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Nocebo hyperalgesia and other expectancy-related factors in daily fibromyalgia pain: Combining experimental and electronic diary methods

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ABSTRACT

Objective: Expectancies are known to shape pain experiences, but it remains unclear how different types of expectancies contribute to daily pain fluctuations in fibromyalgia. This combined experimental and diary study aims to provide insights into how experimentally-derived nocebo hyperalgesia and other, diary-derived, expectancy-related factors are associated with each other and with daily pain in fibromyalgia.
Methods: Forty-one female patients with fibromyalgia first participated in a lab procedure measuring nocebo hyperalgesia magnitude, then filled out an electronic diary 3 times a day over 3 weeks regarding the expectancy-related factors of pain expectancy, anxiety, optimism, and pain-catastrophizing thoughts, and current pain intensity.
Results: Our results indicate that experimentally-induced nocebo hyperalgesia was not significantly related to diary-assessed expectancy-related factors and did not predict daily fibromyalgia pain. Higher levels of the self-reported expectancy-related factors pain expectancy and pain catastrophizing, but not anxiety and optimism, predicted moment-to-moment pain increases in fibromyalgia, after controlling for current pain, moment-of-day and all other expectancy-related factors.
Conclusion: Our exploratory research findings indicate that self-reported expectancy-related factors, particularly pain expectancy and pain catastrophizing, are potentially more relevant for predicting daily pain experience than experimentally-induced nocebo hyperalgesia. Further translation of nocebo hyperalgesia is needed from experimental to Ecological Momentary Assessment research. Our findings imply that targeting the decrease in pain expectancy and catastrophizing thoughts e.g., via Cognitive Behavioral Therapy, have potential for improving daily pain levels in fibromyalgia.

1. Introduction

Pain can be shaped by different types of expectancies [1,2]. Psychological learning mechanisms such as conditioning or verbal instructions can shape outcome expectancies that can in turn modulate symptom perception [1,2]. An example of outcome expectancy is a patient's expectation and experience of pain worsening upon being verbally informed about a treatment's inefficacy. Expectancies of upcoming pain (i.e., pain expectancies), as well as expectancy-related factors such as anxiety, catastrophizing, and optimism have been found to be associated with pain [1,3–5]. Yet, their combined role in shaping pain experiences in chronic pain conditions, such as fibromyalgia, is fairly unknown. Given that expectancies play an important role for pain modification in fibromyalgia [6], research is needed on how different expectancy-related factors can impact the perceived changes in daily pain.

Experimental and diary studies have shown that higher pain expectancy is associated with increases in (subsequent) pain experiences [4,7–10]. In patients with chronic pain, greater pain expectancy has been found to be associated with increased pain intensity in daily-life [4]

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and also an indicator of future pain trajectory and quality of life [8,11]. Pain-related fear and anxiety have been associated with overprediction of daily pain, where patients expected to experience more pain than their actual self-reported pain [12,13]. Pain catastrophizing has been also associated with cognitive and emotional aspects of pain that alter pain perception [14]. In fibromyalgia, both maladaptive (pain catastrophizing) and adaptive (pain coping) cognitions have been found to impact changes in daily pain intensity [15]. Morning pain intensity predicted the upcoming pain cognitions in the afternoon, which in turn mediated the end-of-day pain intensity [15]. Moreover, optimism has been found to have a beneficial association with pain experience [16]; as daily pain and fatigue levels increased in fibromyalgia, having higher optimism has been found to facilitate engagement in painful activities and the pursuit of personal goals [17].

Nocebo hyperalgesia (i.e., pain expectancies based on previously-learned associations) can further contribute to pain increase [2]. Given that more established methods of nocebo hyperalgesia induction are lacking outside of the lab, it remains to be investigated whether nocebo hyperalgesia measured in the lab predicts daily pain levels in fibromyalgia. Experimental studies have shown that lower optimism, higher anxiety, and higher pain catastrophizing are associated with stronger nocebo effects [2,18]. However, in these studies, psychological characteristics were assessed as general traits, whereas their assessment via diary methods can provide additional information on daily changes. The magnitude of experimentally-induced nocebo hyperalgesia might reflect a general characteristic for expecting negative pain-related outcomes, which could influence cognitions and emotions underlying the state-like changes in expectancies and pain.

The current study combining experimental and electronic diary study methods investigates the association of both experimentally-induced nocebo hyperalgesia and diary-derived self-reported expectancy-related factors with each other and with pain in female patients with fibromyalgia. Data on nocebo hyperalgesia were taken from a larger experimental study [19] and the other factors were assessed in the same patient sample via an electronic diary for 3 times a day over 3 weeks. The current study objectives are three-fold and are exploratory given their novelty. First, we explore the relationships of nocebo hyperalgesia with self-reported expectancy-related factors (i.e., pain expectancy, anxiety, pain catastrophizing, and optimism) and pain averaged over 3 weeks. Second, we explore whether each self-reported expectancy-related factor predicts moment-to-moment change in pain, controlling for current pain and moment-of-day. Third, we explore whether nocebo hyperalgesia and self-reported expectancy-related factors together predict moment-to-moment change in pain, again controlling for current pain and moment-of-day. Hereby, we provide a multi-faceted account of the role of both experimental and self-reported expectancy-related factors in fibromyalgia pain.

2. Materials and methods

2.1. Design & participants

This study is part of a larger prospective study (ICTRP Identifier: NL8244, registration date: 17-12-2019, link: https://trialsearch.who.int/Trial2.aspx?TrialID=NL-OMON24049, disclaimer: no analysis has been done prior to pre-registration) approved by the Medical Ethical Committee Leiden The Hague Delft (NL67541.058.18). The larger study [19] consisted of two experimental sessions, at baseline and at one-month follow-up, where nocebo hyperalgesia was induced (via conditioning combined with verbal suggestions) and reduced (via extinction) per session in patients with fibromyalgia and healthy controls. Here, we investigated the potential group differences between patients and healthy controls in the induction and reduction of nocebo hyperalgesia, and the potential stability of these effects over one month. Additionally, as part of the current study, only the patient group filled out the electronic diary for 3 weeks following the baseline experimental session. The current study was carried out in accordance with Declaration of Helsinki. Since fibromyalgia is more common in women than in men [20], the present study included only female patients to ensure that the current results could be better compared to existing research. Patients were required to meet the criteria for a fibromyalgia diagnosis from a rheumatologist, which was confirmed through a telephone screening where patients provided information about the year, location, and provider of their diagnosis. All patients additionally filled in the Fibromyalgia Survey Questionnaire (FSQ) [21] to confirm the presence of key fibromyalgia symptoms. Patients were excluded if they had received a medical diagnosis other than fibromyalgia that accounted for their chronic pain symptoms (such as rheumatoid arthritis or polyarthritis) or if they had severe physical or mental health conditions unrelated to fibromyalgia (such as cancer or schizophrenia). Further details on the participation requirements for the experiment and the screening procedure are reported elsewhere [19]. Forty-one female patients with fibromyalgia (M age $\pm$ SD = 37 $\pm$ 10.3, range 20–58) first participated in a lab experiment at the Leiden University Treatment and Expertise Center (LUBEC) to measure the magnitude of experimentally-induced nocebo hyperalgesia [19], and subsequently filled out an electronic diary app on their smartphone for 21 days. All participants provided written informed consent. A monetary compensation up to €100 was awarded for participating in all parts of the study with additional travel costs.

2.2. Nocebo hyperalgesia assessment

A well-established nocebo-conditioning paradigm combined with verbal suggestions was used for inducing nocebo hyperalgesia in the lab [22]. Nocebo effects on pressure pain on the thumb nail were induced by leading participants to expect that the activation of a sham Transcutaneous Electrical Nerve Stimulation (TENS) device would lead to pain worsening compared to its deactivation. After repeated pairing of sham activation of the TENS device and a stronger pressure pain applied, a test phase commenced in which pressure pain intensity was similar between sham activation and non-sham activation of the TENS device. Differences in pain intensity (0–10 Numeric Rating Scale, NRS) reported to the sham-activated and sham-deactivated trials in the test phase were calculated to derive a nocebo hyperalgesia score, with a higher score indicating stronger nocebo hyperalgesia. Detailed descriptions of the lab procedures and the calculation of nocebo hyperalgesia scores are reported elsewhere [19].

2.3. Electronic diary assessment

At the end of the lab session, the diary app (Ethica Data Services Inc., Toronto, Canada) was downloaded on participants' smartphones. Participants were prompted to fill in questionnaires in the upcoming 3 weeks for 3 times a day at semi-random moments (morning: 09:00–11:00, afternoon: 14:00–16:00, evening: 19:00–21:00), where a time was randomly selected per time block. Each questionnaire took 2–5 min. The first prompt was sent on the first Monday morning following the lab session. If participants failed to fill in a questionnaire within 30 min after notification, the questionnaire became unavailable to avoid late responses. Participants were able to fill in possible comments via the app or contact researchers for any questions. Researchers monitored participants' response progress and sent standardized weekly motivation messages to increase compliance.

2.4. Measures

In the diary study, the current pain intensity was assessed by the question "How much pain do you experience at the moment?", rated on a 0 ("no pain") to 10 ("worst pain imaginable") NRS. Next moment's pain expectation was assessed with "How much pain do you expect in the {next assessment moment} (morning/afternoon/evening)?", rated on the same NRS as pain intensity. Current anxiety was assessed with

"How much anxiety do you feel at the moment?", rated on a 0 ("not at all anxious") to 10 ("extremely anxious") NRS. Based on previous daily diary research [23], current catastrophic thinking related to pain was assessed with three items ($\alpha = 0.90$, the mean rating per item was used for this calculation) that each represent a subscale from the Pain Catastrophizing Scale (PCS) [24]. The item "At the moment I am afraid that the pain will get worse" represents the subscale "magnification", "At the moment I am constantly thinking about how much it hurts" represents the subscale "rumination", and "At the moment I feel that the pain overwhelms me" represents the subscale "helplessness". Each item was rated on a 0 ("strongly disagree") to 10 ("strongly agree") NRS. Current optimism was assessed with the item "At the moment I feel optimistic", rated on a 0 ("strongly disagree") to 10 ("strongly agree") NRS.

2.5. Statistical analyses

All analyses were conducted using the statistical software R (version 4.2.2) [25]. Missing observations in diary data were skipped from analysis. To examine the *zero-order* relationships of experimentally-induced nocebo hyperalgesia with diary-assessed self-reported expectancy-related factors (pain expectancy, anxiety, pain catastrophizing, and optimism) and pain, Pearson's *correlation* was used. A composite score for pain catastrophizing was first calculated by averaging the scores on the 3 items at each given moment. Diary-assessed variables were averaged across the 63 measurement moments (3 × 21 days), meanwhile skipping missed moments, before calculating Pearson's *correlation*.

Since self-reported diary assessments (level one) are nested within individuals (level two), multilevel analyses were conducted to answer the remaining research questions. The intra-class correlation (ICC) coefficient was calculated for the null model (without entering any variables) to confirm the multilevel structure of the data. Pain expectancy, anxiety, pain catastrophizing, optimism, and pain ratings were shifted 1 assessment moment earlier to investigate their predictive role in next-moment pain (e.g., morning pain expectancy predicting afternoon pain, controlling for morning pain).

To examine whether each of the self-reported expectancy-related factors predicts moment-to-moment change in pain, four multilevel analyses were conducted. Either previous-moment pain expectancy, anxiety, pain catastrophizing, or optimism was entered in each model as fixed effects, controlling for previous-moment pain and next-moment moment-of-day (with two dummy variables). Next moment's pain was modeled as the dependent variable.

To examine whether experimentally-induced nocebo hyperalgesia and self-reported expectancy-related factors together predict moment-to-moment change in pain, another multilevel analysis was conducted. Experimentally-induced nocebo hyperalgesia and self-reported previous-moment pain expectancy, anxiety, pain catastrophizing, and optimism were entered as fixed effects, controlling for previous-moment pain and next-moment moment-of-day. Next moment's pain was modeled as the dependent variable. All models included a random intercept for participants. The mean of nocebo hyperalgesia was centered around the grand mean, given that this was the only time-constant estimate. The mean of each time-varying estimate was centered within-persons [26]. This generates two estimates for the same variable in the model: between-person mean-centered and within-person mean-centered predictor. The former involves taking the mean value of a particular variable for each individual across time and then subtracting this from the overall mean of that variable across individuals. This helps assess how an individual's mean score on a given variable relates to their response on the dependent variable, compared to the overall mean across individuals. The latter relates to how a particular variable fluctuates within an individual over time, relative to their own mean value for that variable. This helps assess the effect of deviations from an individual's own mean score on the dependent variable. Data was checked for assumptions of linearity and normality using scatterplots and Q-Q plots, respectively.

3. Results

A sample of 41 participants generated 1909 observations across 3 weeks, yielding a missing response rate of 26%. Detailed descriptions of the sample are reported elsewhere [19]. None of the assumptions from any of the analyses were violated. Aggregation of diary data across 41 patients and 63 measurement moments indicated daily pain to be of moderate intensity on average ($M = 4.81$, $SD = 1.47$). Amongst all aggregated diary-assessed variables, pain catastrophizing was the highest-scored item and showed the highest mean variability between patients (see Table 1). Nocebo hyperalgesia was induced experimentally (as the mean score was above 0); however, its magnitude was not large ($M = 0.23$, $SD = 0.97$), while it also showed the smallest mean variability between patients compared to self-reported expectancy-related factors (Table 1) [19].

3.1. Nocebo hyperalgesia's relationship with self-reported expectancy-related factors and pain

Zero-order relationships were assessed using Pearson's *r* as shown in Table 1. Results showed that experimentally-induced nocebo hyperalgesia magnitude did not significantly predict mean self-reported expectancy-related factors or mean pain assessed in the following 3 weeks.

3.2. Self-reported expectancy-related factors predicting moment-to-moment change in pain

Each self-reported expectancy-related factor was entered into a separate multilevel model. Their partial lagged relationships with next-moment pain, after controlling for previous-moment pain and next-moment moment-of-day, are shown in Table 2. The multilevel structure of the data was confirmed by a significant intercept of the null-model (ICC = 0.52). The explained variance of the four models (*Pseudo-R^2*) ranged between 0.59 and 0.64, with the pain-expectancy model explaining the largest variance in pain (*Pseudo-R^2*: 0.64) with the best model fit (*AIC*: 4784.15). In all models, the moment-of-day covariate was positively related to pain, where patients reported the lowest pain in the morning, compared to afternoon and evening ($p < .001$). Also, the covariate previous-moment pain was a positive predictor of next-moment pain in all models based on between-person ($p < .001$) and within-person ($p < .001$) values. After controlling for these

Table 1
Means, SDs, and zero-order correlations of experimentally-induced nocebo hyperalgesia with self-reported expectancy-related factors and pain averaged over 63 measurement moments across patients with fibromyalgia ($N = 41$).

	Nocebo Hyperalgesia[a]				
	M	SD	Pearson's r	p-value	95% CI
Nocebo Hyperalgesia[a]	0.23	0.97	–	–	–
Mean Pain Expectancy	5.18	1.47	0.11	0.50	[−0.21, 0.41]
Mean Anxiety	3.42	1.45	0.26	0.12	[−0.06, 0.52]
Mean Pain Catastrophizing	6.42	4.67	−0.07	0.69	[−0.37, 0.25]
Mean Optimism	6.29	1.05	0.24	0.15	[−0.08, 0.51]
Mean Pain	4.81	1.47	0.07	0.69	[−0.25, 0.37]

Note.
a: Nocebo hyperalgesia was measured at a single moment, with data missing of 2 patients due to a technical error.
Pearson's *r*: refers to Pearson's *correlation* with nocebo hyperalgesia.
95% CI: 95% Confidence Interval referring to Pearson's *correlation*.

Table 2
Summary of four multilevel models of self-reported previous-moment expectancy-related factors predicting next-moment pain, controlled for previous-moment pain and next-moment moment-of-day, across patients with fibromyalgia ($N = 41$).

	Next-Moment Pain				
Model (Pain Expectancy)	b	SE	t-value	df	95% CI
Intercept	4.50***	0.06	75.81	1461	–
Afternoon	0.43***	0.08	5.23	1461	[0.01, 0.04]
Evening	0.49***	0.08	5.95	1461	[0.01, 0.04]
Pain.cb	1.02***	0.04	23.48	1461	[0.24, 0.31]
Pain.cw	0.21***	0.03	8.27	1461	[0.03, 0.07]
Pain Expectancy.cb	0.01	0.04	0.24	1461	[0.00, 0.00]
Pain Expectancy.cw	0.29***	0.03	9.86	1461	[0.04, 0.09]
Model	*Pseudo-R^2*: 0.64 *AIC*: 4784.15				
Model (Anxiety)					
Intercept	4.34***	0.06	73.48	1472	–
Afternoon	0.58***	0.08	6.99	1472	[0.04, 0.09]
Evening	0.78***	0.08	9.62	1474	[0.04, 0.09]
Pain.cb	1.03***	0.02	42.64	1472	[0.45, 0.59]
Pain.cw	0.32***	0.03	12.51	1472	[0.10, 0.13]
Anxiety.cb	−0.01	0.02	−0.30	1472	[0.00, 0.00]
Anxiety.cw	0.01	0.02	0.25	1472	[0.00, 0.00]
Model	*Pseudo-R^2*: 0.62 *AIC*: 4913.10				
Model (Pain Catastrophizing)					
Intercept	4.34***	0.06	71.68	1432	–
Afternoon	0.56***	0.09	6.59	1432	[0.04, 0.09]
Evening	0.77***	0.08	9.42	1432	[0.04, 0.09]
Pain.cb	1.01***	0.03	37.72	1432	[0.40, 0.53]
Pain.cw	0.29***	0.03	9.24	1432	[0.04, 0.08]
Pain Catastrophizing.cb	0.04	0.02	1.42	1432	[0.00, 0.01]
Pain Catastrophizing.cw	0.05	0.03	1.58	1432	[0.00, 0.01]
Model	*Pseudo-R^2*: 0.59 *AIC*: 4792.14				
Model (Optimism)					
Intercept	4.35***	0.06	73.51	1455	–
Afternoon	0.57***	0.08	6.79	1455	[0.04, 0.08]
Evening	0.75***	0.08	9.32	1455	[0.04, 0.08]
Pain.cb	1.02***	0.03	36.36	1455	[0.37, 0.51]
Pain.cw	0.32***	0.03	12.50	1455	[0.07, 0.13]
Optimism.cb	0.00	0.04	0.11	1455	[0.00, 0.00]
Optimism.cw	0.01	0.03	0.27	1455	[0.00, 0.00]
Model	*Pseudo-R^2*: 0.62 *AIC*: 4852.63				

Note.
b is the unstandardized estimate.
CI: Confidence Interval.
.cb: between-person mean-centered predictor.
.cw: within-person mean-centered predictor.
Pseudo-R^2: Explained variance of the model.
AIC: Akaike's Information Criterion, with a lower score indicating a better model fit.
*** $p < .001$ (two tailed).

covariates, fluctuations in pain expectancy within a patient predicted their next-moment pain levels ($b = 0.29$, $p < .001$) based on the within-person mean centered value (denoted as '.cw'). Specifically, if a patient's pain expectancy at a given moment was 1-point higher than their own average pain expectancy across all assessments, this would be associated with a 0.29-point higher pain at the next moment ($p < .001$). Looking at the between-person mean centered value (denoted as '.cb'), a higher pain expectancy at a particular time point did not significantly predict the next-moment pain ($b = 0.01$, $p = .81$). Moreover, neither the within-person nor between-person values of previous-moment anxiety, pain catastrophizing, or optimism significantly predicted the next-moment pain, after controlling for previous-moment pain and next-moment moment-of-day (see Table 2).

3.3. Experimentally-induced and self-reported expectancy-related factors predicting moment-to-moment change in pain

Next, we entered all experimentally-induced and self-reported expectancy-related factors into the same multilevel model. Their partial lagged relationships with next-moment pain, after controlling for previous-moment pain and next-moment moment-of-day, are displayed in Table 3. The explained variance of the model (*Pseudo-R^2*: 0.60) was comparable to the four models displayed in Table 2, but with a better model fit (*AIC*: 4370.52). Results show that the moment-of-day covariate was positively related to pain, where patients reported the lowest pain in the morning, compared to afternoon and evening ($p < .001$). Previous-moment pain was a positive predictor of next-moment pain based on between-person ($b = 1.02$, $p < .001$) and within-person ($b =$

Table 3
Summary of multilevel model of both experimental and self-reported previous-moment expectancy-related factors predicting next-moment pain, controlled for previous-moment pain and next-moment moment-of-day, across patients with fibromyalgia ($N = 41$).

	Next-Moment Pain				
Fixed Coefficient	b	SE	t-value	df	95% CI
Intercept	4.52***	0.06	71.10	1305	–
Afternoon	0.38***	0.09	4.35	1305	[0.01, 0.04]
Evening	0.48***	0.09	5.42	1305	[0.01, 0.04]
Pain.cb	1.02***	0.05	21.30	1305	[0.22, 0.30]
Pain.cw	0.20***	0.03	6.06	1305	[0.01, 0.05]
Nocebo Hyperalgesia.gmc[a]	−0.01	0.04	−0.25	1305	[0.00, 0.00]
Pain Expectancy.cb	0.01	0.05	0.13	1305	[0.00, 0.00]
Pain Expectancy.cw	0.30***	0.03	9.44	1305	[0.04, 0.09]
Anxiety.cb	−0.02	0.03	−0.62	1305	[0.00, 0.01]
Anxiety.cw	−0.00	0.02	−0.12	1305	[0.00, 0.00]
Pain Catastrophizing.cb	0.06*	0.03	1.97	1305	[0.00, 0.01]
Pain Catastrophizing.cw	0.01	0.04	0.38	1305	[0.00, 0.00]
Optimism.cb	0.05	0.04	1.15	1305	[0.00, 0.01]
Optimism.cw	0.04	0.03	1.32	1305	[0.00, 0.01]
Model	*Pseudo-R^2*: 0.60 *AIC*: 4370.52				

Note.
[a] Nocebo hyperalgesia was measured at a single moment, with data missing of 2 patients due to a technical error.
b is the unstandardized estimate.
CI: Confidence Interval.
.gmc: grand-mean centered predictor.
.cb: between-person mean-centered predictor.
.cw: within-person mean-centered predictor.
Pseudo-R^2: Explained variance of the model.
AIC: Akaike's Information Criterion indicating the model fit.
*$p < .05$; *** $p < .001$ (two tailed).

0.20, $p < .001$) values. Controlling for all other variables, nocebo hyperalgesia did not predict next-moment pain ($b = -0.01$, $p = .80$). Based on within-person mean-centered values, only the fluctuations in previous-moment pain expectancy within a patient predicted their next-moment pain levels ($b = 0.30$, $p < .001$). Previous-moment anxiety ($b < 0.00$, $p = .91$), pain catastrophizing ($b = 0.01$, $p = .70$), and optimism ($b = 0.04$, $p = .19$) did not significantly predict next-moment pain. Based on between-person mean-centered values, only previous-moment pain catastrophizing ($b = 0.06$, $p = .049$) significantly predicted next-moment pain, whereas previous-moment pain expectancy ($b = 0.01$, $p = .90$), anxiety ($b = -0.02$, $p = .54$), and optimism ($b = 0.05$, $p = .25$) were not significant predictors. This indicates that higher pain catastrophizing than average in the group at a particular time point significantly predicts the next-moment pain.

4. Discussion

The current study examined for the first time the separate and combined predictive value of experimentally-induced and diary-based self-reported expectancy-related factors on fibromyalgia pain variation. Results showed that experimentally-induced nocebo hyperalgesia did not predict mean diary-assessed expectancy-related factors nor pain over 3 weeks in female patients with fibromyalgia. Self-reported expectancy-related factors pain expectancy and pain catastrophizing, but not optimism and anxiety, predicted moment-to-moment changes in pain. Pain expectancy was related to within-person and pain catastrophizing to between-person increases in moment-to-moment pain. When other expectancy-related factors were not taken into account, only pain expectancy was a predictor of within-person fluctuations in moment-to-moment changes in pain. Our results highlight the importance of moment-to-moment changes in expectancy-related factors in understanding moment-to-moment changes in fibromyalgia pain. In particular, pain expectancy and pain catastrophizing seem promising for predicting daily pain fluctuations in fibromyalgia. These exploratory research findings could be useful in generating hypotheses in future EMA research.

We examined whether experimentally-induced nocebo hyperalgesia could be a good proxy for predicting expectancy-related factors and daily pain in fibromyalgia. In the lab, small nocebo hyperalgesia effects on pressure pain were induced [19]. Possibly, these effects were only small because experimentally-evoked pressure pain was not fear- or anxiety-inducing enough to generate strong nocebo effects [27,28]. Daily pain experiences of patients are potentially more harmful, unpredictable, and longer in duration compared to safe and controlled experimentally-evoked pain experiences. These differences between experimentally-evoked and daily pain experiences may also partially explain why no associations were found between nocebo hyperalgesia and daily levels of pain expectancy, anxiety, optimism, and pain catastrophizing, nor pain. Future studies are recommended to consider the external-validity of nocebo-conditioning paradigm to better align with daily life and Ecological Momentary Assessment (EMA) studies, for instance by involving patients in the design of clinical research [29].

Our results for pain expectancy are in line with previous studies indicating that pain-related expectancies modify pain intensity, similar to self-fulfilling prophecies [4,8,9,30]. In the current study, we observed that the mean pain expectancy ratings were overall higher than the mean pain ratings assessed over 3 weeks, emphasizing that patients might be overpredicting their upcoming pain intensity. Our findings demonstrated that higher within-person fluctuations in pain expectancy predicts an increase in next-moment pain, after controlling for previous-moment pain and next-moment moment-of-day. Interestingly, additionally taking account of all other expectancy-related factors resulted in almost the same prediction estimate as not taking them into account in the model. Potentially, this could indicate that pain expectancy might share little statistical variance with the other expectancy-related factors. Moreover, pain catastrophizing predicted between-person differences in moment-to-moment pain increase. Although the contribution found is small, the direction of our finding corresponds with the literature [14,15].

To the best of our knowledge, the current study was the first in combining experimentally-induced and self-reported expectancy-related factors in predicting pain in fibromyalgia. However, the external validity of experimentally-induced nocebo hyperalgesia is limited and future studies could consider supporting the experimental measurement of nocebo hyperalgesia with additional self-report questions assessing previously-learned associations related to pain expectancies. Moreover, while developing the diary items, we paid special attention to target momentary experiences by including the phrase “at the moment” and limited the number of items per construct to one to reduce its burden on participants [31,32]. However, the validity of diary items could not be measured by, for instance, comparing them to validated questionnaires. Using validated questionnaires next to diary items could be considered at study begin to check validity. Also, we detected state-like changes in pain expectancy and pain catastrophizing to predict upcoming pain intensity. However, future EMA studies are recommended to also investigate whether state-like measures and trait-like measures, for example assessed via questionnaires, provide comparable findings for pain prediction. Moreover, the statistical power to detect cross-sectional and between-person effects, such as the relationship between nocebo hyperalgesia measured in a single moment with repeated diary assessments of other expectancy-related factors, was limited due to our study only including 41 participants. For the within-person effects, such as the pain expectancy predicting next moment’s pain, we had much higher power due to the relatively large number of observations per person [33]. Lastly, we assessed pain based on a general abstraction of patients’ specific nature of symptoms, without taking into consideration potential variations experienced due to the widespread nature of pain in fibromyalgia. Future studies examining more fine-grained pain differences could consider incorporating additional questions on pain localization, pain unpleasantness, or the functional impact of pain into their EMA design.

Overall, our findings show that self-reported, but not experimentally-induced, expectancy-related factors, i.e., diary-assessed pain expectancy and pain catastrophizing, are associated with moment-to-moment pain changes in fibromyalgia, highlighting the role of top-down processes in pain modulation. Lab-based nocebo hyperalgesia was not significantly related to diary-assessed expectancy-related factors or pain, potentially due to their heterogeneity. Our exploratory research findings require further translation from experimental to EMA research. If replicated, our findings could be useful for interventions targeting pain. More specifically, interventions such as Cognitive Behavioral Therapy (CBT), Acceptance and Commitment Therapy (ACT) or mindfulness could target pain expectancy and catastrophizing thoughts to decrease daily pain levels in fibromyalgia.

CRediT authorship contribution statement

Merve Karacaoglu: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Kaya J. Peerdeman:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Julian D. Karch:** Writing – review & editing, Formal analysis. **Henriët van Middendorp:** Writing – review & editing, Methodology, Conceptualization. **Andrea W.M. Evers:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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