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Exploring the Effects of State Anxiety on the Nocebo Effect with Mood as a Moderator

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Contents

Abstract

The term nocebo effect stands for an increase in symptoms due to negative expectations held by an individual. State anxiety has been suggested as a potential mechanism of the nocebo effect, as it has been found to increase negative symptom expectancies. Positive mood inductions have shown promise in reducing, or even preventing the rise of pain hyperalgesia. To further explore these effects, this study investigated whether higher state anxiety levels increased the nocebo effect in the context of a pain conditioning task with verbal suggestions. Additionally, the moderating effect of mood on this relationship was examined. During the study, participants filled in questionnaires on state anxiety and mood, after which a nocebo effect induction took place using a pain conditioning task with verbal suggestions. Data of 37 participants was analysed. The results showed no significant nocebo effect as a result of the conditioning procedure ($t(36) = 1.64$, $p = .109$). No significant effect of state anxiety on nocebo hyperalgesia was present ($F(1, 35) = .188$, $p = .667$), with an R^2 of .005, nor was there a significant moderating effect of positive ($F(3, 33) = .71$, $p = .56$) or negative mood ($F(3, 33) = 1.28$, $p = .295$) on that relationship. The topic calls for further research, as finding ways to prevent or reduce the nocebo effect has important clinical implications.

Rationale

This paper was conducted in the context of a bachelor's project for students graduating from the International Bachelor of Psychology programme at Leiden University. I would like to thank my bachelor project supervisor Dr. Aleksandrina Skvortsova for her continued help and support in the process of writing this paper, as well as my second bachelor project supervisor Dr. Stefanie Meeuwis for her assistance in choosing and refining my topic.

Introduction

The term nocebo effect stands for an increase in symptoms due to negative expectations held by an individual. Nocebo can therefore be understood as the negative counterpart of the more widely known placebo effect, which is a positive response to treatment driven by positive treatment efficacy-related expectations (Geers et al., 2019). A healthcare professional carrying out their ethical obligation of informing a patient on the potential side-effects of pharmacological treatment or a medical procedure may, by doing so, increase the likelihood of the patient experiencing said side-effects (Barnes et al., 2019). Despite having a non-pharmacological basis, both placebo and nocebo effects significantly contribute to treatment outcomes and the severity of side-effects resulting from medical intervention (Geers et al., 2019). Nocebo effects have been found to account for between 40% and 100% of drug side effects (Barnes et al., 2019). They are also linked to non-compliance to treatment, as well as to dropping out of pharmaceutical interventions (Kern et al., 2020). The responsibility to inform patients of side-effects and the seemingly negative effect of doing so constitutes an ethical dilemma. This demands more research to uncover the working mechanisms of the nocebo effect in general, as well as finding effective ways of preventing or reducing it (Barnes et al., 2019).

There has been increasing interest and extensive research carried out on the nocebo effect in the context of pain, with studies making use of various types of experimental pain manipulations (Petersen et al., 2014). Especially in pain related nocebo research, classical conditioning paradigms with verbal suggestions have been found to be highly relevant (Bartels et al., 2014), as classical conditioning seems to play a role in modulating pain sensitivity (Miguez et al., 2014). Classical conditioning is the associative process that takes place when an initially neutral stimulus (conditioned stimulus, CS) is paired with a biologically relevant stimulus (unconditioned stimulus, US). An association between the two is formed and a conditioned response (CR) similar to the unconditioned response (UR) naturally caused by the US begins to be evoked by the CS (Miguez et al., 2014). A widely known example of this process are Pavlov's dogs, in which the sound of a bell (CS) was paired with food (US) and the dogs began to salivate (CR) as soon as they heard

the bell, without the presence of food. In pain research, classical conditioning has been found capable of bringing about both analgesic and hyperalgesic effects. Analgesia stands for a decrease in pain, whereas hyperalgesia means an increase in pain (Price, 2015). The findings on conditioned analgesia are fairly consistent, while the literature on conditioned hyperalgesic effects remains contradictory (Miguez et al., 2014). Verbal suggestions are commonly used in combination with classical conditioning in nocebo research, as several studies have found that negative verbal suggestions (such as telling a patient that a procedure will be painful) may play a role in inducing hyperalgesia (Colloca et al., 2008). Findings from studies including verbal suggestions and classical conditioning can thus have major clinical relevance for example for patients suffering from chronic pain (Colloca & Miller, 2011).

The nocebo effect can result from a variety of psychosocial factors within and outside the context of treatment. These can include environmental factors, the quality and quantity of verbal and non-verbal communication between the treatment provider and patient (Elsenbruch et al., 2019), as well as individual characteristics of a patient. Such individual factors can encompass genetic factors, personality, as well as past experience (Kern et al., 2020). In the following paragraph, the effects of one of such factors, namely state anxiety, on nocebo effect will be explained.

Anxiety is characterised by physiological hyperarousal and negative cognitions of oneself and the future (Renner et al., 2018). State anxiety reflects how one feels in this particular moment. This is in contrast to trait anxiety, which refers to a more permanent state (Fox, 2008). In a prospective cohort study on the contribution of individual factors to nausea in first-time chemotherapy patients, it was found that higher state anxiety positively predicted nausea expectancy, which consequently resulted in higher risk of developing post-chemotherapy nausea (Meissner et al., 2019). A recent systematic review on the influence of stable personality traits summarised the findings of several studies on the effects of individual factors on the placebo/nocebo response (Kern et al., 2020). Positive correlations were found between anxiety sensitivity and the nocebo effect, but several studies also found no significant association between anxiety-related measures and the nocebo effect. While these findings are not all about state anxiety specifically, the contradictory findings

suggest a need for further research on the effects of anxiety on nocebo (Kern et al., 2020).

Moods can be defined as diffuse affective states that are generally fairly long in duration, but lower in intensity when compared to emotions (Fox, 2008). There is limited research available on the influence of mood on the nocebo effect, but a study by Geers et al. (2019) found that inducing positive mood can act to reduce and block the formation of the nocebo effect. The mechanisms behind such effects are still unknown and call for further research. A focus on mood in the context of nocebo brings with it a major clinical implication. Namely, implementing a positive mood induction approach might not have to affect the ethically required delivery of side-effect information to patients in order to be effective (Geers et al., 2019). If levels of anxiety or mood do in fact affect the likelihood of nocebo effect, such individual differences should be taken into account when assessing a patient (Woo, 2015), as well as in creating and implementing a treatment plan for an individual (Kern et al., 2020).

The current study aims to add to the knowledge base of the effects of state anxiety and mood on the nocebo effect in the context of a pain conditioning task. In our model, level of state anxiety is considered a predictor for the nocebo effect, and mood a moderator for this relationship. Two research questions were considered. The first being whether higher levels of state anxiety significantly increase the nocebo effect, the second whether mood significantly moderates this relationship. I chose to study mood as a moderator, as to see whether positive mood could act to cancel out the effect of state anxiety on the nocebo effect. My goal was to explore whether the use of positive mood induction interventions for anxious patients would be worth pursuing further. My research questions were studied only in the context of males, as the data used comes from an experiment in which only males were included. Studying these questions can help provide more insight into the effectiveness of positive mood induction in reducing or completely preventing the nocebo effect. It can also increase understanding on the contribution of anxiety to the severity of the nocebo effect, as well as assist in creating interventions that take into account the individual characteristics of a patient. My first hypothesis states that the level of state anxiety has a significant positive relationship with the nocebo effect. I expected that higher level

of state anxiety would act to increase the strength of the nocebo effect. My second hypothesis states that mood significantly moderates the relationship between state anxiety level and the nocebo effect. For this hypothesis, the moderating effects of both positive and negative mood were studied individually. I expected that more positive mood would reduce the likelihood of a nocebo effect and vice versa.

Methods

Study design

My research questions were studied within the context of a larger, randomised, placebo-controlled double-blind study within the Health, Medical, and Neuropsychology department at Leiden University. The data was collected at the laboratory of the Faculty of Social Sciences of Leiden University between March and November 2017. The experiment looked into the effects of oxytocin on placebo and nocebo effects in a pain conditioning task with verbal suggestions. Participants were randomly assigned to one of two groups: an experimental (oxytocin) group or a placebo group. The experimental group received 40 IU of oxytocin nasal spray, while the placebo group received the same volume of a placebo nasal spray. The randomization was performed by the Clinical Pharmacy of the Leiden University Medical Center. For this, block randomization with the block size of 8 was used. The researchers received a randomization list with the group assignment only after the end of the study. The study protocol was approved by the Medical Ethical Committee of the Leiden University Medical Center (number NL60185.058.16) and the study was preregistered as a clinical trial on www.trialregister.nl (NTR6506). All participants provided written informed consent and were reimbursed for their time and participation.

Participants

For this experiment, 80 healthy male volunteers between the ages 18 and 36 were included, half of which (placebo group) will be taken into account when answering the presented research questions. Only male participants were recruited, as previous research has reported oxytocin increasing placebo analgesia only in men (Kessner et al., 2013). Additionally, there is strong evidence suggesting that females are more sensitive to thermal pain (heat, cold) than males (Racine et al., 2012). As a heat pain device was used in this study, this difference might have affected the results.

Finally, menstrual cycles in females can result in changes in oxytocin levels, which could have potentially interfered when studying the effects of oxytocin in women (Rash & Campbell, 2014). Apart from female gender, the exclusion criteria ruled out participants with current diagnosis of psychiatric disorders, chronic or acute pain complaints, heart and lung diseases, high or low blood pressure, current use of analgesic medication, as well as those with alcohol or recreational drug abuse. The participants were asked to not consume alcohol or take part in intense physical exercise for up to 12 hours prior to the experiment. They were also be requested to refrain from consuming caffeinated drinks and smoking up to 2 hours before the experiment. For the purpose of my research questions, only participants in the placebo (non-oxytocin) group ($N = 37$) will be taken into account in order to control for the effects of oxytocin.

Procedure

Those interested in participating in the experiment were first asked to fill in an online questionnaire on Qualtrics (Provo, UT) in order to check the in- and exclusion criteria. After the answers had been screened by the researchers, eligible participants were invited to take part in the lab experiment, which lasted for 2 hours. The testing ended after 80 participants had completed the experiment.

Upon arrival to the lab, participants received information regarding the experiment, after which any questions were answered. At this point each participant was asked to sign an informed consent form. Two experimenters were present at the lab to conduct the experiment. One provided the participant with instructions, the other controlled the equipment used. To begin the study, participants were asked to fill in several questionnaires on a computer. After completing the questionnaires, participants were familiarized with the heat pain device used in the calibration and conditioning phases of the study, after which pain calibration took place. For each participant, temperatures eliciting low, moderate, and high pain levels were found. Following this, participants were administered either oxytocin or placebo nasal spray, depending on whether they have been allocated to the experimental or the placebo group. The group allocation was done in a double-blind, randomized manner as described in the study design. After the spray had been administered, participants received verbal suggestions regarding the upcoming conditioning task. A 30-minute

waiting time preceded the conditioning task in order for the effects of oxytocin to reach its peak (Striepens et al., 2013). Participants were provided with magazines with neutral content to read during this time. Once 30 minutes had passed, the pain conditioning task took place. After the task, participants were asked to fill in some final questionnaires, after which they were debriefed and monetarily compensated for their time.

Experimental manipulations

Verbal suggestions. Before the pain conditioning task, each participant received verbal instructions regarding the experiment. Participants were told that the aim of the experiment was to investigate how oxytocin would influence a TENS (transcutaneous electrical nerve stimulation) device. They were told that during the experiment, colours on a computer screen would be presented indicating how the electrodes would be affecting pain sensitivity. A red cue on the computer screen indicated that the electrodes would increase pain sensitivity, a green cue that the electrodes would decrease pain sensitivity, and a yellow cue would indicate that the device is inactive and thus would not affect ones pain sensitivity. In reality, the TENS device remained inactive throughout the experiment. This information was only used as a cover story in order to possibly strengthen the effects of the conditioning procedure.

Pain calibration. The pain stimuli was administered using a standardized heat pain application device (ATS-II, Medoc Advanced Medical Systems, Ramat Yishai, Israel). The device has built-in, reliable safeguards to ensure the temperatures remain at a safe level. The heat stimuli was applied to the dorsal site of the non-dominant arm, approximately five centimeters above the wrist. The calibration procedure was then performed, in which three levels of heat stimulation were determined for each participant. First, one's pain detection threshold (low pain) was found (equal to 1 on a 0-10 numeric rating scale (NRS) with 0 = no pain at all, 10 = worst pain imaginable). Second, a temperature described by the participant as moderate pain (equal to 4 on the 0-10 NRS). Third, a temperature described as high but tolerable pain (equal to 8 on the 0-10 NRS). These were determined by applying one sequence of ascending temperatures to the participant's arm with a peak temperature lasting for 4 seconds. The between-stimulus interval was set to 15 seconds. During this sequence,

participants were asked to rate each individual heat stimulus on an NRS ranging from 0-10. After a pain level of 7 or above was reached, the calibration procedure was stopped. If the participant failed to distinguish between the two, the calibration procedure was repeated. The participant was only allowed to continue to the next phase of the study if the calibration was successful on the first or second try. Otherwise the participant was excluded from the study, debriefed, and reimbursed for the time invested.

Pain conditioning task. The conditioning task consisted of two phases of stimulus sequences: a learning phase and a testing phase. The learning phase consisted of a total of 36 stimuli. Participants experienced 12 low pain stimuli paired with a green cue on a computer screen, 12 moderate pain stimuli paired with a yellow cue, and 12 high pain stimuli paired with a red cue. The stimuli were presented in a randomized fixed order. During the testing block, participants were given a total of 30 moderate pain stimuli, presented with green (placebo condition), yellow (control condition), and red (nocebo condition) cues. Each colour was presented 10 times. The conditioning continued without a break from the learning phase into the testing phase. Throughout the procedure, the peak temperature lasted for 4 seconds. The stimuli reached and cooled down from peak temperature at the rate of 8 degrees per second. The interstimulus interval was set to 4 seconds. The order of the stimuli was based on a randomized fixed order: 4 sequences were created prior to the experiment and each participant was randomly allocated to 1 of 4 sequences. In order to avoid habituation and sensitization to pain, the location of the thermode on the forearm was changed twice: after the 22nd stimulus of the learning phase, and after the 8th stimulus of the test phase (every 22 stimuli). After each stimulus, the participants were again asked to verbally rate how painful they experienced the stimulus on a 11-point NRS.

Instruments and materials

Visual stimuli. E-Prime (version 2.0) software installed on a desktop computer was used to present the visual cues during the pain conditioning task. The resolution of the screen was 1280x1024 pixels. Participants were seated approximately 60 cm away from the screen. The visual cues (green, yellow, red) were shown for two seconds before the start of each heat stimulus. During the cues, the whole screen turned the colour of the cue.

Questionnaires. Mood was assessed using the short version of the Positive and Negative Affect Schedule (PANAS-SF). The version used consists of 5 items for measuring positive affect and 5 items for measuring negative affect on a 5-point Likert scale (1=not at all, 5=very much). Higher scores indicated higher positive and higher negative affect, respectively. An example of an item measuring positive affect is “excited” and an example of an item measuring for negative affect is “hostile”. Participants indicated for each item to what extent they had felt this way over the past week. (Watson et al., 1988).

Baseline state anxiety levels of participants was measured using the short version of the Spielberger State-Trait Anxiety Inventory (STAI-Ss). This questionnaire consists of 6 items for which participants were asked to give answers on a 4-point Likert scale (1=not at all, 4=very much). An example of an item is “I feel upset”, to which the participant indicated to what extent they feel this way (Marteau & Bekker, 1992).

Other included questionnaires not related to my research question were the Revised Life Orientation Test (LOT-R) used to measure optimism (Scheier et al., 1994) and the neuroticism and extraversion scales of the short version of the Eysenck Personality Questionnaire-Revised (EPQ-RSS) to measure neuroticism and extraversion (Eysenck & Eysenck, 1985).

A closing questionnaire was included to ask participants about how they experienced the study. They were asked to answer the following questions: “Do you think you received oxytocin or placebo?”; “What do you think was the aim of this experiment?”; “Have you heard anything about this experiment from other people? If yes, what?”.

Statistical analysis

A statistical analysis of the data was performed using the IBM Statistical Package for Social Sciences (SPSS) version 26 (Armonk, New York, USA). The level of significance was set at 0.05 for all statistical tests. Only participants in the placebo group ($N = 37$) were taken into account in the analysis. To define nocebo effect scores

in the existing data, ratings in response to the first yellow trials (control condition) of the testing phase were substracted from ratings in response to the first red trials (nocebo condition) of the testing phase.

Univariate techniques (descriptives) were used to find the mean and standard deviation of the sample. Skewness and kurtosis measures were used to assess the assumption of normality. Skewness measures indicated that state anxiety scores were non-normally distributed in the sample with skewness of 1.02. Additionally, measures of negative mood were found to be positively skewed (skewness = 1.714). Log10 transformation was carried out for these two variables, after which state anxiety scores were no longer positively skewed (skewness = .395). The negative mood variable remained non-normally distributed with skewness of 1.279. The transformed variables were used for the remaining analysis. For other variables, the assumption of normality was met. To assess linearity, a scatterplot of nocebo effect scores against each of the variables with a superimposed regression line was plotted. Visual inspection of the plots indicated a linear relationship between the nocebo effect and all independent variables. A scatterplot was also used to assess homoscedasticity, the visual inspection of which indicated that the assumption of homoscedasticity was met for all variables. The assumption of independence of residuals was checked using the Durbin Watson statistic, which indicated negative autocorrelation. Outliers were checked for using the z test. The cut-off for considering a score to be an outlier was anything below -3.29 or above 3.29. This corresponds to ± 3 standard deviations (SD). No outliers were found to be present in the data.

For the main analysis, a paired-samples t-test comparing the first red (nocebo) trials and the first yellow (control) trials was used to test for a significant nocebo effect. A simple linear regression analysis was carried out to check for whether level of state anxiety significantly affected nocebo effect in men. To find out whether mood significantly moderated the relationship between level of state anxiety and nocebo effect, PROCESS macro for SPSS was used to perform a moderation analysis for both negative mood and positive mood as moderators (Hayes & Little, 2018).

Results

Descriptive statistics for the sample can be found in Table 1. The significance of the nocebo effect was tested using a paired-samples t-test comparing the means of the first red (nocebo) trials and the first yellow (control) trials of the testing phase of the conditioning task. The learning phase of the conditioning task was not relevant for the analysis. No significant nocebo effect was present in the nocebo sample ($N = 37$). The mean nocebo trial score ($M = 3.67$, $SD = 1.67$) did not mark a statistically significant increase in pain ratings when compared to the mean control trial score ($M = 3.31$, $SD = 1.85$), with a mean difference of $M = -.35$, 95%CI [-.79, .08], $t(36) = 1.64$, $p = .109$. The effect size for this analysis ($d = 0.27$) indicates a small to medium effect size.

For the hypothesis that the level of state anxiety has a significant positive relationship with nocebo effect in men, a one-tailed simple linear regression analysis was performed, with level of state anxiety as the independent variable and nocebo effect as the dependent variable. A non-significant regression equation was found for this model ($F(1, 35) = .188$, $p = .667$), with an R^2 of .005. This effect size of the whole model suggests that state anxiety only explains .5% of the nocebo effect.

Table 1.

Descriptive Statistics for Predictors and the Outcome Variable.

Variable	*M*	*SD*	Range
State anxiety	9.46	2.18	6.00-16.00
Positive mood	27.00	7.60	16.00-50.00
Nocebo effect	.35	1.31	-3.00-2.50
Negative mood	12.46	2.86	10.00-21.00

For the hypothesis that mood significantly moderates the relationship between state anxiety level and nocebo effect, a simple moderation analysis was performed using PROCESS macro for SPSS (Hayes & Little, 2018). First the analysis was performed with state anxiety level as the independent variable, nocebo effect as the dependent variable, and the measure of positive mood as the moderator. See Table 2 for model summary. The overall moderation model was statistically nonsignificant

($F(3, 33) = 1.28$, $p = .295$). Similarly, the interaction between state anxiety level and positive mood measure was found to be statistically nonsignificant ($B = .0056$, 95% CI [-.024, .036], $p = .7056$). Therefore, positive mood was not found to significantly moderate the relationship between state anxiety and nocebo effect.

Table 2.

Moderation effect of Positive Mood on the Relationship between State Anxiety and Nocebo Effect N = 37.

					CI95% for *b*	
Predictor	*b*	*se*	*t*	*p*	Lower	Upper
State anxiety	-.19	.42	-.45	.66	-1.03	.66
Positive mood	.003	.14	.02	.98	-.27	.28
State anxiety x Positive mood	.006	.01	.38	.71	-.02	.04

Note. Fit for model $R^2 = .10$, $F(3, 33) = 1.28$, $p = .31$.

Next, the same analysis was repeated with state anxiety level as the independent variable, nocebo effect as the dependent variable, and negative mood as the moderator. See Table 3 for model summary. The overall moderation model was statistically nonsignificant ($F(3, 33) = .71$, $p = .56$). Similarly, the interaction between state anxiety level and positive mood measure was found to be statistically nonsignificant ($B = .048$, 95% CI [-.06, .16], $p = .3763$). Therefore we can conclude that negative mood was also found to not moderate the relationship between state anxiety and nocebo effect significantly.

Table 3.

Moderation effect of Negative Mood on the Relationship between State Anxiety and Nocebo Effect N = 37.

					CI95% for *b*	
Predictor	*b*	*se*	*t*	*p*	Lower	Upper
State anxiety	-.63	.67	-.94	.35	-1.98	.73
Negative mood	-.51	.48	-1.06	.30	-1.50	.47

State anxiety x Negative mood	.05	.05	.90	.38	-.06	.16

Note. Fit for model $R^2 = .06$, $F(3, 33) = .71$, $p = .56$.

Discussion

The aim of this study was to further explore the relationships between state anxiety, mood, and nocebo effect in the context of a pain conditioning task. The results did not demonstrate a significant nocebo effect. The most important findings were that state anxiety level was not found to significantly affect the nocebo effect, nor were positive and negative mood found to significantly moderate the relationship between state anxiety and the nocebo effect.

As mentioned in the previous paragraph, no significant nocebo effect was found in the sample. This could be due to the small sample size, but the effect size, which is independent of sample size, indicated only a small to medium effect (d = 0.27). This suggests that even in a larger sample there may not be a statistically significant nocebo effect present. As the current study only included males, an idea worth considering could be gender differences in the effectiveness of this mechanism. This thought is supported by findings that more studies report a significant nocebo effect in females than in males (Vambheim & Flaten, 2017). While a number of past studies have found pairing classical conditioning and verbal suggestions to be a highly effective mechanism in inducing the placebo effect (Colloca et al., 2008), the findings in regard to the nocebo effect have been less consistent (Miguez et al., 2014). Taking that into account, the current findings would fit the profile of past research. No significant results were found for the first hypothesis, which estimated that the level of state anxiety has a significant positive relationship with nocebo effect. This is somewhat in line with previous, mixed findings on the effect of anxiety-related measures on nocebo effect. A study by Meissner et al. (2019) studied the effect of state anxiety on the nocebo effect and found a significant effect, with higher anxiety predicting more negative expectation, which in turn lead to increased post-chemotherapy nausea. This difference in findings could be due to their study looking at post-chemotherapy nausea as opposed to pain. In light of the methodological downfalls in exploring the effects of state anxiety in the context of pain hyperalgesia in this study, as well as the previous, promising research findings, continued research

into this area is still encouraged. Results for the second hypothesis of mood acting as a moderator between the level of state anxiety and the nocebo effect also presented nonsignificant findings for both negative and positive mood. Previous findings of positive mood potentially acting to reduce or block the formation of the nocebo effect have been reported, although in these cases mood has been investigated as a predictor, as opposed to a moderator between anxiety and the nocebo effect (Geers et al., 2019). It should also be kept in mind that this area of research is new and very few studies have previously explored the effects of mood on the nocebo effect. Further research is therefore encouraged, making use of clear positive mood inductions and possibly focusing more on mood as a predictor rather than a moderator for the nocebo effect.

A notable limitation of the study was that only male participants were included. For the purpose of the study in the context of which my research questions were examined, this distinction was necessary. However, this would not be the case in a research design not involving oxytocin. All in all, the full research design included tasks and questionnaires not required for answering the research questions at hand, which may have affected the questionnaire scores and pain ratings of participants. That being said, the measures of mood and state anxiety used in the analysis were administered to participants right before the pain conditioning task. This allowed for accurate results without other tasks potentially influencing mood or state anxiety between the questionnaires and the pain conditioning phase. Another limitation was that there was no experimental control for any of the independent variables, with no positive mood induction taking place. An important limitation was also the small sample size ($N = 37$), which decreases statistical power. Finally, even after transformation, the assumption of normality was not met for negative mood, which could skew the final results. The strengths of this study include the good psychometric qualities of questionnaires used, as well as the methods utilized for inducing a nocebo effect that have been found effective in previous studies.

The findings of this study highlight the importance of a having a study design fully suitable for the research questions examined. Despite the lack of significant findings, further exploration on the effects of state anxiety and mood on the nocebo effect in the context of pain conditioning, using more specialised study designs could be encouraged on the basis of previous, significant study results. Finding ways to

prevent or reduce pain hyperalgesia brought on by classical conditioning and verbal suggestions remains an important area of research due to its clinical relevance in training treatment providers to take into account personal characteristics of an individual when creating treatment plans for their patients, and thus potentially improving the quality of life for numerous people. Future studies into the field should include a larger, more representative sample of the population, including both genders. Future research should also include study designs that employ the experimental manipulation of mood and state anxiety variables. This would allow for an even better understanding of the precise effects of these variables on the nocebo effect. Especially including mood manipulation in the study design could be beneficial, taking into consideration the findings on positive mood inductions reducing or preventing the nocebo effect altogether in a clinical setting. It should, however, also be considered that perhaps state anxiety and mood simply do not have a significant effect on the nocebo effect, in which case attention should be turned to other potential predictors and moderators.

To conclude, this study found no significant effects of state anxiety on the nocebo effect. Similarly, no significant findings were present when looking at the moderating effects of positive and negative mood on the relationship between state anxiety and the nocebo effect. Future research is necessary with more specialized designs, including experimental control over independent variables, such as state anxiety and mood.

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