Moreover, we additionally investigated the stability of these effects after a 1-month follow-up. In an experimental study, we accordingly induced nocebo effects on pressure pain using conditioning combined with (closed-label) verbal suggestions about the pain-increasing function of a sham TENS device, and then reduced these effects through extinction. The same experimental procedures were repeated after one month. Our reasoning for this time selecting closed-label instructions, over open-label, and extinction, over counterconditioning, was to mimic the acquisition and recovery of nocebo effects as they might occur in daily life. Contrary to our expectations, we did not find clear group differences in the induction and reduction of nocebo hyperalgesia. Also, across all participants, the magnitude of nocebo hyperalgesia and its extinction was stable after one month. These findings may have positive implications for clinical practice whereby patients with fibromyalgia may not be necessarily at greater risk of nocebo hyperalgesia compared to healthy individuals. However, future replication studies in patients with chronic pain are warranted.

In **chapter 5**, we aimed to identify whether nocebo hyperalgesia magnitude predicts mean pain intensity over 3 weeks in patients with fibromyalgia. We combined our experimental findings from **Chapter 4**, where we additionally assessed expectancy-related factors (i.e., pain expectancy, anxiety, pain catastrophizing, and optimism) and pain intensity in the same

patient sample, using an electronic diary three times a day (morning, afternoon, evening) over the three weeks following the baseline experimental session. Our findings indicated that experimentally-induced nocebo hyperalgesia did not predict daily pain, and was unrelated to other expectancy-related factors, in patients with fibromyalgia. Nevertheless, we did find evidence for higher pain expectancy and pain catastrophizing being associated with moment-to-moment increases in pain. Diary-reported factors related to nocebo hyperalgesia, specifically pain expectancy and pain catastrophizing, seem to be promising for future consideration regarding understanding pain progression in fibromyalgia.

Taken together, in the current dissertation we have identified novel strategies for manipulating nocebo hyperalgesia. We found that nocebo effects can be successfully induced on pressure pain, an ecologically-valid pain modality for musculoskeletal disorders such as fibromyalgia. Moreover, open-label counterconditioning seemed promising as a novel intervention strategy for reducing nocebo hyperalgesia. Second, we investigated the predictors of nocebo hyperalgesia acquisition and recovery and found that individuals with lower dispositional optimism and higher trait anxiety might be at greater risk of acquiring nocebo hyperalgesia. These traits were, however, also predictive of better recovery from nocebo hyperalgesia. Moreover, higher susceptibility to nocebo hyperalgesia was also a predictor of recovery from nocebo hyperalgesia. Third, we did not observe stronger nocebo hyperalgesia, nor a stronger resistance to extinction, in patients with fibromyalgia compared to healthy controls. These effects were also stable across groups after a month. Contrary to our expectations, being a patient, compared to being healthy, was not a risk-factor for acquiring nocebo hyperalgesia. Fourth, we found evidence that diary-reported factors related to susceptibility to nocebo hyperalgesia, but not experimentally-induced nocebo hyperalgesia, can predict pain progression in fibromyalgia. All in all, findings in the current dissertation provide insights into the role nocebo hyperalgesia in pain. This work suggests that negative expectancies could be targeted via learning-based interventions to minimize nocebo effects and to reduce (chronic) pain in clinical settings.